Palladium Catalysed C(sp^3)–H Functionalisation of Aldehydes and Amines using Transient Imine Directing Groups

A Thesis submitted by

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I confirm that the work presented within this document is my own. Clear acknowledgement has been made when referring to the work of others, or where help has been received.

Acknowledgements

This thesis is dedicated to my Dad, Paul St John-Campbell (1957–2015). My Dad was a man of exceptional compassion, humour and resilience, who always made the best of every situation. He is deeply missed, but his legacy will forever live on in me and my sisters, and for generations to come. Many thanks to my mum Eva and sisters Zoe and Ann-Marie for their emotional support. Also to all of my friends that came to visit me in London over the past three years, for never changing no matter how long we've been apart.

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Abstract

Transition metal catalysed C–H functionalisation can enable more straightforward routes to small molecules by installing new C–C or C–X bonds in place of existing C–H bonds. C(sp^3)−H functionalisation is a particular challenge, and typically requires the presence of amide-bound directing groups with distinct installation and removal steps, reducing efficiency.

Transient directing groups bind to the substrate reversibly, facilitating directing group installation, C–H functionalisation and directing group removal, tracelessly and in one-pot. This thesis will describe the development of novel transient *imine* directing groups for the functionalisation of both aldehydes and amines.

Section 3.1 describes the development of a direct β-C(sp^3)–H arylation of tertiary aldehydes. Catalytic *N*-tosylethylenediamine was the optimal transient directing group for the arylation, however a large range of alternative amines were explored. Numerous aryl iodides and aldehydes could be used to form the products in good yields. The transient imine mechanism was supported through NMR studies and the isolation of an underivatised palladacycle.

Section 3.2 explains methylene C–H arylation of secondary aliphatic aldehydes. Milder reaction conditions and β-aniline amide directing groups, which provided chelation through the carbonyl oxygen in a 6-membered palladacycle, provided the best results. The structures of the transient imino-amide directing groups were explored and compared with the parent acid. In Section 3.3, the first transient directing group promoted intramolecular C(sp^3)–H annulation reaction was developed, using an amino-ether TDG. This is the only example of oxidative addition of a less reactive C–Br bond (vs C–I) using this approach.

Section 3.4 describes applying 'reverse' transient imines for amine functionalisation. A simple aliphatic aldehyde was designed and developed, derived from an acetal precursor, that promotes selective γ-C(sp^3)–H arylation of unprotected primary amines. Detailed mechanistic studies have been conducted to provide insight on the dual catalytic cycle.

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i. Glossary of Abbreviations, Acronyms and Symbols

AQ aminoquinoline

Ar generic aromatic substituent

Boc *tert*-butyloxycarbonyl

CMD concerted metalation deprotonation

COD 1,5-cyclooctadiene

DCE dichloroethane

DG directing group

DIPA diisopropylamine

DMAP 4-dimethylaminopyridine

DMS dimethyl sulfide

DMSO dimethylsulfoxide

DOE design of experiment

FG functional group

HFIP hexafluoroisopropanol

HRMS high-resolution mass spectrometry

IMes 1,3-dimesitylimidazol-2-ylidene

KIE kinetic isotope effect

NHC N-heterocyclic carbene

NMR nuclear magnetic resonance

R generic group

RPKA reaction progress kinetic analysis

RSM recovered starting material

TDG transient directing group

TFA trifluoroacetic acid

THF tetrahydrofuran

THP tetrahydropyran

TIDG transient imine directing group

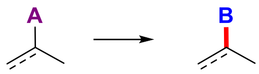
TOLS turnover limiting step

X, Y generic atom or substituent

1. Introduction

1.1 C–H Functionalisation in Organic Synthesis

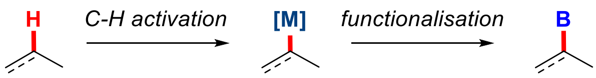
Historically, when approaching the synthesis of an organic molecule, the reactivity of C–H bonds is generally ignored, with attention focused on the transformations of pre-exiting functional groups; i.e., how to get from A to B? (Scheme 1.1).



Scheme 1.1: Traditional synthetic approaches from pre-functionalised starting materials

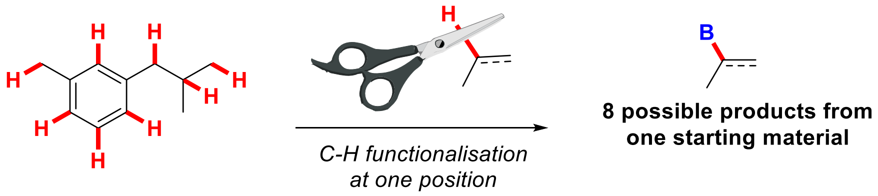
What is often not considered however, is how to get to A. Often the synthesis of starting materials, whether it be a halide, metal or other functionality, could potentially require multiple expensive steps, reducing efficiency. Additionally, natural chemical feedstocks are commonly needed, already functionalised at the desired position, to provide access to the “A”’s.

Functionalisation of a C–H bond bypasses the need for pre-functionalised starting materials, so that the desired “B” functionality can be accessed directly, typically following activation of the C–H bond by a transition metal (Scheme 1.2).



Scheme 1.2: C–H Activation and functionalisation

An additional advantage is related to the inherent nature of C–H bonds in organic molecules. Considering the C–H bond as a point for retrosynthetic disconnections, a large range of isomers could be accessed by a single transformation involving the cleavage and functionalisation of a single C–H bond (Scheme 1.3). As a result, there is vast potential for the last stage functionalisation of industrially relevant compounds.

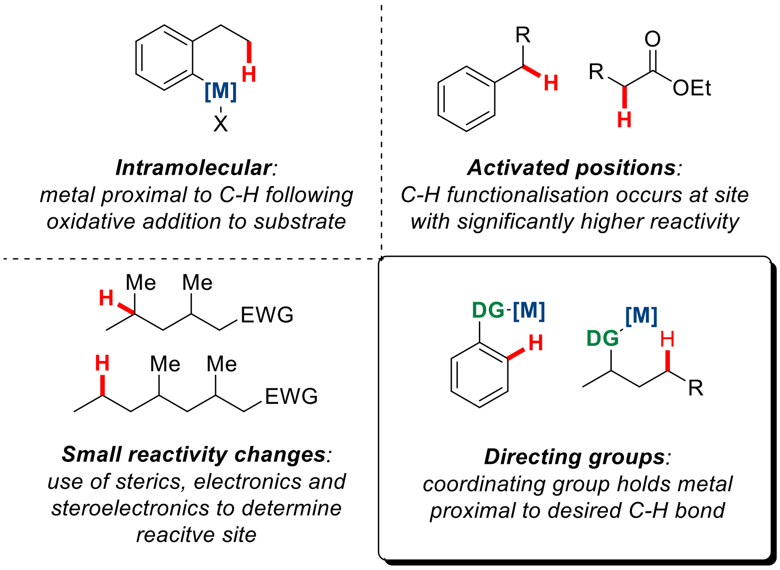


Scheme 1.3: C–H Functionalisation for divergent synthesis

Examples of C–H functionalisation with transition metals date back as far as 1894[1] with iron and 1931[2] with gold, however modern C–H functionalisation can be traced to the 1960's and 70's where intramolecular C–H activation occurred on organometallic compounds with ligands bearing saturated alkyl chains. At this time Shilov also developed platinum catalysed C–H activation of methane.[3] In the late 1970's it was also observed that iridium complexes could be used to dehydrogenate saturated systems.[4] Since these early findings, efforts to make C–H functionalisation a viable synthetic approach have been extensive, with huge advances seen in the past 20 years on both aromatic and aliphatic substrates.

Although potentially hugely powerful, C–H functionalisation is not without its limitations. These are related to the poor reactivity of C–H bonds, but more significant is the major regioselectivity problem. As C–H bonds are ubiquitous, selectively functionalising one position over many others with essentially equal reactivity seems almost impossible.

Regioselectivity in C–H functionalisation has been addressed with a variety of techniques, including intramolecular methods,[5] reaction at activated positions,[6,7] exploiting inherent minute changes in reactivity[8] and the focus of this thesis: directing groups (Scheme 1.4).



Scheme 1.4: Approaches for site-selective C–H functionalisation

Directing groups are tethered to the substrate; they function as chelating groups which interact with the metal centre *via* Lewis basic interactions, this enables the metal to be brought in close proximity to the desired C–H bond. This interaction weakens the C–H bond by causing orbital overlap between the C–H σ-bonding orbital with vacant orbitals on the metal (σ-donation) and the C–H σ*-antibonding orbital with filled orbitals on the metal centre (π-backdonation).[9] It also allows the discrimination over other C–H bonds on the molecule, as they would be too distal from the directing group. Directing groups can be monodentate or bidentate and are arguably the most robust method of achieving site-selective C–H functionalisation.[10,11]

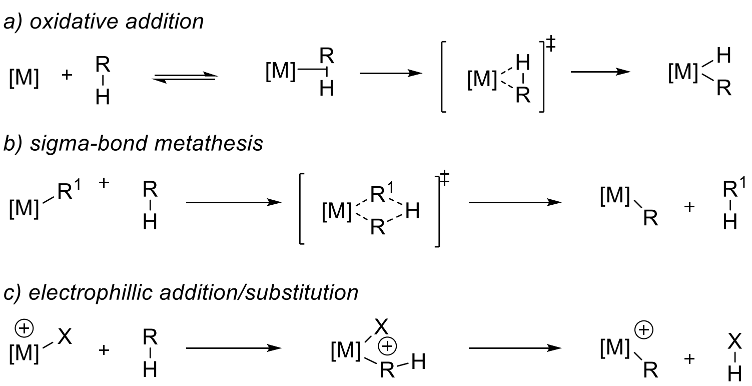
Although it will not be discussed in detail here, bespoke directing groups for the functionalisation of C(sp^2)–H bonds have enabled the selective functionalisation of not only *ortho*-, but also remote *meta*- and *para*-C–H bonds. These directing groups vary enormously in size and coordinating groups, which are typically split into strong (N-based) and weak (carbonyl based), and can be used to install a diverse range of functional groups using a broad range of transition metals.[12–16]

Directing groups for the selective functionalisation of C(sp^3)–H bonds are less well developed, and their progress from early stoichiometric studies to current state-of-the-art will be discussed in Section 1.3.

Also covered are transient directing groups for the functionalisation of both C(sp^2)–H and C(sp^3)–H bonds (Section 1.4). This approach offers a major advance in directed C–H functionalisation due to the removal of the discrete directing group installation and cleavage steps needed in traditional strategies.

1.2 Mechanisms for the Activation of C–H Bonds

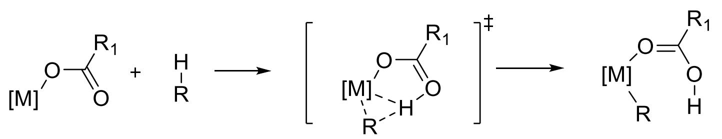
Understanding the mechanisms of chemical reactions is invaluable for the improvement in current, and the development of future synthetic methods. This is also apparent for C–H functionalisation. Three potential mechanisms for C–H activation are shown in Scheme 1.5: a) oxidative addition, b) sigma bond metathesis and c) electrophilic addition/substitution.[9]



Scheme 1.5: Mechanisms of C–H functionalisation

Oxidative addition (Scheme 1.5a) is a well-accepted mechanism for C–H activation and is typical for electron rich complexes of the late transition metals (Re, Fe, Ru, Os, Ir, Pt) when in low oxidation states. For these instances, the change in oxidation state (+2) and geometry on formation of the two new bonds during oxidative addition does not have a large energy barrier. Early transition metals (groups 3 and 4) with a d^0 electronic configuration cannot electronically undergo oxidative addition, and so C–H activation of these complexes occurs *via* σ-bond metathesis (Scheme 1.5b). This mechanism usually requires an alkyl or hydride ligand on the metal. σ-Bond metathesis is a concerted process where the two new bonds are made as the other two bonds are cleaved in the transition state. Late and post-transition metals (Pd^{II}, Pt^{II}, Pt^{VI}, Hg^{II}) in strong polar solvents have been observed to undergo C–H activation *via* an electrophilic substitution mechanism (Scheme 1.5c). Here, the H atom is formally substituted by the metal following electrophilic attack of the metal on the carbon centre.

However, more recently understood, and the mechanism by which many examples covered here using Pd^0 or Pd^{II} catalysis are thought to proceed by, is redox neutral concerted metalation deprotonation (CMD).[5,17] The premise of this mechanism is that a base, typically a carboxylate, carbonate or phosphoric acid, can assist in cleavage of the C–H bond (Scheme 1.6). Yu has shown that pyridone groups can also act as a carboxylate surrogate for CMD.[18] The base that formally deprotonates the C–H can be inner-sphere (bound to the metal) or outer-sphere (external, unbound).[19]

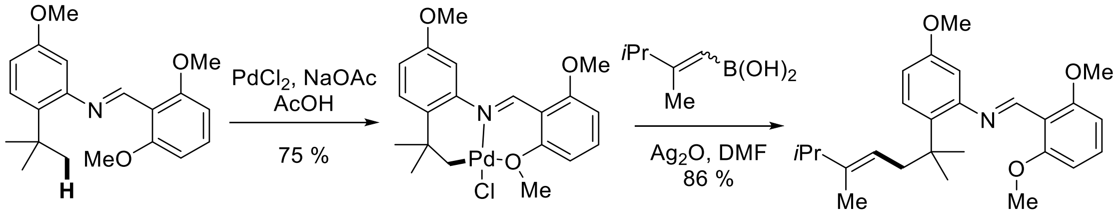


Scheme 1.6: Inner-sphere concerted metalation deprotonation (CMD) with a carboxylate

1.3 Directed Functionalisation of $C(sp^3)$–H Bonds

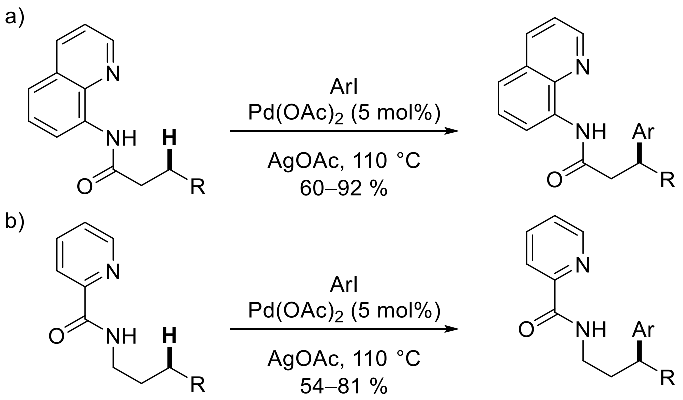
Directing groups for $C(sp^3)$–H functionalisation present a diverse range of structures. Nitrogen-containing heterocycles (such as pyridine) on the substrate can function as non-removable directing groups.[20] Non-permanent directing groups have typically been limited to bidentate and monodentate (with the assistance of a ligand) amides. Oxime based directing groups have also been demonstrated for some transformations.[10,21,22] Although a small number of examples using more abundant transition metals (Fe, Co, Ni, Cu), or other noble metals (Ir, Ru) have been developed, palladium catalysis is without doubt the most common method of achieving directed functionalisation of $C(sp^3)$–H bonds.[10]

The earliest examples of directed C(sp^3)–H functionalisation involved stoichiometric quantities of palladium. An important example by Sames in 2002 is shown in Scheme 1.7.[23] In this work, a bidentate imine-methoxy directing group was used to direct the activation of the primary C−H bond of a *tert*-butyl group, to synthesise the core scaffold of the natural product Teleocidin B4. This formed an intermediate palladacycle, which was subsequently alkenylated *via* transmetalation and reductive elimination.



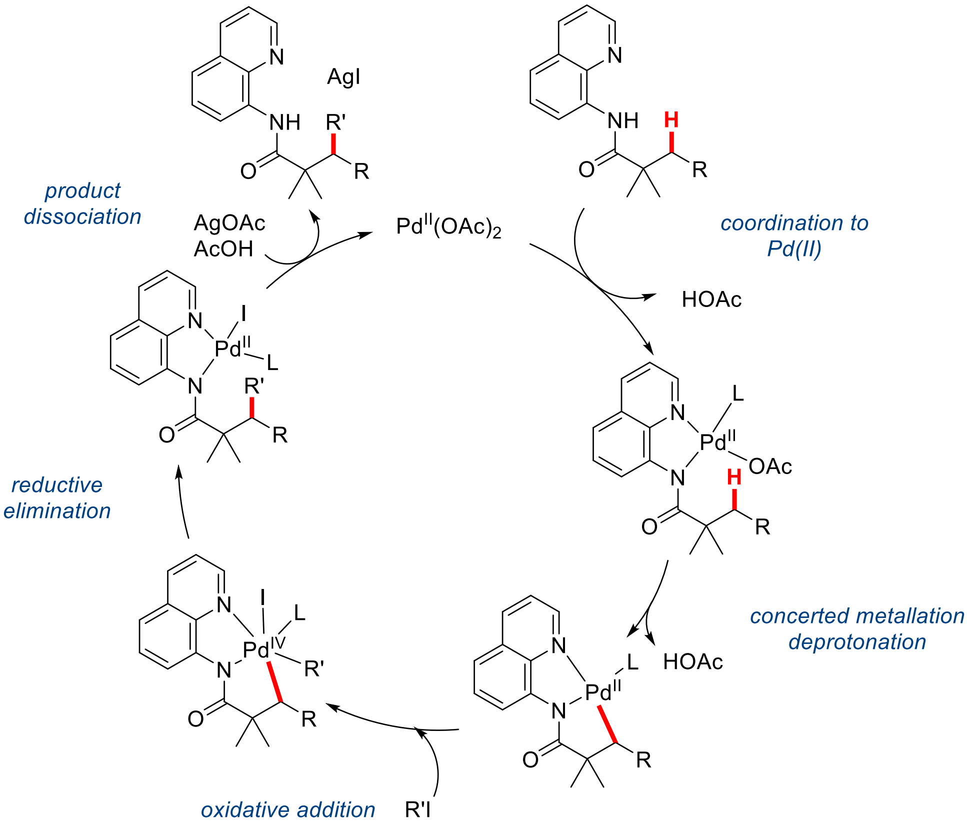
Scheme 1.7: C(sp^3)–H functionalisation with stoichiometric palladium

Early stoichiometric examples such as this, paved the way for the development of the first catalytic method, which was revealed by Daugulis in 2005. This seminal study covered the direct arylation of carboxylic acid derivatives using an aminoquinoline directing group (Scheme 1.8a) as well as the γ-arylation of amine derivatives with a picolinamide directing group (Scheme 1.8b).[24]



Scheme 1.8: Daugulis' seminal examples of catalytic directed C(sp^3)–H functionalisation: a) β-C(sp^3)–H arylation of acid derivatives using an 8-aminoquinoline directing group b) γ-C(sp^3)–H functionalisation using a picolinamide directing group

With the highly effective 8-aminoquinoline amide directing group, primary, secondary and benzylic β-C–H bonds were arylated in good to excellent yields (Scheme 1.8a). It is noteworthy that when multiple reactive centres are present further arylation occurs readily. This highlights another potential issue in C–H functionalisation; that of controlling over-reactivity on further C–H bonds. When a cyclohexyl amide was used, a di-*cis*-arylated product was obtained, the stereochemistry of which was confirmed by X-ray crystallography. In a later study, Daugulis presented the potential reaction mechanism for 8-aminoquinoline directed C(sp^3)–H functionalisation (scheme 1.9).[25]

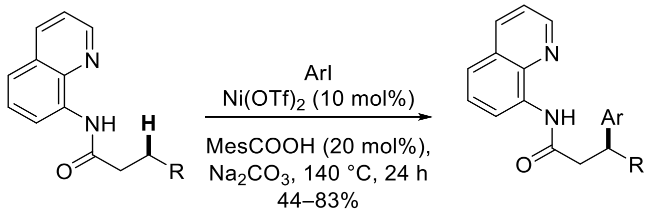


Scheme 1.9: Mechanism for aminoquinoline directed C–H functionalisation

Following bidentate coordination of the aminoquinoline amide, the mechanism is thought to proceed by concerted metalation deprotonation, assisted by the acetate anion to give a bicyclic palladacycle. Oxidative addition of the coupling partner affords a Pd^{IV} intermediate, which after reductive elimination of the C–C bond followed by dissociation affords the product and regenerates Pd^{II}.

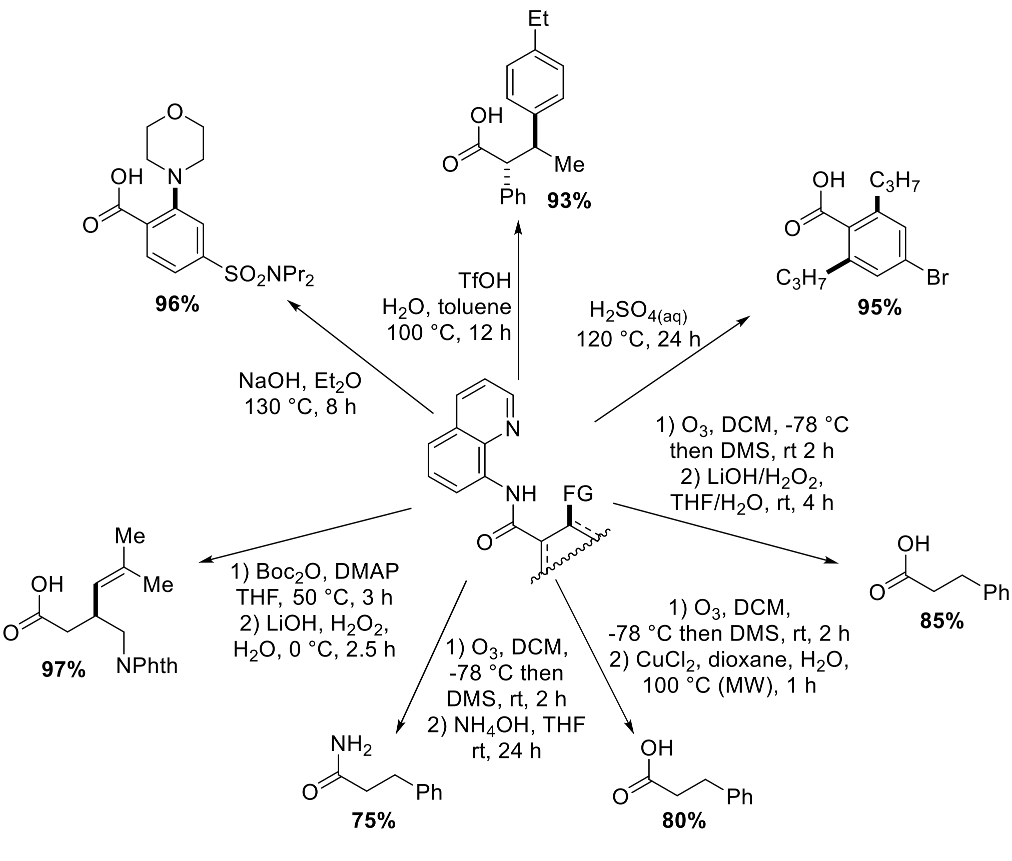
Arylation of amine derivatives with an amide-bound picolinamide directing group was possible on primary, methylene and aromatic C–H bonds (Scheme 1.8b).[24] Contrary to the β-arylation of acid derivatives with 8-aminoquinoline, arylation on methyl groups directed by the picolinamide only formed the monoarylated products, indicating that benzylic centres are inactive for this transformation.

Since the seminal study by Daugulis, the 8-aminoquinoline group has been shown to be a versatile tool for the functionalisation of C(sp^3)–H bonds.[26] For example, C−H functionalisation with earth abundant nickel catalysis has also been achieved with this directing group (Scheme 1.10).[27]



Scheme 1.10: Nickel catalysed C(sp^3)–H functionalisation using 8-aminoquinoline directing group

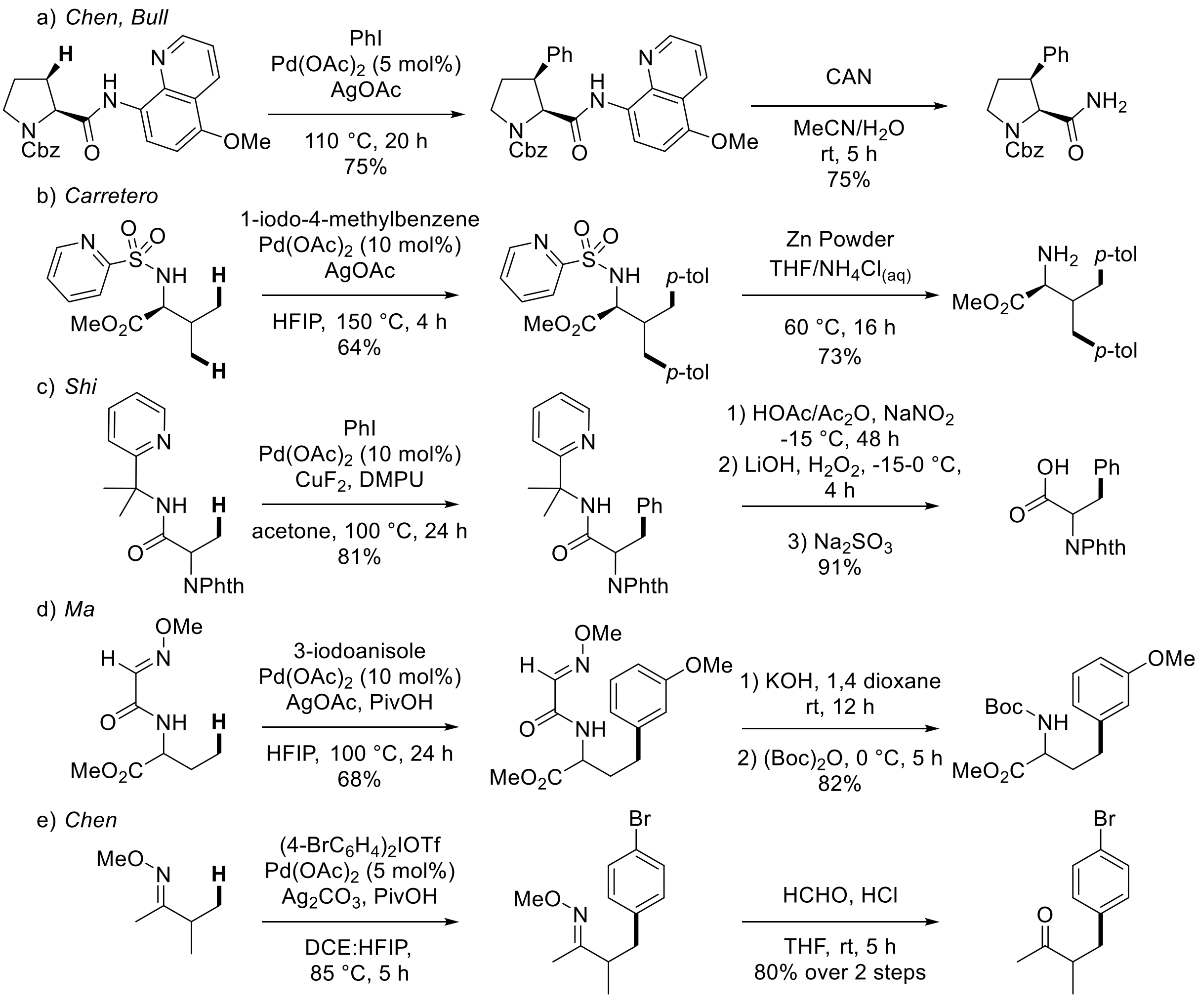
The drawback with the 8-aminoquinoline directing group is the cleavage of the strong amide linkage to access the desired products. Harsh conditions are typically required which reduces functional group tolerance and makes this DG strategy largely incompatible with late state functionalisation. A summary of aminoquinoline removal methods is given in Scheme 1.11.



Scheme 1.11: Approaches for 8-aminoquinoline amide cleavage

The aminoquinoline amide can be cleaved to the corresponding acid with strong acids[28,29] or bases[30] coupled with high temperatures. A well-used stepwise approach for cleavage of aminoquinoline following C–H functionalisation performs a Boc-derivatisation of the amide nitrogen followed by treating the Boc-amide with lithium peroxide.[31] Maulide has recently proposed ozone as a milder method of removing the directing group, to access the free acid or primary amide products.[32] The majority of the above methods for aminoquinoline removal can suffer with poor functional group tolerance, meaning that although the C–H functionalisation step may be possible on a diverse range of substrates, accessing the desired products by removing the directing group is an additional challenge of compatibility.

The undesirable conditions required for the aminoquinoline cleavage (see Scheme 1.11) led to the development of new directing groups, with the objective to provide a more facile DG removal step. For select examples and their associated cleavage, see Scheme 1.12.



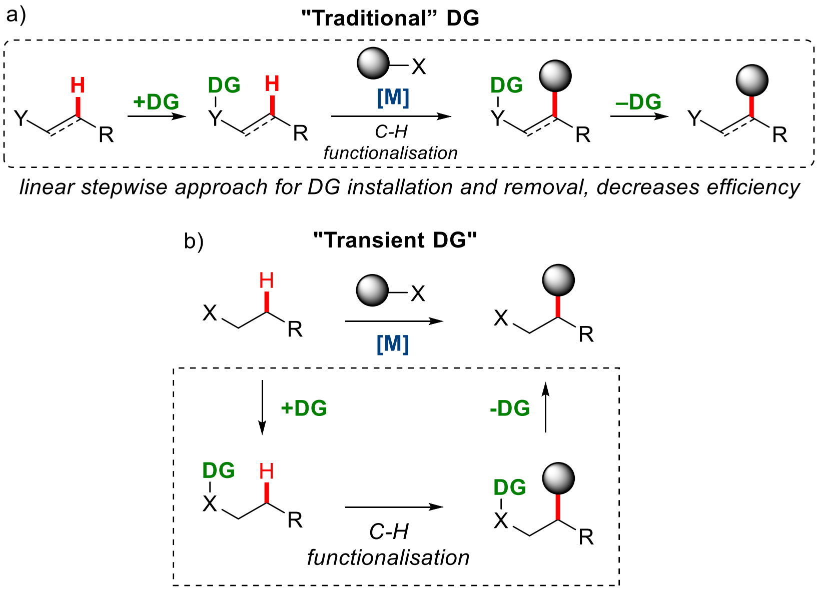
Scheme 1.12: C(sp^3)–H arylation using removable directing groups

An aminoquinoline directing group functionalised with a methoxy group at the 5-position of the ring was developed as a readily removable alternative to 8-aminoquinoline by Chen.[33] The directing group was used by Bull for the 3-arylation of pyrrolidine (Scheme 1.12a) and the amide was cleaved at room temperature using ceric ammonium nitrate (CAN). Carretero demonstrated that an *N*-(2-pyridyl)sulfonyl amide could be used for the arylation of amino-acid derivatives with a reductive Zn removal of the directing group (Scheme 1.12b).[34] The 'pip' directing group was first established by Shi, who showed that following a palladium mediated arylation, cleavage could be facilitated in high yields and low temperatures to afford the free arylated acid (Scheme 1.12c).[35] Ma showed that 2-methoxyiminoacetyl (MIA) was an effective auxiliary for the arylation of amino-acid derivatives, which was readily hydrolysed by potassium hydroxide at room temperature (Scheme 1.12d).[36] An additional example, by Chen, uses a simple oxime ether directing group which could be cleaved in a one-pot hydrolysis step to afford the free ketone in high yields (Scheme 1.12e).[37] Unlike the other examples however, the arylation requires a more reactive diaryliodonium salt coupling partner, which may be attributable to the poorer directing ability of the monodentate oxime.

Although these directing groups are more readily cleaved, they don't remove the necessity of the directing group cleavage step, and related installation step, which can negate the improvement in efficiency compared to the 'A to B' methods highlighted previously (Scheme 1.1).

1.4 Transient Directing Groups for C–H Functionalisation

Transient directing groups (TDGs), are reversibly bound to a substrate, so that the directing group installation and removal steps occur in one-pot with the key C–H functionalisation (Scheme 1.13).



Scheme 1.13: Traditional *vs* transient directing groups for C–H functionalisation

This approach exploits a labile linkage between the directing functionality and an inherent and useful functional group on the substrate, providing a much more step-efficient route to C–H functionalisation. Transient directing groups for the functionalisation of C(sp^2)–H and C(sp^3)–H bonds will be covered here.

Transient directing groups, as have been developed to date, can be organised into one of four categories, based on their mode of bonding to the substrate. The reversible linkages exploited for C–H functionalisation thus far have been based on either phosphinites, enamines, *exo*-imines or *endo*-imines (Figure 1.1). *exo*-Directing groups feature an *exo*-cyclic π-bond in the metallacycle, and *endo*-directing groups contain an *endo*-cyclic π-bond (see Figure 1.1).[38] Generally, the term 'transient directing group' has been used interchangeably to refer to either the formed directing group, or the additive which forms the directing group.

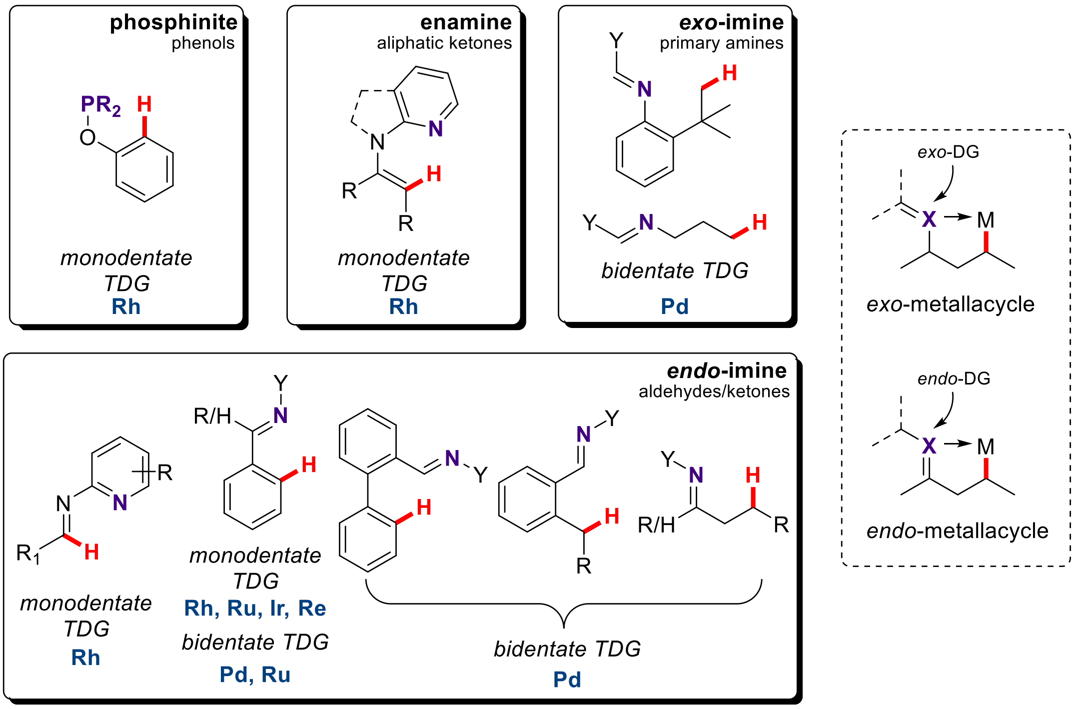
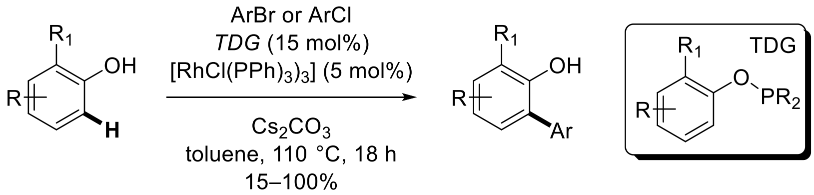


Figure 1.1: Families of transient directing groups for C–H functionalisation. Primary binding sites shown in purple, for bidentate TDGs, secondary binding sites can be built into diverse Y groups on the imine

Transient phosphinite linkages (OPR_2) have been successfully applied for the rhodium catalysed *ortho*-functionalisation of phenols. The catalytic condensation of amines and aldehydes to form imines and enamines to promote reactions is a concept commonly used in organocatalysis,[39] but only very recently has this reactivity been exploited for the formation of reversible directing groups in C–H functionalisation. Enamine TDGs have been shown to facilitate the formal α-functionalisation of ketones, using rhodium catalysis. Transient imine directing groups (TIDGs) have been much more developed from the seminal example in early 2016 and over the course of this thesis. They can be split into *endo*-imines, for the functionalisation of aldehydes and ketones, and *exo*-imines, for the functionalisation of amines. For *exo*-imines, the strategy can be used for the δ-functionalisation of 2-*tert*-butylanilines and the γ-functionalisation of aliphatic primary amines using bidentate TIDGs and palladium catalysis. Young has recently shown that the γ-functionalisation of aliphatic primary amines could also be achieved *via* a transient directing group formed from carbon dioxide.[40] *endo*-Imines can functionalise aldehydic C–H bonds, where the binding of the TDG is from the installed pyridine, not the imine nitrogen, using rhodium. Additionally, both monodentate and bidentate *endo*-TIDGs can promote *ortho*-functionalisation of benzaldehydes or aromatic ketones with a variety of metals. With bidentate TDGs and palladium catalysis, TIDGs are also able to direct δ-functionalisation of 2-formyl biaryls and sp^3 benzylic or β-functionalisations of aldehydes and ketones. Each of these TDG families and their applications will be discussed in the following sections (1.4.1–1.4.4).

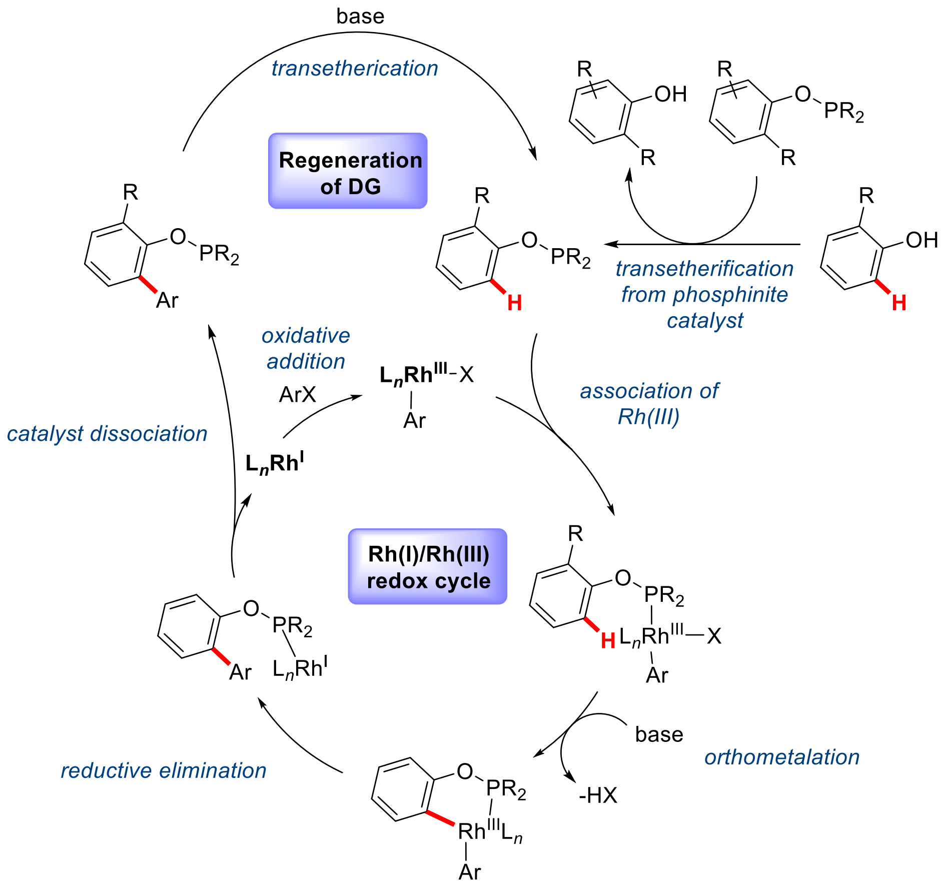
1.4.1 Transient Phosphinite Directing Groups

Bedford first communicated the concept of a catalytic transient phosphinite directing group for the *ortho*-arylation of phenols using Wilkinson's catalyst in 2003 (Scheme 1.14).[41,42]



Scheme 1.14: *Ortho*-C–H arylation of phenols *via* a transient phosphinite directing group

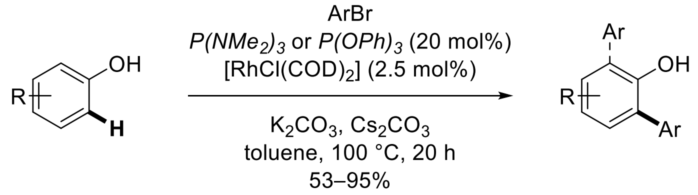
In comparison to typical biaryl formation methods such as Suzuki or Stille coupling reactions, which require introduction and subsequent loss of stoichiometric amounts of boronic ester/acid or organotin groups; the developed *ortho*-arylation was highly atom economical and efficient. The phosphinite cocatalysts used for each example were derived from the starting material phenol in every case; as although any OAr group on the added phosphinite would suffice, this method assisted in purification. The reaction proceeded smoothly with electron rich, electron poor and sterically hindered aryl bromides. Aryl chlorides could also be used with reduced yields. In some cases, arylation at the *ortho*-position of the installed aromatic was observed, directed by the phenol. Although 2-*tert*-butyl substituted phenols formed the product in the best yields, smaller 2-substituents could be used with a decrease in yield [79% for 2-*tert*-butyl phenol and 21% for 2-methylphenol with 4-iodoanisole]. No reaction occurred on unsubstituted phenol. This issue was resolved in the follow up paper by changing the catalyst to [RhCl(COD)$_2$] with P(NMe)$_3$ as the cocatalyst, achieving a 71% yield of 2,2-diarylated phenol.[42] In this subsequent study, the scope of the 2-substituted phenols was extended to include heterocyclic examples. Competition experiments suggested that the oxidative addition was not rate determining for the aryl bromides.



Scheme 1.15: Proposed mechanism for Bedford's *ortho*-C–H arylation of phenols with a transient phosphinite directing group

The proposed reaction mechanism is given in Scheme 1.15, whereby initial transetherification affords the phosphinite derivative of the phenol, which coordinates to the Rh^{III} catalyst following oxidative addition of the aryl halide. This complex undergoes *ortho*-metalation to give a 5-membered rhodacycle. Although the *ortho*-arylation of phenols is highly unfavoured due to the formation of an unstable 4-membered metallacycle, the inclusion of a phosphorus atom leads to a 5-membered system, facilitating the reaction. From this intermediate; reductive elimination occurs, regenerating the Rh^{I} catalyst and affording the product phosphinite, which can then transetherify with another molecule of phenol starting material to turn over the directing group.

Inoue published a comparable reaction for phenol arylation, with the marked difference being the initial formation of the phosphinite, which in this case was from the reaction of the phenol starting material with 20 mol% $P(OPh)_3$ or $P(NMe_2)_3$ (Scheme 1.16).[43]

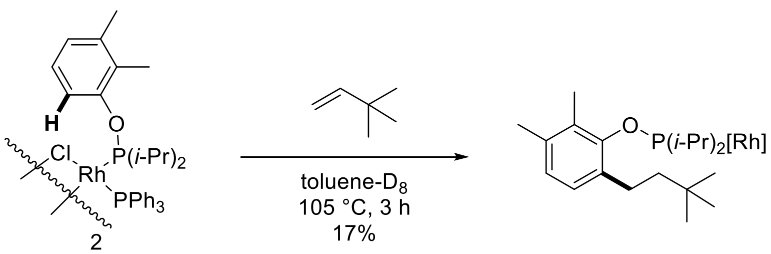


Scheme 1.16: *Ortho*-arylation of phenols by Inoue

Similar to Bedford's modified conditions using the $P(NMe_2)_3$ phosphinite source,[42] Inoue's reaction did not require *ortho*-substituted phenols, and formed the diarylated products in preference to the monofunctionalised species. The aryl iodide scope was not explored however both electron rich and poor phenols were arylated in good to excellent yields.

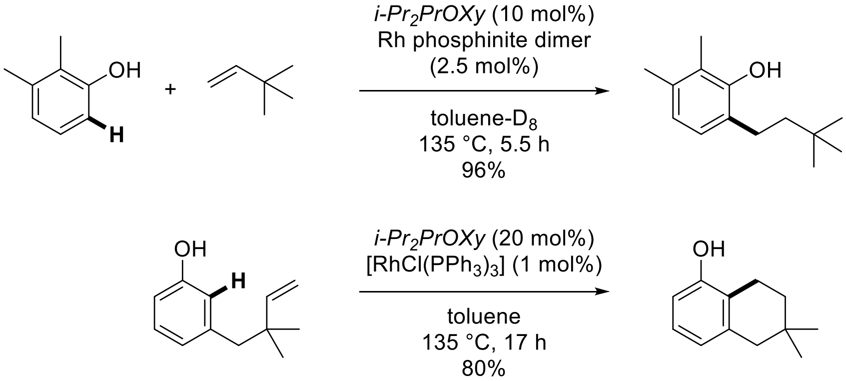
Bedford, Caffyn and Prashar showed simple chlorodiisopropylphosphine adducts of rhodium, either pre-formed or formed *in situ*, were also highly effective catalysts for the *ortho*-arylation of phenols.[44] Bedford also applied the transient phosphinite methodology to the arylation of tyrosines.[45]

In 2005, Ellman published a combined experimental and theoretical investigation of the transient phosphinite method and applied the methodology to the alkylation of phenols with alkenes.[46] In this study, various rhodium phosphinite complexes were synthesised which exhibited preagostic interactions between the rhodium centre and the *ortho*-C–H of the phenol; this is supported by computational studies, ^{1}H NMR chemical shifts and bond angles/distances in the crystal structures (agostic interactions are defined as 3-centre-2-electron bonds where the electron density of the C–H bond is donated to the metal centre, whereas preagostic interactions are between agostic and hydrogen bonding). Synthesis of any cyclometalated complexes was unsuccessful however one complex could be alkylated in low yield on treatment with neohexane and heating (Scheme 1.17).



Scheme 1.17: *Ortho*-alkylation of Rh-phosphinite complex

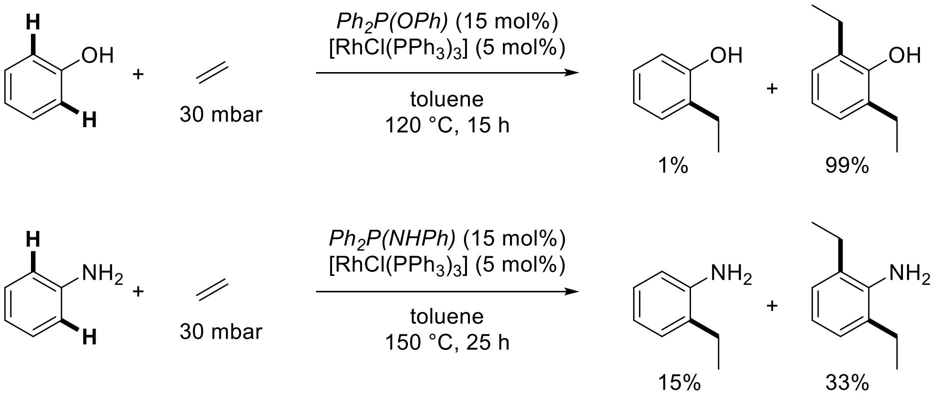
The yield of this reaction could be improved by addition of triphenylphosphine or the uncomplexed phosphinite, supporting that either a bis(phosphine)-phosphinite or related complex might be involved in the alkylation reaction. From this result, catalytic inter- and intramolecular alkylations were developed (Scheme 1.18). The reaction was entirely *ortho*-selective and no alkylation occurred in absence of the phosphinite ligand.



Scheme 1.18: Inter- and intramolecular *ortho*-alkylation of phenols by Ellman

Although the phosphinite dimer proved to be highly active for the alkylation, Wilkinson's catalyst could also be used to form the alkylated phenol in 72% isolated yield with neohexene.

Cole-Hamilton showed that ethene gas could be used to promote the *ortho*-ethylation of phenols and aniline using a phosphinite TDG (Scheme 1.19).[47]

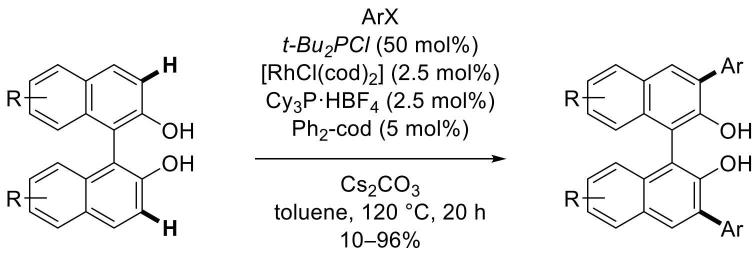


Scheme 1.19: *Ortho*-ethylation of phenol and aniline using a transient phosphinite DG

Interestingly, the *ortho*-alkylation of phenol was promoted with $Pd_2(dba)_3$ in low (5%) GC yield. However, Wilkinson's Rh catalyst was exceptionally more efficient and the diethylated phenol was formed in 99% GC yield. *Ortho*-, *meta*- and *para*-cresol were also suitable substrates, with better selectivity for the monofunctionalised product when using *meta*-cresol due to the steric influence of the methyl group. Lower yields were obtained using aniline although the

48% yield with 15 mol% of the $Ph_2P(NHPh)$ additive strongly implied that some transamination occurred to turn over the TDG.

BINOL and its derivatives are highly privileged ligands for asymmetric catalysis. Recently, Ye used the transient phosphinite approach for the straightforward synthesis of BINOL derivatives (Scheme 1.20).[48]

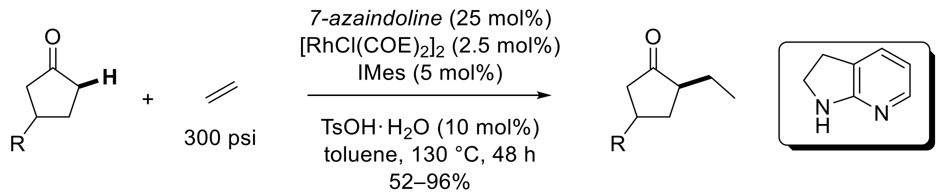


Scheme 1.20: *Ortho*-arylation of BINOLs using a transient phosphinite DG

Using this methodology, a large range of diarylated BINOL or related bisphenol adducts were formed in good to excellent yield. Monoarylation was favoured for highly sterically congested aryl halides. Both enantiomers of the product could be isolated following chiral resolution. Ye later showed diaryliodonium triflates were also suitable coupling partners for the *ortho*-arylation of BINOLs.[49]

1.4.2 Transient Enamine Directing Groups

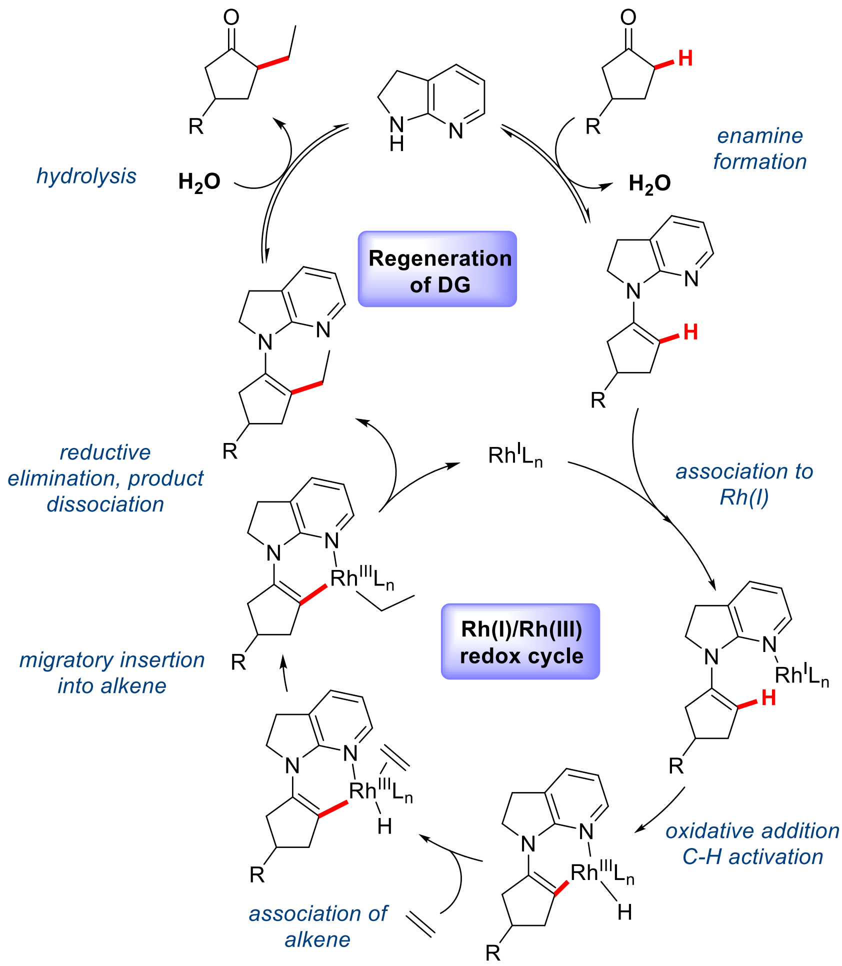
Dong first demonstrated the use of enamine TDGs in the form of the rhodium catalysed α-alkylation of ketones, using alkenes as alkylating agents (Scheme 1.21).[50] The reaction is mono-selective, determined by the equilibrium of enamine formation favouring the least hindered (starting material) ketone.



Scheme 1.21: α-alkylation of cyclopentanones

Although other amines were attempted, 7-azaindoline was the only TDG able to form the desired enamine and enable coordination to the catalyst, *via* the pyridine N, to direct the C–H activation. Tosic acid served as a catalyst for enamine formation and no reaction occurred in its absence. The NHC ligand (IMes), which can promote Rh oxidative addition to enamine

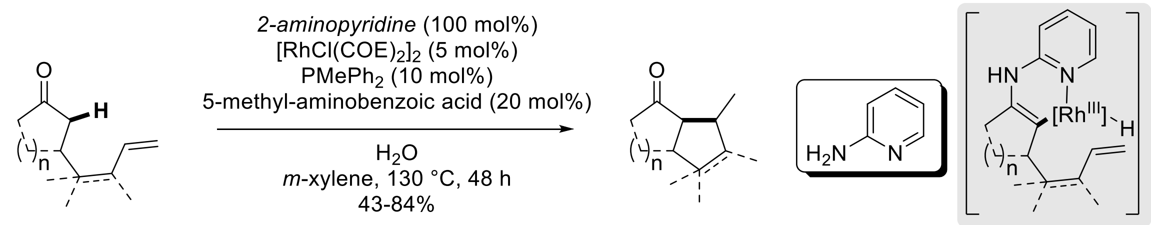
C–H bonds, led to greatly enhanced yields. Substitution at the 3-position of cyclopentanone was explored, affording the ethylated products in good to excellent yields in the presence of other potential coordinating groups such as esters, nitriles, thioethers, amides and alcohols; although diastereoselectivity was moderate (1:1 to 2.9:1). The reaction was gram scalable, with the ethylated 3-methylcyclopenanone product isolated in 75% yield. Cyclohexyl and acyclic ketones could be functionalised however they were less reactive and not isolated. This was also the case with alternative alkenes. Crystal structures of various Rh-enamine complexes were obtained supporting the coordination of the pyridine nitrogen to the Rh centre and oxidative addition of the enamine C–H, as proposed in the mechanism (Scheme 1.22). A single alkenylation was demonstrated with diphenylethyne which led to the unhydrolysed enamine product in 61% yield. This was later developed to a full study using alkyne coupling partners, to afford β,γ- or rearranged α,β-enones.[51]



Scheme 1.22: Mechanistic cycle for the α-alkylation of cyclopentanones

For the rhodium catalysed alkylation, condensation of the amine with the ketone generates the active enamine substrate. The pyridine N then coordinates the Rh^{I} catalyst, allowing C–H activation *via* an oxidative addition pathway. Ethene coordinates to the complex, followed by migratory insertion into the Rh–H bond. Reductive elimination furnishes the product enamine while regenerating Rh^{I}. Hydrolysis of the product turns over the amine.

Dong also developed an intramolecular variant, this time using simple 2-aminopyridine as the TDG (Scheme 1.23). An aniline additive was used to facilitate condensation of 2-aminopyridine with the ketone substrate through transimination.



Scheme 1.23: Intramolecular α-alkylation of cyclopentanones using an enamine TDG strategy

The reaction could be used to form a range of bi- and tricyclic systems; however, the Thorpe-Ingold effect was critical with no cyclisation occurring on less substituted ketone substrates. Styrene derivatives were also found to be effective. Additionally, it was shown that using ruthenium catalysis and the same TDG, 6-*exo*-trig cyclisations could also be promoted.

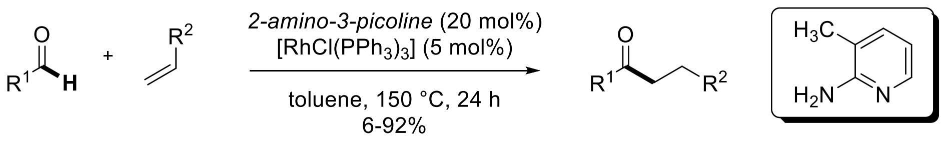
Non-directed enamine-promoted C–H functionalisations have also been described using related photoredox catalytic methods *via* hydrogen atom transfer (HAT); however, they will not be discussed in this thesis.[52,53]

1.4.3 Transient Imine Directing Groups for the Functionalisation of Aldehydes

Imine formation between aldehydes and primary amines is facile, making aldehydes an obvious candidate for the development of transient imine directing groups. Additionally, the formyl group is a versatile handle for further functionalisation. Consequently, strategies for aldehyde functionalisation with such *endo*-imine directing groups have seen the most substantial evolution. Jun developed the first examples of transient imine directing groups for the rhodium catalysed functionalisation of aldehydic C–H bonds in the late 1990's. Much later, in 2016, Yu published the seminal example using TIDGs for the functionalisation of C(sp^3)–H bonds, which triggered the rapid advances of the past few years, enabling the functionalisation of a variety of C(sp^2)–H and C(sp^3)–H bonds with many different transition metals.

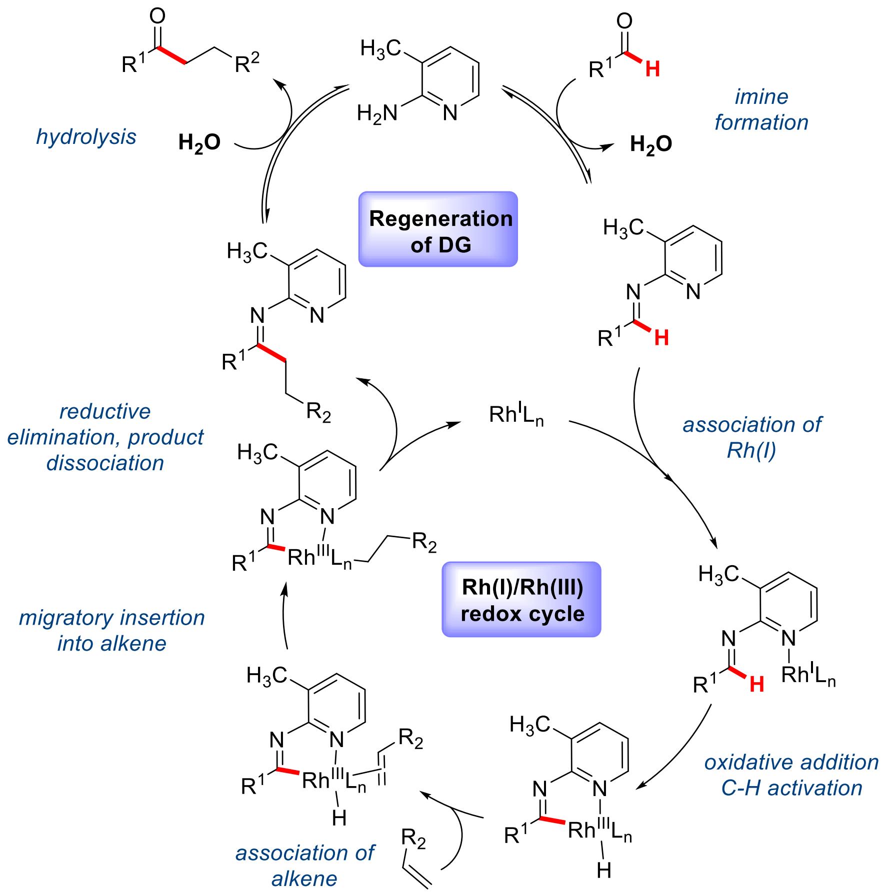
Aldehydic C–H Bonds

The first instances of C–H functionalisation using a TIDG approach were by Jun, for the rhodium catalysed functionalisation of aldehydic C–H bonds. The seminal example used 2-amino-3-picoline as the TDG, which facilitated the reaction of the aldehyde with alkene coupling partners to afford ketones *via* hydroacylation of the alkene (Scheme 1.24).[54]



Scheme 1.24: Seminal example of a TIDG by Jun on the hydroacylation of alkenes

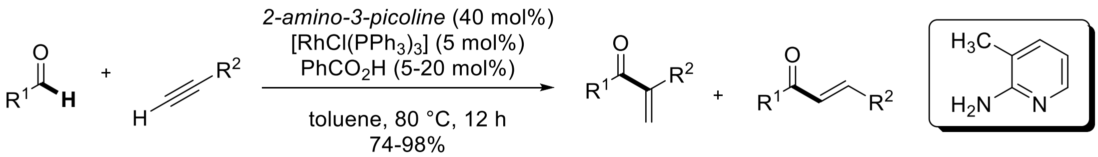
Good to excellent yields were reported with both aliphatic and aromatic aldehydes and alkenes, with only highly hindered pivaldehyde giving a low yield (6%) with 1-pentene. The scope was later extended to heteroaryl aldehydes.[55] The proposed mechanism for the hydroacylation is given in Scheme 1.25.



Scheme 1.25: Mechanism for hydroacylation by Jun

Firstly, the aminopicoline additive condenses with the aldehyde to form the catalytically active imine. The pyridine nitrogen coordinates to the Rh^{I} bringing it proximal to the aldehydic C–H, so C–H activation can occur *via* oxidative addition to form a cyclometalated Rh^{III} hydride intermediate. The alkene associates and migratory insertion occurs forming a C–M bond on the least hindered side of the alkene. This species reductively eliminates, forming the product imine which is hydrolysed under the reaction conditions to form the product ketone and regenerates the aminopicoline organocatalyst. Use of aniline and benzoic acid additives provided an improved catalyst system and low loading of 2 mol% $[RhCl(PPh_3)]$ could be used.[56] The role of these additives is thought to be the promotion of a faster transimination pathway from the aldehyde-aniline imine, catalysed by benzoic acid.

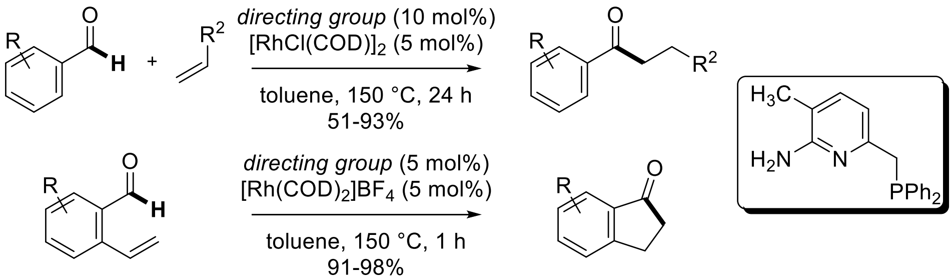
Similarly, Jun showed that this methodology could be applied with terminal alkyne coupling partners to form either branched or linear α,β-unsaturated ketones (Scheme 1.26).[57]



Scheme 1.26: Alkynes as coupling partners for the Rh-catalysed functionalisation of aldehydic C–H bonds

Selectivity was achieved when using aromatic aldehydes, which formed the branched products exclusively in excellent yields. With a hindered *tert*-butyl substituted alkyne, the linear product was formed exclusively. Other combinations of aldehyde and alkyne led to mixtures of the two products. The selectivity of the reaction is determined by the migratory insertion step: when the R^2 group is large, the linear product is formed in higher quantities.

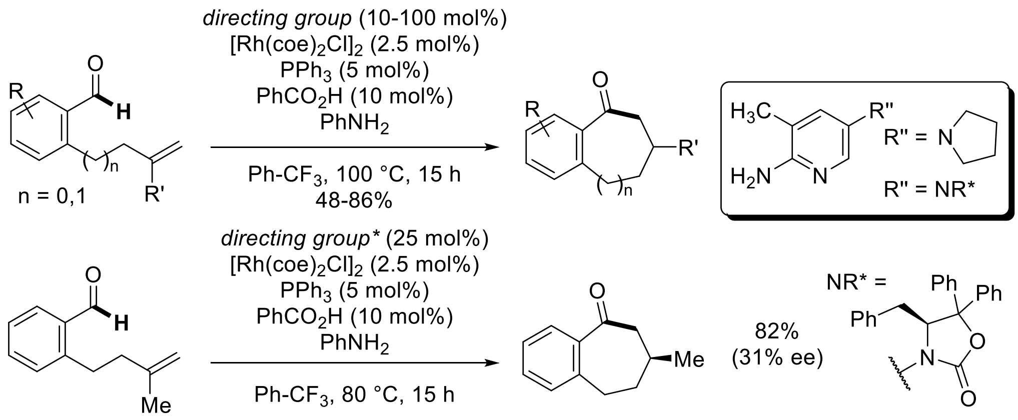
Using a new TDG with a pendant phosphine on the 6-position of 2-aminopicoline, Breit developed an efficient inter- and intramolecular hydroacylation (Scheme 1.27).[58] This secondary coordinating group enhances the binding to the catalyst which in turn increases the effective molarity so that low loadings of 10 or 5 mol% of the TDG could be used. The additional methyl group on the aminopicoline is proposed to force the correct imine geometry.



Scheme 1.27: Inter- and intramolecular hydroacylation by Breit

Both the inter- and intramolecular reactions were tolerant of a variety of functional groups. The intramolecular reaction was highly efficient, with near-quantitative yields seen for all examples in only 1 h.

Douglas later showed that the methodology could be applied to the synthesis of 6- and 7-membered rings with a 2-aminopicoline based TDG containing an amino or cyclic carbamate group at the 5-position (Scheme 1.28).[59]



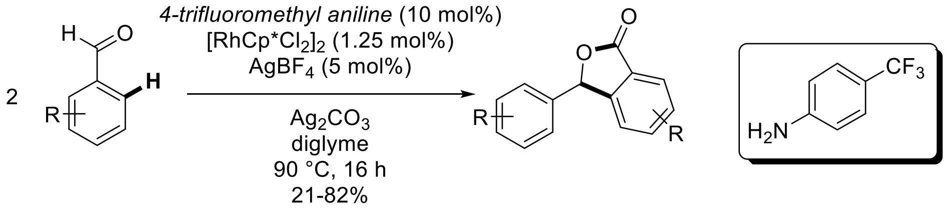
Scheme 1.28: Aldehydic C–H functionalisation for the synthesis of cyclohexanones and cycloheptanones

As well as benzaldehydes, 2-formyl pyrroles with the alkene component bound to the pyrrole nitrogen were also suitable substrates. Using a chiral TDG gave moderate enantioselectivity in the cyclisation.

Ortho-C(sp²)–H Functionalisation of Benzaldehydes

Benzaldehydes are valuable building blocks for chemical synthesis and so methods to form diverse benzaldehydes are desirable. The aldehyde group can itself act as a directing group for *ortho*-functionalisation.[60] In the presence of other strong directing groups however, the directing ability of the aldehyde is typically outcompeted.[61] Formation of a strong N-based directing group *via* a transient imine has the potential to facilitate more robust *ortho*-functionalisations of benzaldehydes.

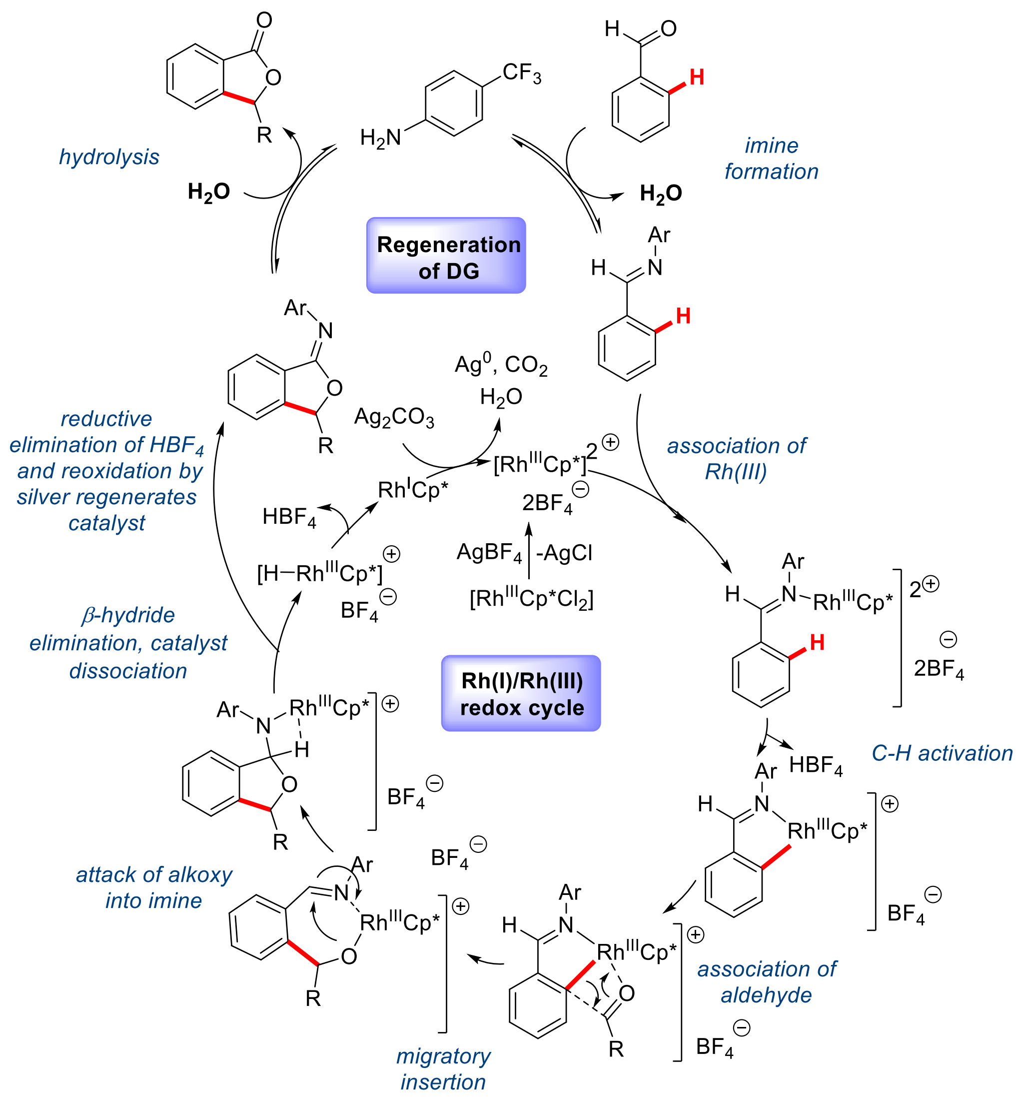
Seayad demonstrated that with rhodium catalysis, a transient imine directing group could facilitate the *ortho*-C(sp^2)–H functionalisation of benzaldehydes and dimerisation to form phthalides (Scheme 1.29).[62]



Scheme 1.29: Seayad's phthalide synthesis

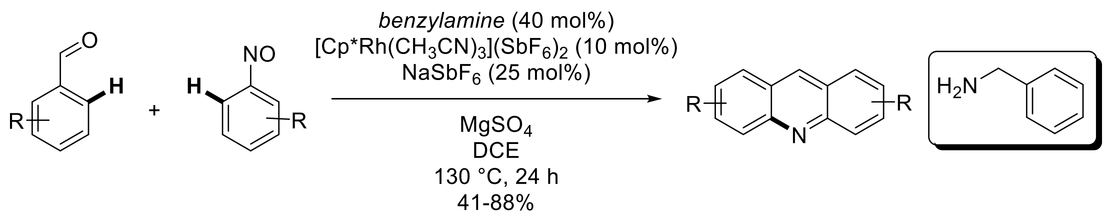
Benzaldehydes with varied electronic and steric properties were suitable substrates generating the phthalide products in good yields. When using a mixture of two aldehydes, with one non- or less reactive to *ortho*-C–H functionalisation, heterocoupling could be facilitated with high selectivity. The proposed catalytic cycle is given in Scheme 1.30.

Imine formation occurs from condensation of the electron poor aniline with the benzaldehyde substrate, promoting formation of the *ortho*-rhodacycle *via* a redox neutral C–H activation step. More electron rich anilines were less effective at promoting the reaction. This intermediate associates to a second equivalent of the aldehyde, to which migratory insertion occurs to give a Rh-alkoxy 7-membered intermediate. This alkoxy group then attacks the electrophilic imine carbon to give a hemiaminal species. The imine is reformed from β-hydride elimination generating a Rh-hydride complex which reductively eliminates HBF_4 to give a Rh^I species which is then reoxidised by silver carbonate to return the catalytically active Rh^{III}. Hydrolysis of the imine turns over the aniline.



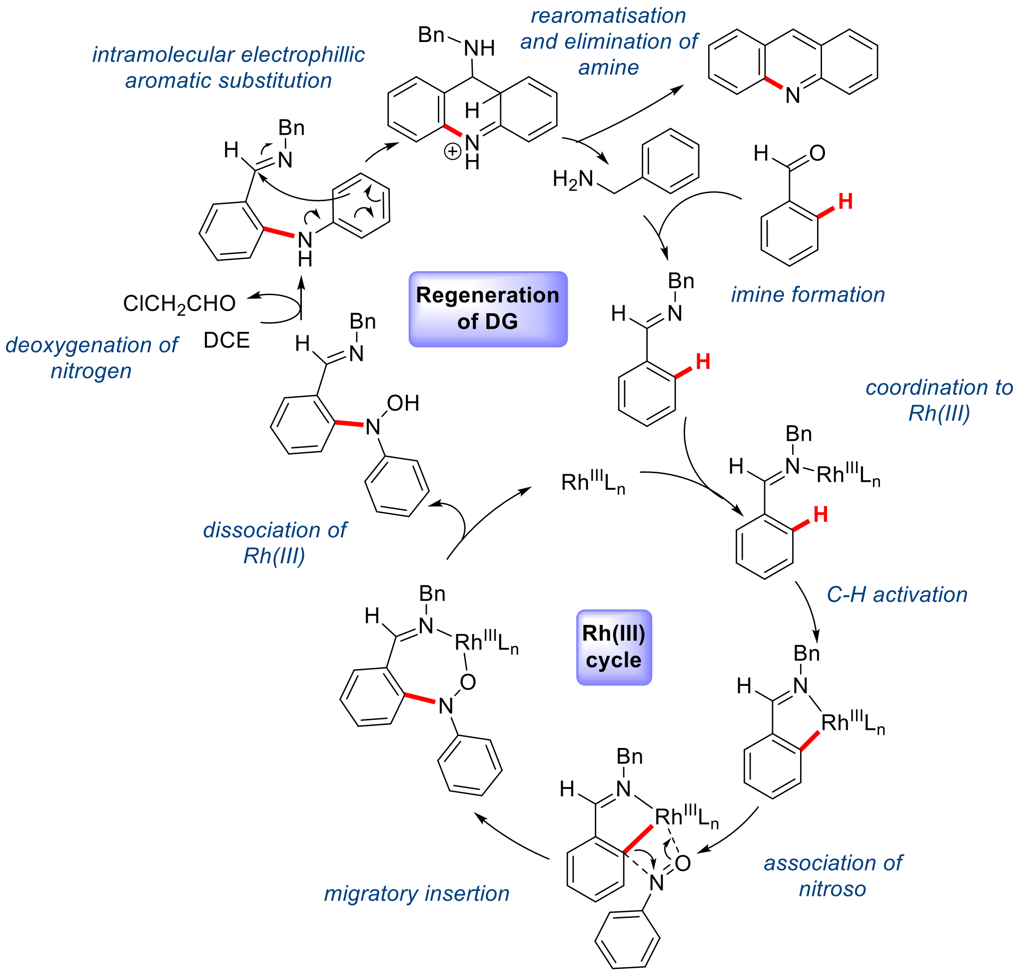
Scheme 1.30: Phthalide synthesis though a transient imine directing group

A transient imine directing group with benzaldehyde substrates could also promote the formation of acridines when using nitrosobenzene coupling partners under Rh^{III} catalysis (Scheme 1.31).[63]



Scheme 1.31: Acridines synthesis from benzaldehydes and aryl nitrosos

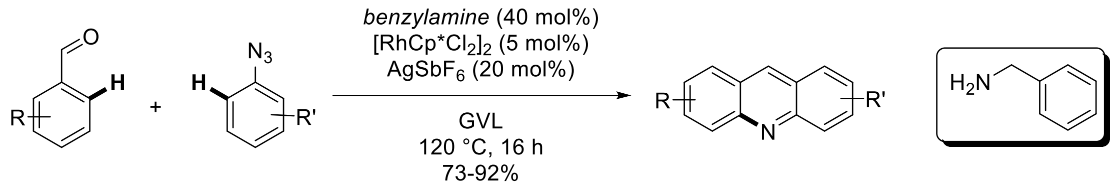
The reaction was tolerant of electron rich and poor substituents on both the benzaldehyde and nitrosobenzene components, forming the acridine products in good yields. The dual mechanistic cycle showing the unusual mechanism for turnover of the amine catalyst is given in Scheme 1.32.



Scheme 1.32: Mechanistic cycle for acridine synthesis

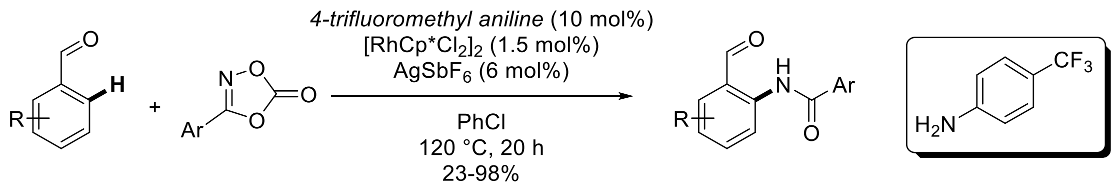
On formation of the *ortho*-rhodacycle, the nitrosobenzene coordinates to the Rh centre triggering migratory insertion. At this stage the catalyst dissociates making the process redox-neutral. Deoxygenation of the hydroxylamine is mediated by the DCE solvent, then intramolecular electrophilic aromatic substitution affords the product. Peculiarly in this reaction, the turnover of the directing group is proposed *via* elimination of the amine, rather than imine hydrolysis as seen in previous examples.

Similarly, aromatic azides could be used as the coupling partner to afford the acridines in a biomass-derived solvent, γ-valerolactone (GVL) (Scheme 1.33).[64] The reaction is mechanistically similar to that when using nitrosobenzene (Scheme 1.32), with the marked difference being loss of N_2 gas from the azide not deoxygenation of a hydroxylamine.



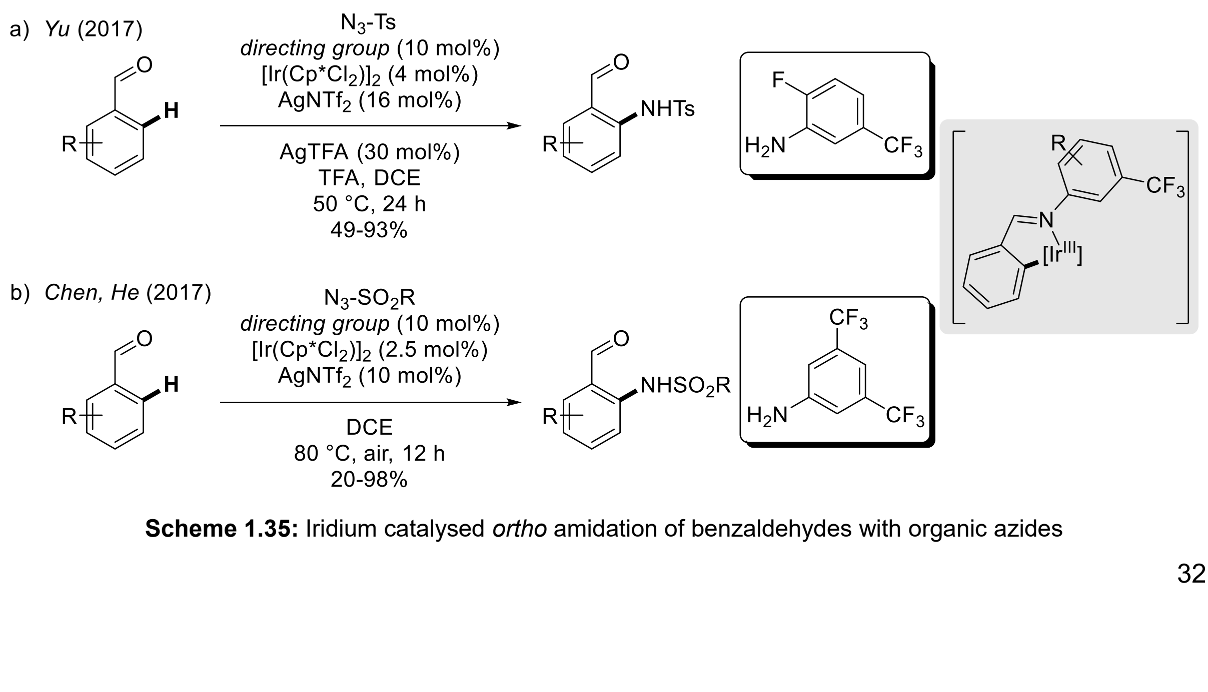
Scheme 1.33: Acridine synthesis with aryl azide coupling partners

Jiao showed that dioxazolones could be used for *ortho*-amination of benzaldehydes enabled by Rh catalysis and a TIDG formed from 4-trifluoromethylaniline (Scheme 1.34).[65] The mechanism of the redox-neutral amination is thought to occur by coordination of the Rh^{III} metallacycle to the nitrogen of the dioxazolone. The Rh–C bond then attacks the dioxazolone C=N through migratory insertion, eliminating CO_2 and affording the product imine, which then undergoes hydrolysis.



Scheme 1.34: Rhodium catalysed *ortho* amination of benzaldehydes with dioxazolines

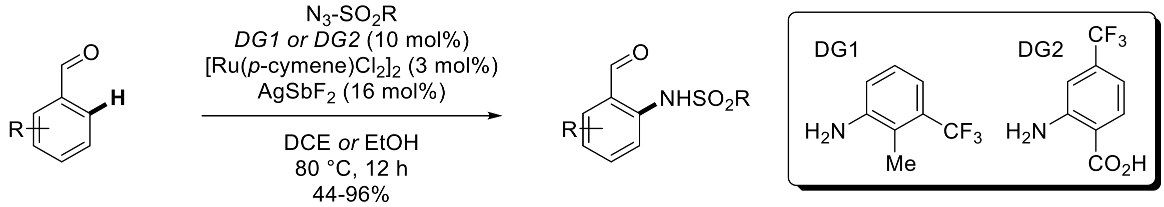
Yu and Chen & He independently developed iridium catalysed *ortho*-amidation of benzaldehydes using electron poor aniline TDGs, with organic azide coupling partners (Scheme 1.35).[66,67]



Scheme 1.35: Iridium catalysed *ortho* amidation of benzaldehydes with organic azides

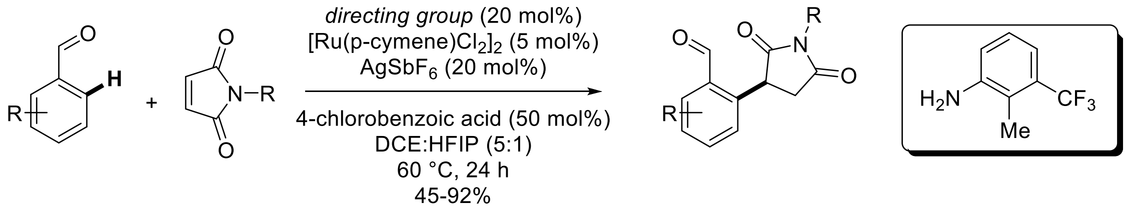
Yu's protocol, using tosyl azide as the coupling partner, displayed remarkable functional group tolerance on the benzaldehyde, and found that the transient imine could promote selective *ortho*-functionalisation even in the presence of other strong coordinating groups. Chen and He's amidation generally gave excellent yields for the benzaldehyde scope, except for heterocyclic 2-thiophenecarboxaldehyde (20%). They also examined alternative organic azides to form a range of 2-functionalised benzaldehydes in good yield. These methods were likely inspired by a process developed by Shi a year earlier, which required a separate acid-mediated imine cleavage step to form the product aldehydes.[68]

Zhang later showed ruthenium(II) catalysis could also be used to mediate *ortho*-amidation with azides (Scheme 1.36).[69]



Scheme 1.36: Ruthenium catalysed *ortho*-amination of benzaldehydes with organic azides

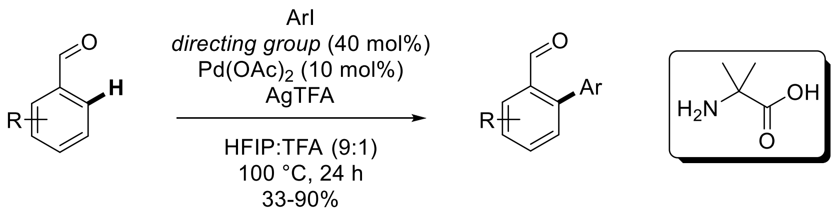
Efficient Ru catalysed *ortho*-alkylation of benzaldehydes was realised by Zhang, when using maleimide coupling partners (Scheme 1.37).[70] Like the iridium and rhodium catalysed reactions, the best TDGs were found to be electron poor anilines.



Scheme 1.37: Ruthenium catalysed *ortho*-alkylation of benzaldehydes by Zhang

The aldehyde scope of the reaction was used to demonstrate the high efficiency and *ortho*-selectivity of the reaction on complex substrates bearing other strong coordinating groups. Generally, all products were formed in excellent yields and further functionalisation of the products afforded diverse spirocyclic pyrrolidines.

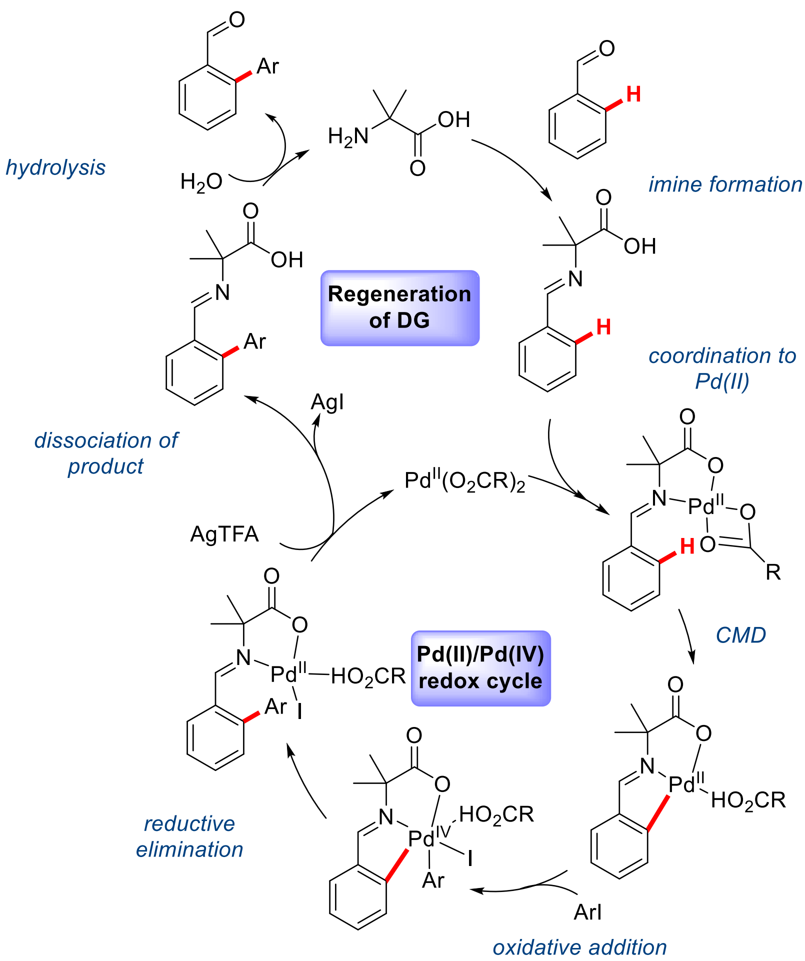
Palladium has been shown by various groups to be an effective catalyst for the *ortho*-functionalisation of benzaldehydes for both C–C and C–X bond formations using transient *endo*-imine directing groups. Yu showed that 2-aminoisobutyric acid gave the optimum bite angle to facilitate the *ortho*-arylation of benzaldehyde substrates with aryl iodides (Scheme 1.38).[66]



Scheme 1.38: Palladium catalysed *ortho*-arylation of benzaldehydes

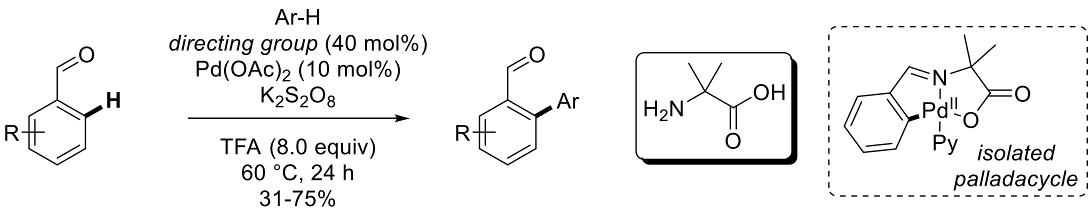
The scope of the benzaldehyde substrate gave good yields for all examples substituted at the *ortho*- *meta*- and *para*-positions with a variety of electron donating and withdrawing groups. Heterocyclic *N*-tosyl-3-formyl indole was also arylated in 82% yield. Lower yields were observed when using *ortho*-substituted aryl iodides. Some heterocycles could be installed in lower yields, particularly when substituted at the 2-position blocking coordination of the N or S atoms to the catalyst. This methodology enabled the synthesis of Boletopsin 11, a fungal natural product.[71] A potential mechanistic cycle for the reaction is given in Scheme 1.39.

The bulky catalytic amino acid forms an imine with the benzaldehyde substrate, which associates the Pd^{II} catalyst. Concerted metalation deprotonation gives the metallacycle which undergoes oxidative addition with the aryl iodide to form a Pd^{IV} aryl species. This reductively eliminates to form the arylated imine, which then hydrolyses.



Scheme 1.39: Mechanistic cycle for the palladium catalysed *ortho*-arylation of benzaldehydes

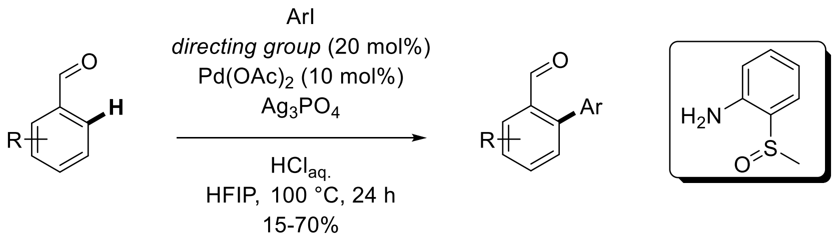
Wang later showed that using Ar-H as the solvent and coupling partner when using potassium persulfate as an oxidant, the same TDG could enable dehydrogenative coupling with benzaldehydes (Scheme 1.40).[72]



Scheme 1.40: Dehydrogenative coupling of benzaldehydes with aryls

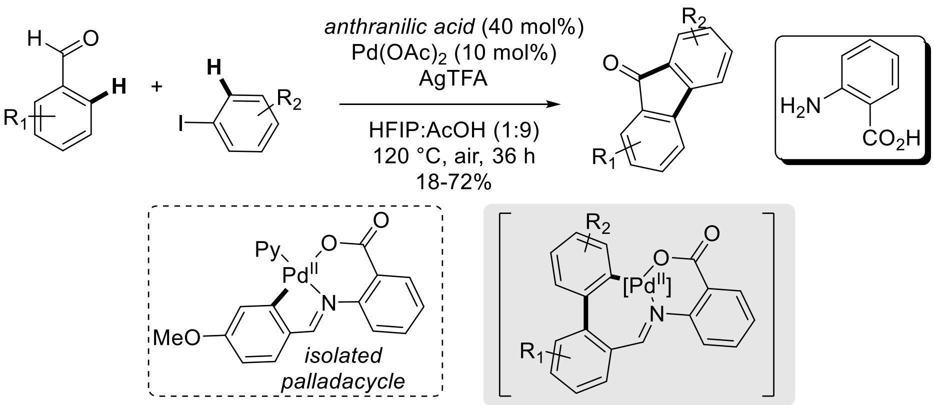
The reaction is mechanistically similar to Yu's arylation, but the aromatic is installed though S_EAr on the aromatic with a Pd^{IV} species formed from oxidation by the persulfate. Moderate to good yields and remarkable *para*-selectivity was observed across the substrate scope.

2-(Methylsulfinyl)aniline could also promote the *ortho*-arylation of benzaldehydes with palladium catalysis (Scheme 1.41).[73]



Scheme 1.41: Palladium catalysed *ortho*-arylation of benzaldehydes with a sulfoxide TDG

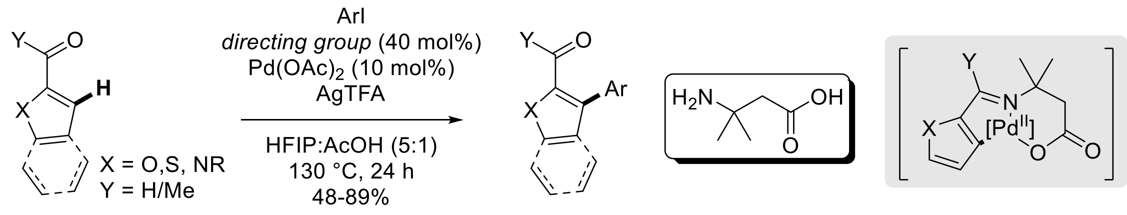
Sorensen showed that when using anthranilic acid as the TDG, under very similar conditions to Yu's arylation (Scheme 1.42), the reaction would continue to promote a second C–H functionalisation at the δ-position of the installed aromatic to form a 7-membered metallacycle (see grey box).[74] The Pd–C bond undergoes migratory insertion into the imine carbon, this forms a palladium imido species, which forms the product imine *via* β-hydride elimination. This step furnishes a palladium hydride species, which is thought to reductively eliminate to form Pd^0 (see Scheme 1.30 for this mechanism with Rh), which is returned to active Pd^{II} by reoxidation by silver(I). The imine is hydrolysed under the reaction conditions to form fluorenone products.



Scheme 1.42: Dehydrogenative coupling of benzaldehydes with aryls

The fluorenones were formed in low to moderate yields. A palladacycle was isolated, supporting the role of the transient imine in the catalytic cycle. Additionally, the antiviral drug Tilorone was synthesised using this approach.

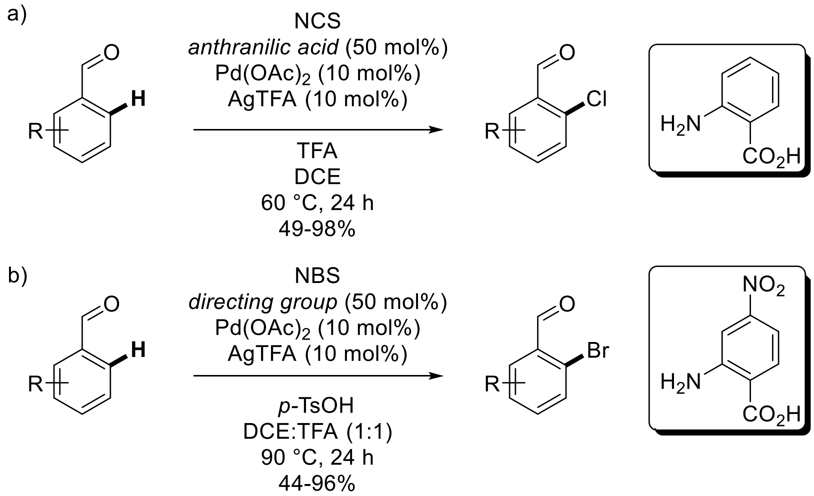
Ge showed that a TIDG formed from 3-amino-3-methylbutanoic acid could facilitate the 3-arylation of five-membered heterocycles with a 2-formyl or keto-group (Scheme 1.43).[75]



Scheme 1.43: Arylation of 5-membered heterocycles

Thiophenes, furans, and N-protected pyrroles and indoles were arylated in good yields. The thiophene products and related derivatives displayed interesting optical properties.

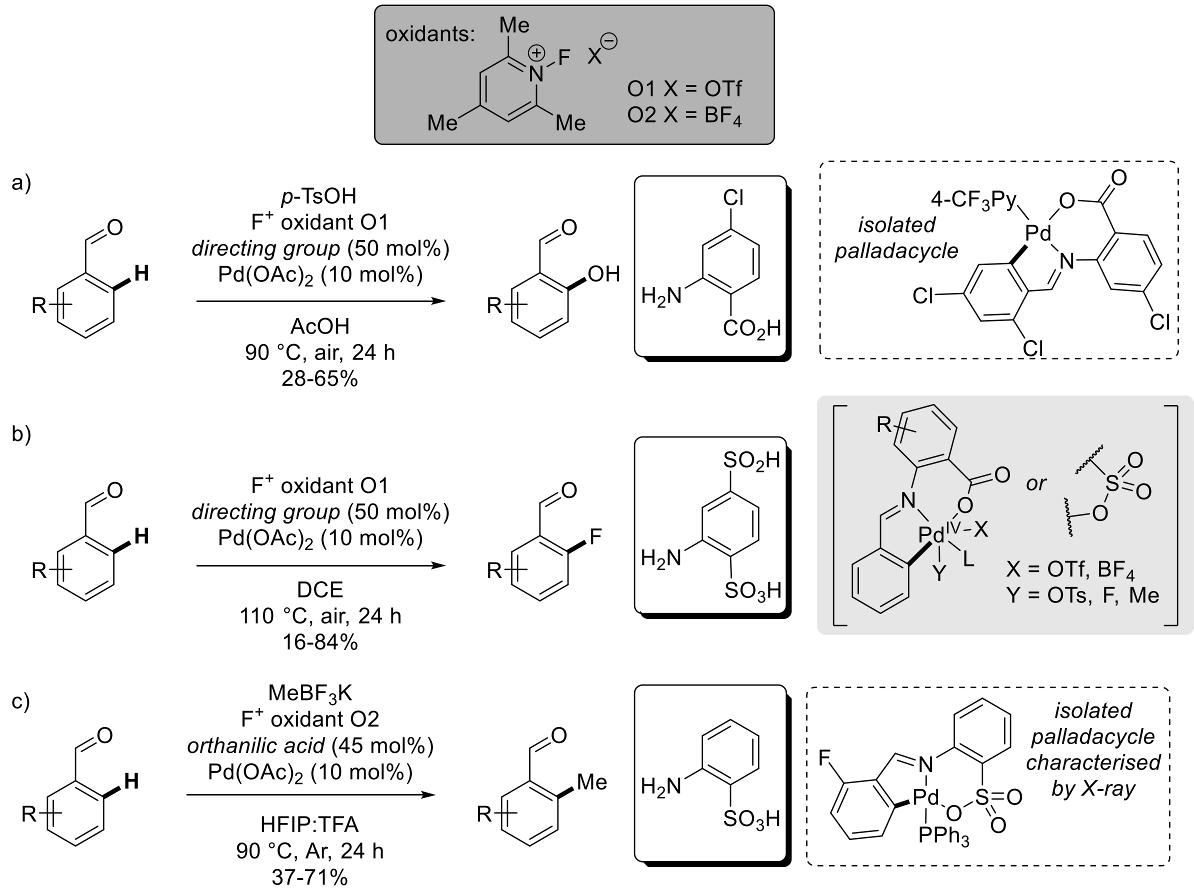
Palladium catalysed *ortho*-chlorination and bromination of benzaldehydes with NCS and NBS respectively was achieved by Yu using anthranilic acid TDGs (Scheme 1.44).[66]



Scheme 1.44: *Ortho*-halogenation of benzaldehydes

Both halogenations demonstrated high functional group tolerance and selectivity of the 2-position of the aldehyde despite the presence of the other N-based coordinating groups. Difunctionalisation occurred on *para*-substituted benzaldehydes. When no TDG's were present, only trace yields of halogenation were observed.

Sorensen pioneered the use of F^+ oxidants coupled with a TIDG strategy, enabling *ortho*-hydroxylation, fluorination as well as methylation of benzaldehydes with anthranilic acid (2-aminobenzoic acid) or orthanilic acid (2-aminobenzenesulfonic acid) derived TIDGs (Scheme 1.45).[76,77]

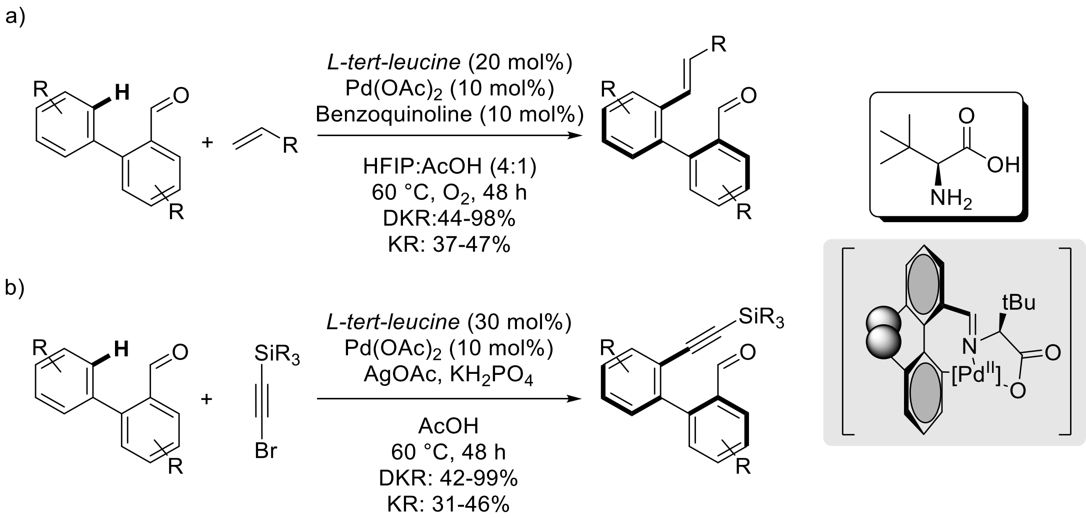


Scheme 1.45: Hydroxylation, fluorination and methylation by Sorensen

These three reactions have a common intermediate formed from oxidation of the *ortho*-metallacycle by the F^+ oxidant, forming a Pd^{IV} species (see grey box). Ligand exchange (for the hydroxylation) or transmetalation (for the methylation) afford suitable reductive elimination substrates to form the desired products. The O source for the hydroxylation reaction (Scheme 1.45a) was tosic acid, and a palladacycle was isolated as a pyridine adduct, which showed the bidentate coordination of the anthranilic acid TIDG.[76] A *bis*-sulfonic acid TDG and DCE as a solvent were optimal to promote C–F reductive elimination to form 2-fluorobenzaldehydes (Scheme 1.45b),[77] although some competitive C–Cl reductive elimination occurred. Orthanilic acid itself was optimal in facilitating the methylation reaction (Scheme 1.45c), where potassium methyl trifluoroborate was the source of the methyl group. Trifluoroborate salts bearing β-hydrogens were not tolerated, limiting the alkylation to methylation only. A phosphine stabilised palladacycle was isolated and characterised by X-ray crystallography.

δ-Functionalisation of 2-Formyl Biaryls

Shi was the first to demonstrate that a chiral TIDG could provide high enantioselectivities for the atroposelective synthesis of axially chiral biaryls (Scheme 1.46).

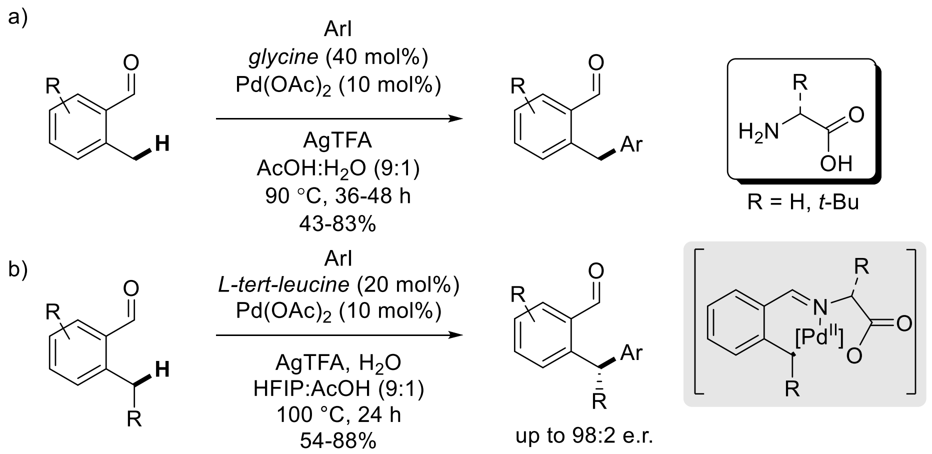


Scheme 1.46: Atroposelective C–H functionalisation of 2-formyl biaryls

In the first instance, a Heck-type coupling was developed (Scheme 1.46a).[78] The steric requirements, and hence conformational stability of the substrate, determined whether the reaction proceeded *via* dynamic kinetic resolution (DKR) or kinetic resolution (KR) pathways. The alkynylation (Scheme 1.46b) occurred *via* oxidative addition of the C–Br bond and reductive elimination steps.[79] The alkyne was further functionalised and the methodology also exploited to provide new, short syntheses of (+)-isoschizandrin and (+)-steganone. Both reactions demonstrated very high *ee's* across all DKR and KR reactions.

Benzylic C(sp^3)-H Functionalisation of o-Alkyl-Benzaldehydes

In January 2016, Yu demonstrated the first C(sp^3)-H functionalisation using transient imine directing groups.[80] Here, both the racemic and enantioselective benzylic arylation of *o*-alkyl benzaldehydes was accomplished with simple and readily available α-amino acids (Scheme 1.47).

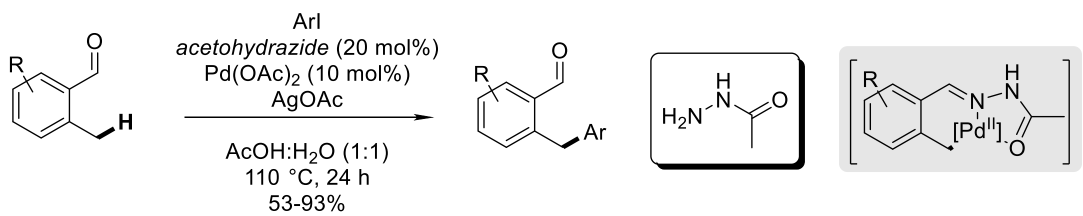


Scheme 1.47: Racemic and enantioselective benzylic C(sp^3)–H arylation of benzaldehydes

In the racemic reaction (Scheme 1.47a), glycine was the optimal amino acid and the reaction required a highly acidic HFIP:AcOH solvent system and silver trifluoroacetate. Only trace amounts of products were seen when the reaction was conducted in DCE, toluene, dioxane or MeCN, which are frequently used solvents for C(sp^3)–H functionalisation reactions when using amide-bound DGs. Water was beneficial to turn over the transient directing group and prevent the decomposition of the imine, which is thought to occur at high imine concentrations. Substitutions on the aldehyde had little effect on the reaction yield however when using *ortho*-substituted or heteroaryl iodides the yield decreased slightly.

High enantioselectivities for the benzylic arylation of *o*-alkyl benzaldehydes were observed when using bulky L-*tert*-leucine as the TDG (Scheme 1.47b). The origin of the enantioselectivity is proposed to be from the steric interactions between the R group and the side chain of the amino acid. Compared to the *o*-tolualdehydes, slightly more forcing conditions were required, related to the more difficult methylene C–H activation. No *ortho*-substituted or heteroaromatic aryl iodides were demonstrated.

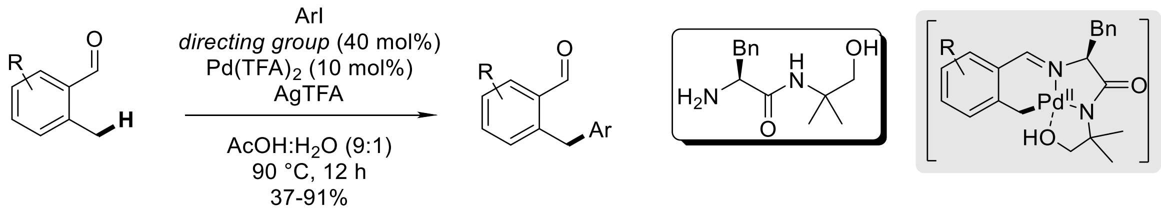
Palladium catalysed benzylic arylation could also be promoted by a transient acetohydrazone linkage (Scheme 1.48).[81]



Scheme 1.48: Acetohydrazone as a transient imine directing group for benzaldehyde arylation

Catalytic amounts of the acetohydrazide additive facilitated the arylation by forming a transient acetohydrazone group which could bind the Pd^{II} catalyst effecting a CMD-type C–H activation to form the metallacycle given in the grey box. The acetic acid solvent is proposed to facilitate formation of the acetohydrazone directing group. Alternative oxidants including other silver salts, copper salts and even sodium thiosulfate could promote the reaction in lower yields. Different coupling partners such as aryl bromides, tosylates and triflates were completely unreactive. Excellent yields were observed with electron poor and electron rich aryl iodides, though only trace product was seen when using *ortho*-substituted examples. A 4-pyridyl group was installed in 42% yield.

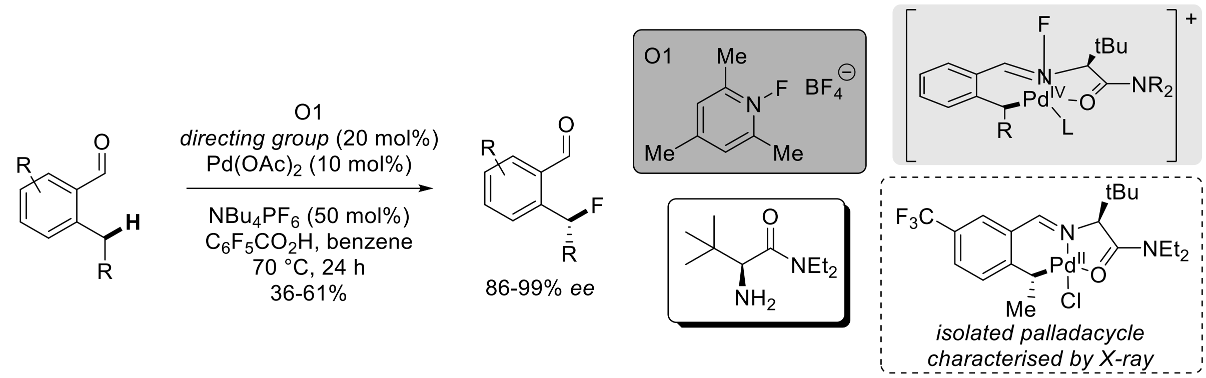
Jung and Kin recently showed that a tridentate directing group could assist in the palladium catalysed benzylic C–H arylation of benzaldehydes (Scheme 1.49).[82]



Scheme 1.49: A tridentate TIDG derived from an amino amide for the benzylic arylation of o-tolualdehydes

Electron rich benzaldehydes gave greater yields in the reaction, and lower yields were observed with sterically hindered aryl iodides. The pendant alcohol group was thought to enhance binding of the palladium catalyst. Changing from AgTFA to AgOTf and adding an aniline additive resulted in cyclisation of the products to form anthracenes in moderate yields.

Yu has shown that enantioselective benzylic fluorination was possible with chiral TIDGs and F^+ oxidants (1.50).[83] Here, C–O reductive elimination was a highly competitive pathway, which interestingly gave a different product enantiomer to the inner-sphere C–F reductive elimination (*via* intermediate in grey box), suggesting a different, outer-sphere S_N2 inversion mechanism from attack of the acetic acid when using it as the solvent or co-solvent. According to this study, C–F reductive elimination must proceed *via* a cationic, five-coordinate Pd–F species. With the amino acid, the 5-coordinate reductive elimination intermediate would be neutral, from coordination of the anionic carboxylate. Therefore, with the amino acids, the competitive acetoxylation reaction is favoured, whereas with the amide, the intermediate would be cationic, favouring C–F reductive elimination; this theory was also supported by computation. The C−H activation was shown to be irreversible using deuteration experiments.



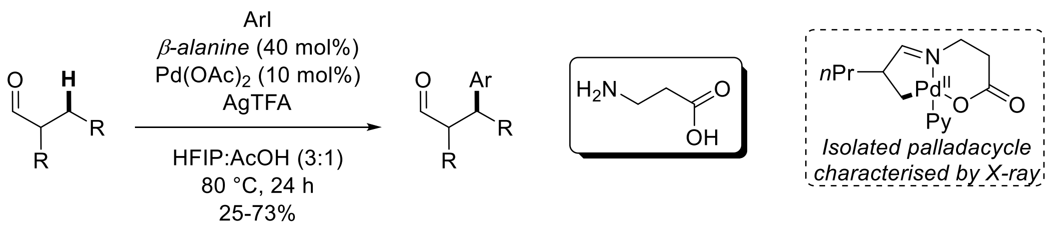
Scheme 1.50: Enantioselective C(sp^3)–H fluorination

To afford the benzylic C–F fluorination products in good yields, the benzaldehydes needed electron withdrawing substituents, with C–O reductive elimination favoured in other cases. On unsubstituted 2-ethyl benzaldehyde, unwanted *ortho*-C(sp^2)–H C–O bond formation occurred. The products were further derivatised, showing the utility of the benzaldehyde group.

β-C(sp^3)–H Functionalisation of Aldehydes

Transient imine directing groups with palladium catalysis can also be used to achieve β-arylation of aliphatic aldehydes. This is most relevant to the work described in this thesis on tertiary aldehydes (Section 3.1), secondary aldehydes (Section 3.2) and intramolecular aldehyde substrates (Section 3.3).

Ge showed that β-alanine could be used as the catalytic additive for β-C(sp^3)–H arylation of aldehydes (Scheme 1.51).[84]



Scheme 1.51: Palladium catalysed arylation of unactivated β-C(sp^3)-H bonds of aliphatic aldehydes

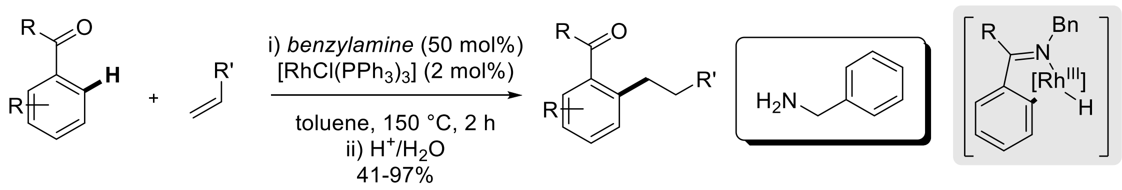
In this study, there was no trend in electronics of the aryl iodide when conducting the scope, and even an *ortho*-trifluoromethyl aromatic was introduced in 61% yield. When using isobutyraldehyde as the aldehyde substrate, a 1:1 mixture of mono and diarylated products was obtained (with each methyl group reacting). Methylene C–H bonds could also react on cyclic and linear substrates in lower yields. Curiously, some benzylic diarylated product was observed in low amounts when using propanal as the substrate, otherwise the reaction was chemoselective for the unreacted β–methyl or methylene positions. A palladacycle was synthesised with a stabilising pyridine ligand, which showed the cyclometalated imine intermediate. Use of methylacrylaldehyde as the substrate ruled out possible oxidation/addition processes to functionalise the β-position of aliphatic aldehydes, supporting the imine mechanism. In absence of β-alanine, no arylation occurred.

1.5.3 Transient Imine Directing Groups for the Functionalisation of Ketones

Ketimines are formed at lower rates than aldimines, making them a more challenging target for functionalisations with *endo*-imine transient directing groups.

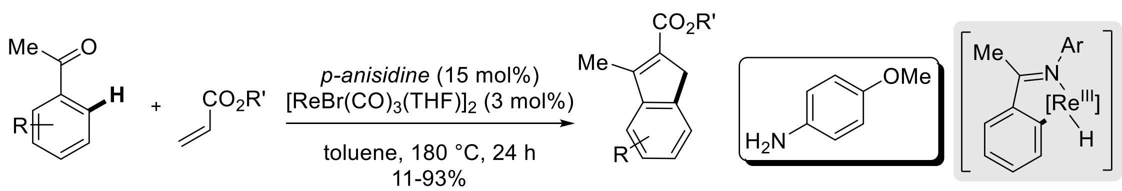
Ortho-C(sp^2)–H Functionalisation of Aromatic Ketones

In 2002, Jun found that benzylamine was optimal to form a TIDG for the *ortho*-alkylation of aromatic ketones (Scheme 1.52).[85] The need for a more reactive amine (c.f. anilines for aldehyde *ortho*-functionalisation) may be related to the lower reactivity of the aryl ketone compared to benzaldehydes. Also related to the higher stability of the ketimine, the reaction required a hydrolysis step to furnish the product ketones.



Scheme 1.52: Rhodium catalysed *ortho*-alkylation of aromatic ketones with alkenes

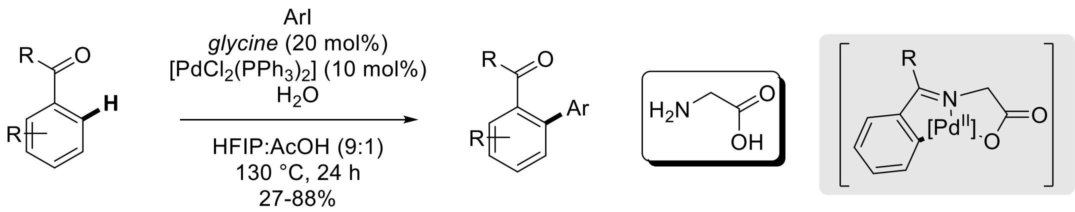
Previous work as described above for benzaldehyde functionalisation had demonstrated a prominent preference for electron poor anilines. Takai found that using rhenium catalysis for aromatic ketone annulation with alkene coupling partners, electron rich aniline TDGs gave the highest yields (Scheme 1.53).[86]



Scheme 1.53: Rhenium catalysed aromatic ketone annulation with anisidine as a TDG

The reaction required activated alkene coupling partners and was also sensitive to electron poor or hindered substituents on the ketone, giving much reduced yields.

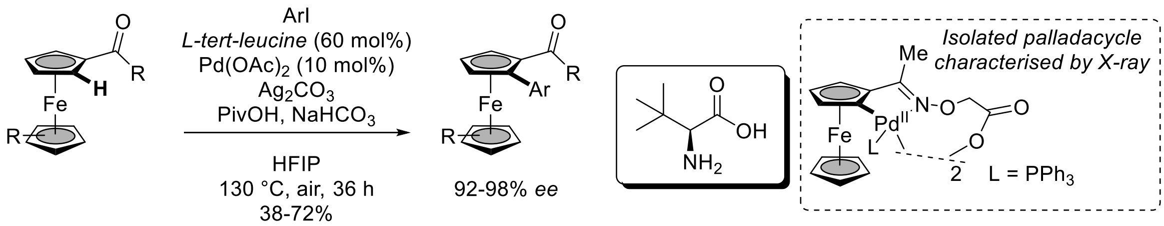
Glycine could be used to form a catalytic, bidentate transient imine directing group to promote the palladium catalysed *ortho*-arylation of aromatic ketones (Scheme 1.54).[87]



Scheme 1.54: Palladium catalysed *ortho*-arylation of aromatic ketones

A variety of aryl iodides were incorporated in good yield bearing electron rich, poor and sterically hindered substituents. Pyridine groups could also be installed in lower yields when substituted at the 2-position relative to the nitrogen. Substituents on the ketone made little difference to the yields, and excellent mono selectivity was observed throughout the scope. Mechanistic studies suggested the C–H activation was irreversible and the TOLS.

Enantioselective arylation of ferrocenyl ketones could be achieved with L-*tert*-leucine as the TDG (Scheme 1.55).[88]

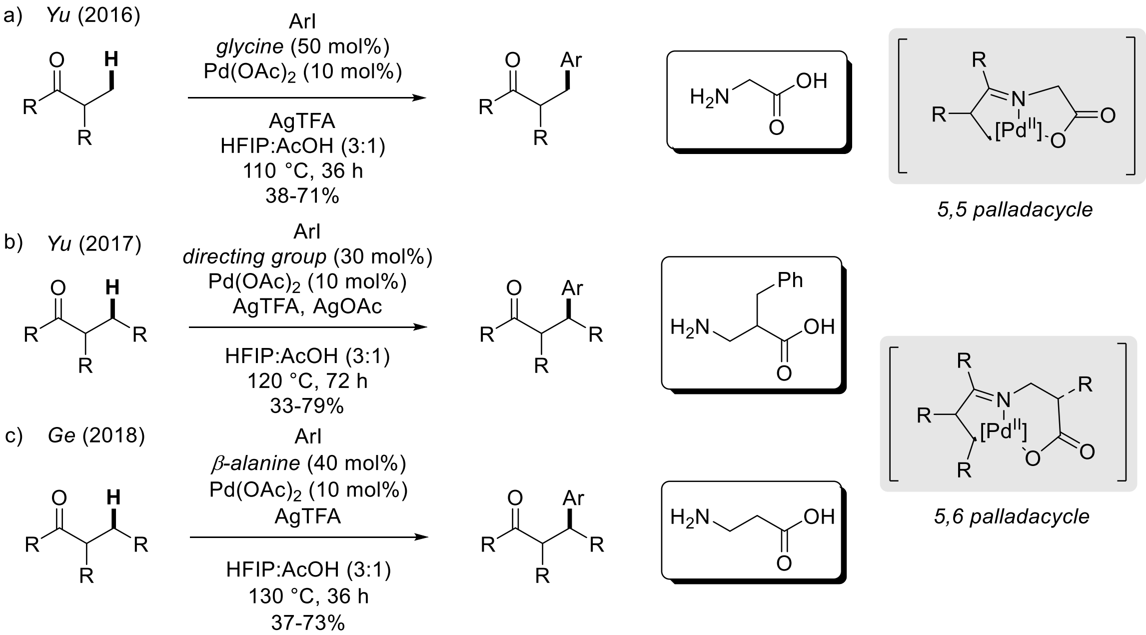


Scheme 1.55: Arylation of ferrocenyl ketones with a TIDG

Excellent *ee*'s were obtained for all examples. Generally, more electron deficient aryl iodides were more reactive, and 2-substituted aryl iodides could not be used. A related (oxime) palladacycle was isolated and characterised by single crystal X-ray diffraction. The methodology was used to synthesise novel ferrocenyl-phosphines as potential ligands.

β-C(sp³)–H Functionalisation of Ketones

α- And β- amino acids can be used to promote the β-C(sp³)–H arylation of aliphatic ketones with palladium catalysis *via* transient imine directing groups (Scheme 1.56).



Scheme 1.56: β-C(sp³)–H arylation of aliphatic ketones

In Yu's seminal paper, glycine facilitated the β-arylation of ketones (as well as *o*-tolualdehydes, Scheme 1.47a), when using slightly modified conditions which exclude the water co-solvent (Scheme 1.56a).[80] The aryl iodide scope was restrictive, with lower yields for electron rich examples and no examples of *ortho*-substituted or heteroaromatic aryl iodides included. Most examples were on β-methyl groups, however methylene C–H bonds could be activated on cyclic systems, with a *cis* product geometry proposed (*via* NOE). Interestingly arylation of a γ-C–H bond could be achieved when no β-hydrogens were present. Aliphatic aldehydes were not tolerated under these reaction conditions.

The scope of the ketone arylation was then extended by Yu to incorporate a larger range of methylene C–H bonds, on linear systems. To achieve this, a 6-membered chelate of the directing group was used, with a benzyl derivative of β-alanine (Scheme 1.56b).[89] A mixture of silver salts (AgOAc and AgTFA) were used to reduce biaryl formation from homocoupling of the aryl iodide. The TDG was optimised by changing substitution on the backbone of β-alanine. Where substitution on the carbon adjacent to the amine gave reduced yields (due to reduced imine formation) a benzyl group at the β-position to the amine proved optimal and enhanced the yield compared to β-alanine itself (71% vs 57%). Long reaction times (72 h) were required for the highest yields. Aryl iodides with various electronic properties were well tolerated however 2-substitued aryl iodides gave lower yields. For the ketone scope, diarylation occurred on substrates with multiple (non-benzylic) β-CH_2 positions. α-Branched ketones gave complex mixtures of products. Ge later showed that β-alanine itself (when used in a slightly higher loading) could promote the β-methylene C–H arylation in good yields (Scheme 1.56c).[90]

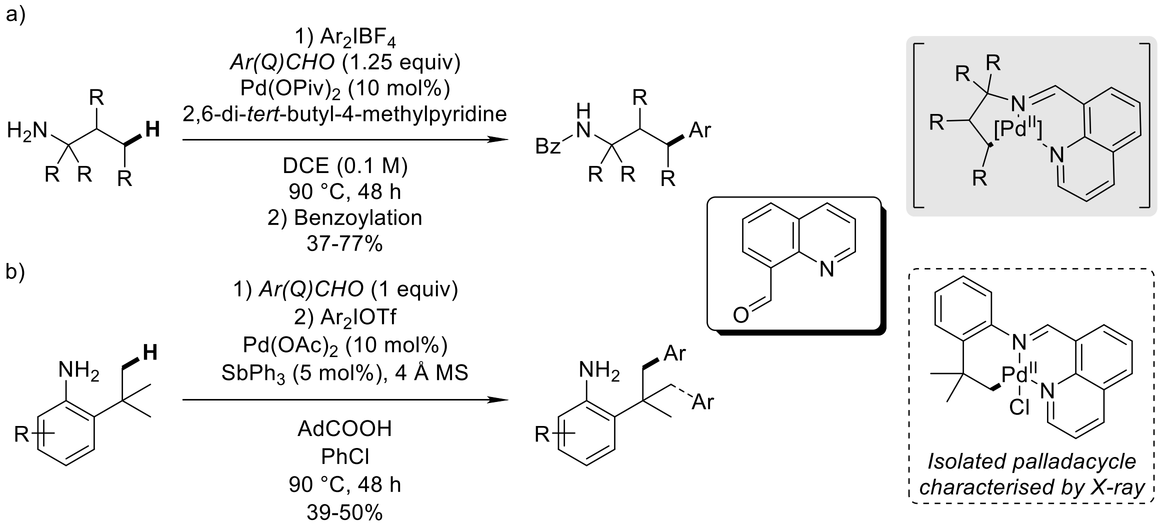
1.5.3 Transient Imine Directing Groups for the Functionalisation of Primary Amines

Due to their strong coordinating ability, amines form stable bis-complexes with palladium, which are inactive to C–H activation.[91] An additional challenge is that of α-oxidation of amines to form inactive imines.[92–94] Free amines have in themselves proven to be suitable directing groups for C–H functionalisation, which will be discussed in more detail in Section 3.4.1.

Dong demonstrated the first C–H functionalisation of free amines using a transient directing group strategy in 2016 (Scheme 1.57).[95] 8-Formylquinoline could form an *exo*-imine directing group to facilitate the selective γ-arylation of aliphatic amines and δ-arylation of 2-*tert*-butylanilines using diaryliodonium salts as coupling partners. The amine products were derivatised by benzylation to assist in purification.

For the γ-arylation of primary aliphatic amines (Scheme 1.57a), no reaction occurred in the absence of the directing group, supporting the proposed role of the transient imine (see grey box). A bulky non-coordinating base (2,6-di-*tert*-butyl-4-methylpyridine) was optimal to neutralise the HBF_4 generated from the counterion of the diaryliodonium salt. Electron poor aromatics were installed in higher yields, for example the 4-anisole product was only formed in 37% yield despite an elevated temperature and longer reaction time, whereas the phenyl group was installed in 70% yield under the standard conditions. An *ortho*-fluoro substituent was well tolerated but no heteroaromatic examples were given. Amines with only one α-substituent were tolerated in lower yields (2-methylbutylamine, 45%). Diarylation occurred on amines bearing two reactive γ-methyl groups and on the new benzylic position of the sterically activated *tert*-amylamine product. Some examples of methylene C(sp^3)–H activation on linear or cyclic substrates were given in good yield. On a large scale it was shown that the quinoline aldehyde could be recovered in 78% yield. The directing group could be used catalytically but the products were formed in reduced yields.

δ-C(sp^3)–H Arylation of aniline derivatives was also demonstrated (Scheme 1.57b).[96] Here the directing group could be used transiently but improved yields were seen when premixing the aniline and stoichiometric aldehyde for 1 h.

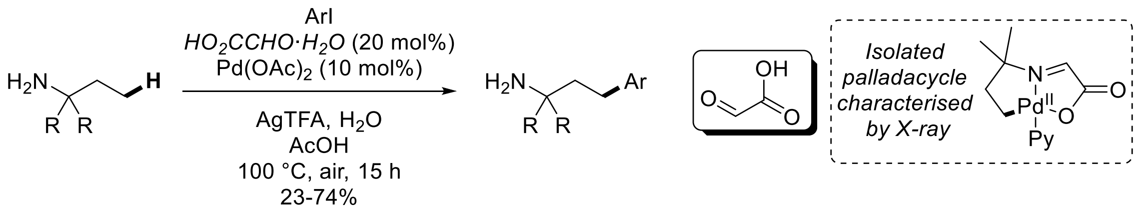


Scheme 1.57: Dong's γ-arylation of primary amines and δ-arylation of 2-*tert*-butyl anilines

The catalytic $SbPh_3$ additive gave slightly improved yields and higher consistency of results. Interestingly no reaction occurred on omission of the molecular sieves, although when they were saturated with water there was not a significant drop in yield, suggesting that the additional surface area was having an effect rather than elimination of water, however no detail was proposed. The adamantane carboxylic acid, which could promote the C–H activation step, was also crucial with no arylation occurring in its absence. Like the γ-arylation, electron poor diaryliodonium salts were most reactive and more nucleophilic electron rich anilines were most reactive. A palladacycle was isolated from the pre-formed imine, which was characterised by X-ray crystallography, supporting the *exo*-imine intermediate (see dashed box). Lui and Chen have since completed a computational study on how the *exo*-imine transient directing group facilitates the rate determining C–H metalation (by an unprecedented outer-sphere deprotonation by a pivalate) by reducing the distortion energy compared to the free-amine directed C–H activation.[19]

The next example to emerge of *exo*-imine directing groups for amine functionalisation was by Ge, who showed that catalytic amounts of glyoxylic acid could promote γ-arylation of *tert*-amylamine derivatives, using more accessible aryl iodides as the coupling partner (Scheme 1.58).[97] In the absence of the aldehyde TDG, the free amine was able to promote the arylation in 10% yield. Although other aldehydes were investigated (including Dong's

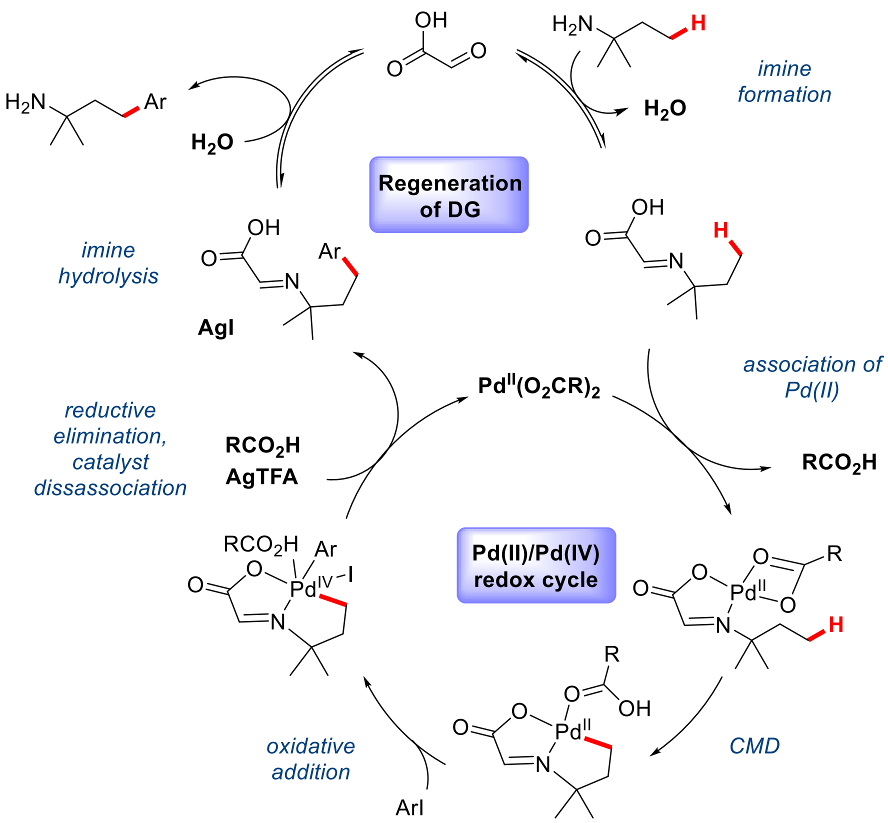
Ar(Q)CHO) only glyoxylic acid could promote the arylation above the background reactivity. Only highly acidic solvent systems were successful, and water was beneficial to the yield.



Scheme 1.58: Ge's γ-arylation of *tert*-amylamine derivatives

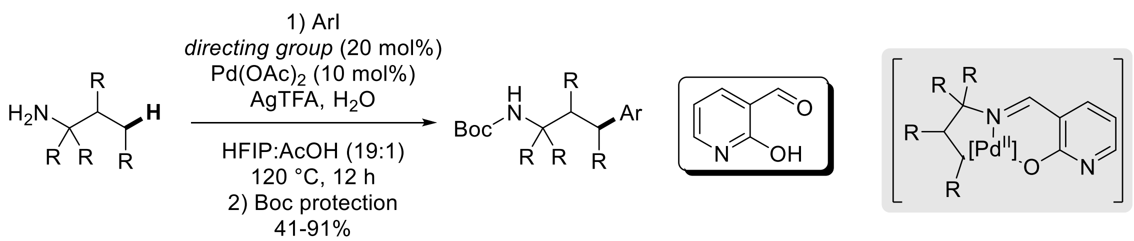
Heterocyclic 2-iodo-2-trifluoromethyl pyridine and 6-iodo-*N*-tosyl indole coupling partners formed the products good yields however *ortho*-substituted aryl iodides were not tolerated. All amines needed a fully substituted α-carbon, due to requirement of the Thorpe-Ingold effect, reduced oxidation and/or reduced formation of inactive bis(amine) palladium complexes. A pyridine derivative of the palladacycle was isolated and characterised by X-ray crystallography (dashed box) demonstrating the 5,5 palladacycle formed following the γ-C–H activation. The palladacycle was an active substrate undergoing arylation in 72% yield with no additional catalyst or directing group. The free amine functionality was exploited in the purification to isolate the products by a simple acid-base workup with no chromatography. A dual catalytic cycle for this process is given in Scheme 1.59, as proposed by Ge.[97]

The transient imine is formed from condensation of the glyoxylic acid with the amine, which then coordinates to the Pd^{II} catalyst. The resulting complex undergoes C–H activation by CMD, then oxidative addition of the aryl iodide followed by reductive elimination furnishes the product imine. Hydrolysis of the imine by water then turns over the directing group.



Scheme 1.59: Catalytic cycle for Ge's γ-arylation of *tert*-amylamine derivatives

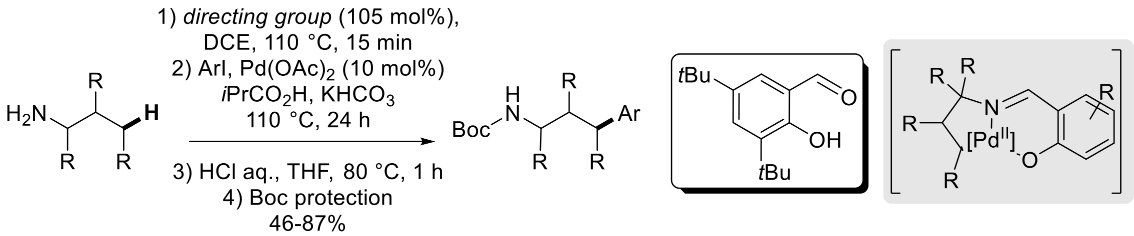
When Ge's study was submitted, a related study by Yu was in review.[98] Yu showed that 2-hydroxynicotinaldehyde could form a highly reactive TIDG for γ-C(sp^3)–H arylation of a broader variety of amine substrates, including those with no additional α-substituents, as well as promoting methylene C–H arylation in comparable yields (Scheme 1.60). Like Dong,[96] the amine products were derivatised, this time with Boc-protection, to enable chromatography of the amine products.



Scheme 1.60: Yu's highly active 2-hydroxynicotinaldehyde TDG for amine arylation

With the cyclohexylamine substrate used for the optimisation, the reaction did not progress in absence of directing group, or with directing groups that do not have the crucial imine forming aldehyde or ketone component, supporting a TIDG mechanism. The aryl iodide scope for the reaction was excellent, even *ortho*-substituted aryl iodides were installed in over 65% yield. Although heteroaryl iodides could not be installed in good yield on the methylene (cyclohexylamine) substrate, when using a linear amine with a reactive β-methyl group, various heteroaromatics could be installed in moderate to good yields. There were few limitations in the amine scope, the α-position of the amine did not require extra substituents, although to achieve functionalisation on methylene groups on linear substrates a temperature of 150 °C and addition of larger amount of water was required and the products were formed in lower yield. On *tert*-amylamine with the activating α-*gem*-dimethyl group, large amounts of benzylic C–H functionalisation occurred on the monoarylated product. On a large scale, with significantly lower loadings of catalyst and directing group (2 mol% and 4 mol% respectively) a 61% isolated yield of the arylated amine was achieved. Kamenecka expanded the scope of the amines using this directing group to a selection of amino esters.[99]

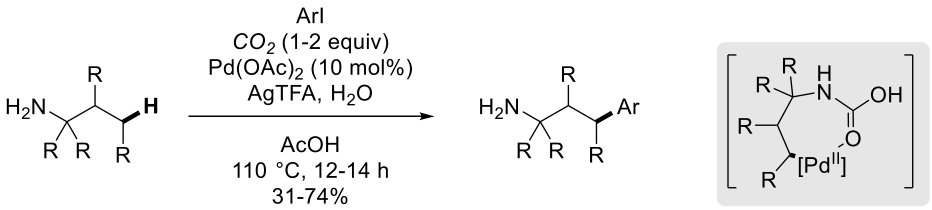
In late 2016, Murakami published another example of amine functionalisation directed by an imine, in this case formed from a salicaldehyde derivative (Scheme 1.61).[100] In this process the directing group is installed and removed in telescoped steps, and the products are also derivatised by Boc-protection. The *tert*-butyl groups on the salicaldehyde are proposed to reduce the formation of inactive bis-*imine* complexes.



Scheme 1.61: Salicaldehyde derived imine directing groups for γ-arylation of primary amines

Generally, the reaction was selective for γ-methyl C–H bonds, however on bicyclic *exo*-2-amino-norbornane (bridgehead) and 2-ethylaniline (benzylic), methylene C–H functionalisation was shown in 55% and 87% yields respectively. The directing group could be used catalytically for the benzylic arylation of 2-ethylaniline, forming the product in a slightly diminished yield (69%). The electronics of the aryl iodide had little effect on the reaction yield although no *ortho*-substituted examples were given.

In 2018, Young showed that a transient directing group formed from CO_2 (added as dry ice, see grey box) could also promote the γ-arylation of aliphatic amines (Scheme 1.62).[40]



Scheme 1.62: γ-arylation of amines promoted by CO_2

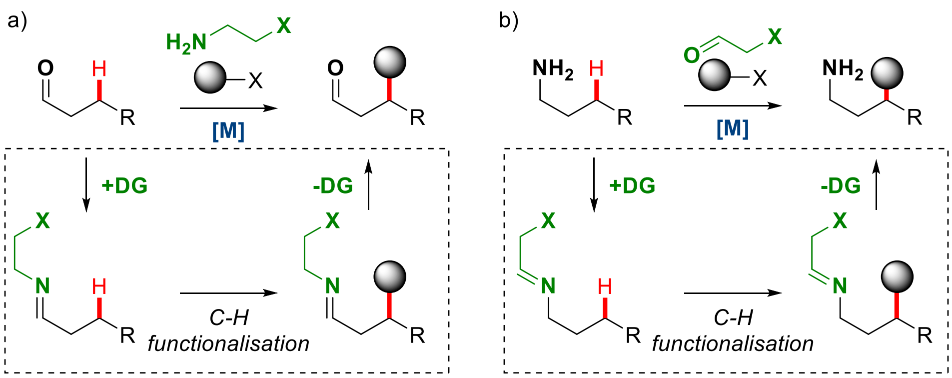
A high KIE showed that C–H activation was the likely turnover limiting step, and some evidence for the carbamate type TDG was obtained using various NMR techniques and pre-reacting the amine with CO_2 and subsequently subjecting the resultant mixture to the reaction conditions. Crucially, the protocol could also enable the γ-arylation of secondary amines by using much higher pressures of CO_2 and a higher AgTFA loading.

In conclusion, transient directing groups have been shown to be able to promote a variety of C–H functionalisation reactions. These ‘next-generation’ directing groups are a significant step forward in terms of efficiency compared to their amide-bound counterparts.[101] In particular, transient *imine* directing groups have seen huge progress over the last 2 years. Despite this, the field is still young and open to extensive further development, to incorporate new C–C and C–X bond forming reactions on a variety of substrates, using diverse catalytic directing groups.

2. Project aims

The aim of this project was to negate the directing group installation and removal steps typically required for C(sp^3)–H functionalisation by developing transient imine directing groups. Doing so would enable a more step and atom efficient approach to C–H functionalisation, providing a breakthrough in the field. At the outset of this investigation (October 2015) there were no literature examples of transient imine directing groups for C(sp^3)–H functionalisation.

Aldehydes are useful functional groups for further derivatisation by a variety of pre-existing synthetic methods. This, and their high reactivity with primary amines to form imines made them an attractive initial target to develop transient imine directing groups. We sought to investigate on a fundamental level whether it was possible to use a catalytic amount of an amine additive to promote the one-pot C–H functionalisation of aliphatic aldehydes using palladium catalysis (Scheme 2.1a). Directing group structures were inspired by well-established amide-bound directing groups, as discussed in Section 1.3. The focus would be to understand how altering the structure of the directing group could modulate the selectivity and yield for C(sp^3)–H arylation as a model reaction. This hypothesis would be applied to tertiary aldehydes (Section 3.1), secondary aldehydes (Section 3.2) and intramolecular aldehyde substrates (Section 3.3).



Scheme 2.1: transient a) *endo*-imine and b) *exo*-imine directing groups for C(sp^3)–H functionalisation of aldehydes and amines

Primary aliphatic amines are highly valuable functional groups present in many bioactive molecules. Hence, as well as the aldehyde functionalisation, one-pot amine functionalisation using aldehyde additives to form a transient imine directing group was considered (Scheme 2.1b, Section 3.4). Through all studies, gaining additional mechanistic understanding was a key goal, to improve current methods, as well as to assist in future development of the field.

3. Results and discussion

3.1 β-C(sp^3)–H Arylation of Tertiary Aldehydes

The initial objective was to use reactive aliphatic aldehyde substrates with amine additives to form transient *endo*-imine directing groups. Directing groups were designed based on amides such as 8-aminoquinoline (Figure 3.1). Due to the nature of the imine, where a sp^2 coordinating group would inherently be the primary binding site, the deprotonatable N binding would be in the secondary site, opposite in orientation to related amide-type directing groups.[102] Additionally, the imine directing group is more flexible, meaning that an entropic penalty may need to be paid to reach the correct orientation for catalyst binding.

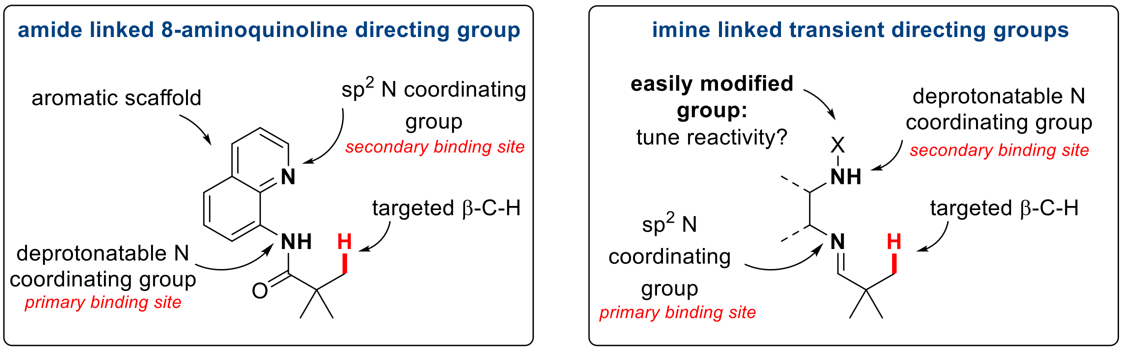
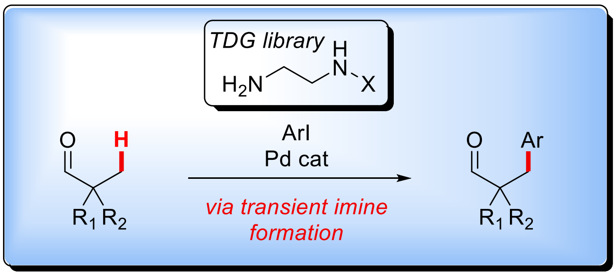


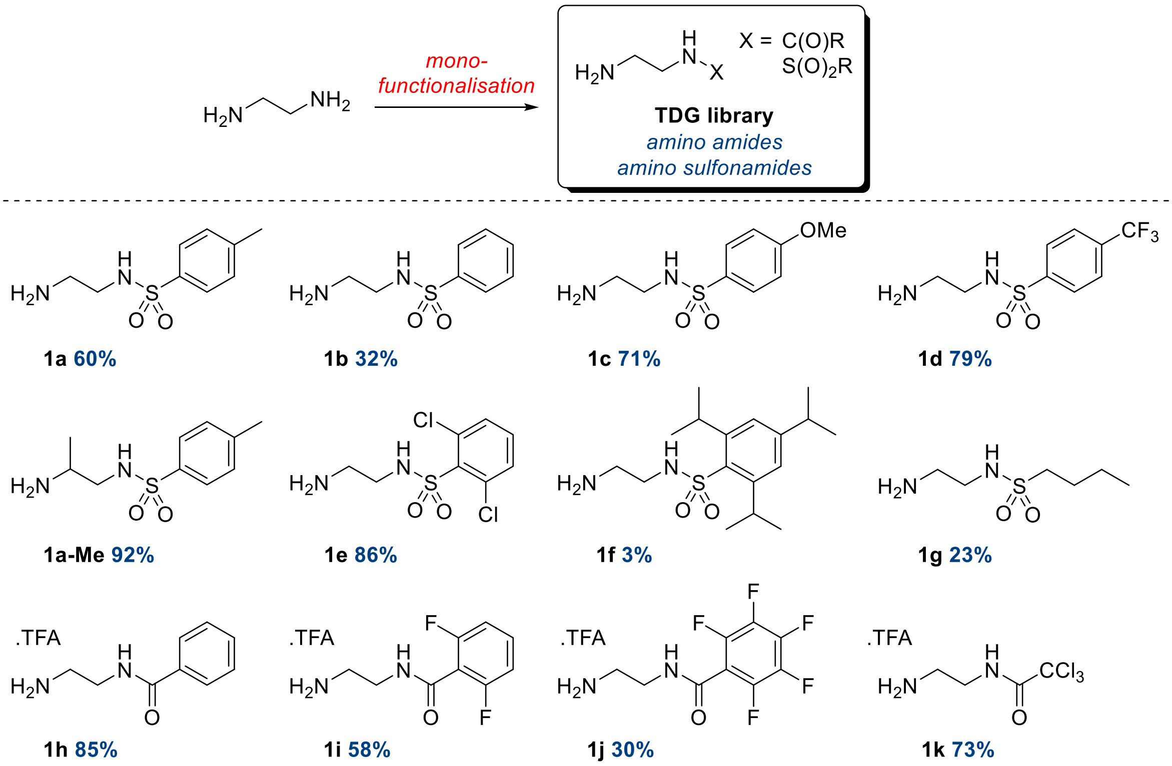
Figure 3.1: Design of TIDGs based on existing amide directing groups

The approach adopted to investigate such novel transient imine directing groups was to create a library of amines, from the mono-functionalisation of ethylenediamine (Scheme 3.2). This would leave a free primary amine for imine formation and a secondary binding site in which a series of amides and sulfonamides could be easily incorporated. This would enable us to tune the sterics and electronics of the secondary deprotonatable N binding site. An ethylene linker between the two binding nitrogens was used, to enable favourable 5,5-bipalladacycle formation following cyclometalation of the β-C–H of the envisaged imine. Investigations would consider how the structure of the resultant imine directing group might affect the yield, rate and selectivity of the reaction, in particular the regioselectivity (aldehydic, α, β, γ), chemoselectivity (methyl, methylene, benzylic) and levels of over-reaction (mono, di, tri). The TDG library would be applied to the β-arylation of aliphatic aldehydes using palladium catalysis as a model reaction (Scheme 3.1).



Scheme 3.1: Use of TDG amine library for the one-pot palladium catalysed β-arylation of aliphatic aldehydes

Amino-sulfonamides were synthesised in one step with excess ethylenediamine. Amino amides (isolated as TFA salts) were formed in two steps from *N*-Boc-ethylenediamine (Scheme 3.2).

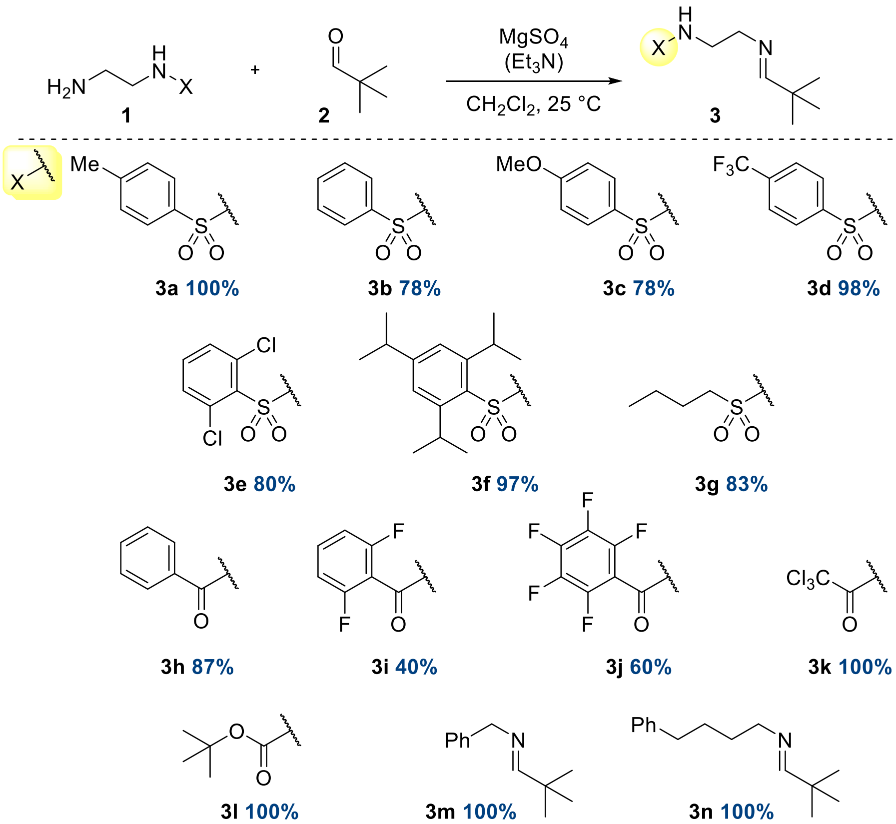


Scheme 3.2: Synthesis of amine library to form transient imine directing groups

Most sulfonamides were synthesised in good yields (**1a-1g**), with lower yields observed for liquid sulfonyl chlorides (Ph and *n*Bu) whereby the fast dissolution resulted in a higher proportion of *bis*-functionalisation. The yield of the bulky triisopropyl sulfonamide was low, most likely also due to *bis*-functionalisation. A sulfonamide bearing a methyl group on the backbone (**1a-Me**) was synthesised in high yield in a similar fashion. For the aryl amide directing groups generally the bulkier, more electron poor acids resulted in lower yields for the amide coupling steps. A trichloroacetamide directing group was synthesised using a similar approach but from the acyl chloride. All other directing groups tested were commercially available.

As a proof of concept, the arylation reaction was first attempted using pre-formed imines. This was to verify that the designed directing groups could in fact bind palladium strongly enough and in the correct orientation for C–H activation. At the outset, pivaldehyde was chosen as the model substrate as, although this would not give us information about the chemoselectivity as it only presented methyl groups, it was commercially available and should have high reactivity due to the Thorpe-Ingold effect. Additionally, the lack of an enolisable proton should improve stability of the substrate.

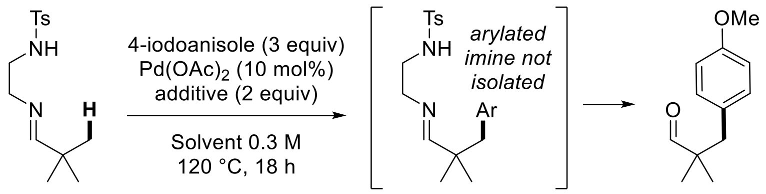
Pivaldehyde imines were synthesised by the standard protocol shown in Scheme 3.3. When using the TFA salt as per the amino-amides, triethylamine was used to neutralise the aminium and facilitate imine formation. Two imines were formed from commercially available benzylamine and 4-phenylbutan-1-amine to provide some monodentate imine directing group examples.



Scheme 3.3: Synthesis of imine substrates

All imines were synthesised in good yields. Imination yields for the amide substrates were lower, this was due to the additional workup needed to remove triethylamine, leading to some hydrolysis. In many cases, small amounts of the *cis*-stereoisomer were present. Despite this, all imines were used as prepared.

Initial hit screening was performed using the *N*-tosylethenediamine imine **3a**. The imine was subjected to various C–H arylation conditions (Table 3.1). The reaction conditions selected were based on a concise optimisation approach as used previously in the group.[103] The coupling partner selected for the reactions was 4-iodoanisole, so that any new aromatic signals would be more easily observed in the crude ^{1}H NMR.



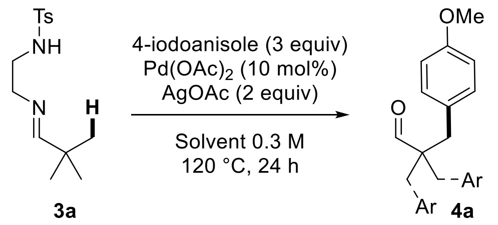
3a **4a**

Entry	Additive	Solvent	yield (%)[a]
1	AgOAc	toluene	trace
2	$AgCO_3$,[b] PivOH[c]	*t*-amyl-OH	0
3	CsOAc	toluene	0
4	AgOAc	none	8 (13)[d,e]
5	K_2CO_3	*t*-amyl-OH	0

Table 3.1: Screening of arylation conditions using *N*-tosylethylenediamine pivaldehyde imine **3a** (0.2 mmol). [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]1 equiv. [c]0.3 equiv. [d]Isolated yield [e]0.4 mmol, 24 h.

Although trace reactivity was seen using silver acetate in toluene, pleasingly when using this silver salt but under neat conditions, significant arylation was achieved. On scale up to 0.4 mmol, the yield was improved to 13%, isolated using column chromatography. This enhanced yield on scale is likely due to improved stirring of the solvent-free reaction. Notably, following the work-up of a filtration though Celite in EtOAc, the main product was the arylated aldehyde, although some arylated imine was observed. This means that the reaction constituted a one-pot C–H arylation and directing group cleavage, already an advantage over the amide-bound directing groups as discussed in Section 1.3. It was found that a neutral aqueous work-up led to full hydrolysis of the imine products enabling accurate calculation of arylated aldehyde yields by ^{1}H NMR.

The solvent for the reaction was investigated (Table 3.2). At this stage it became apparent that some di- and triarylated species were being formed in some cases, the yield of which could also be calculated from the [1]H NMR spectra of the reaction crudes.

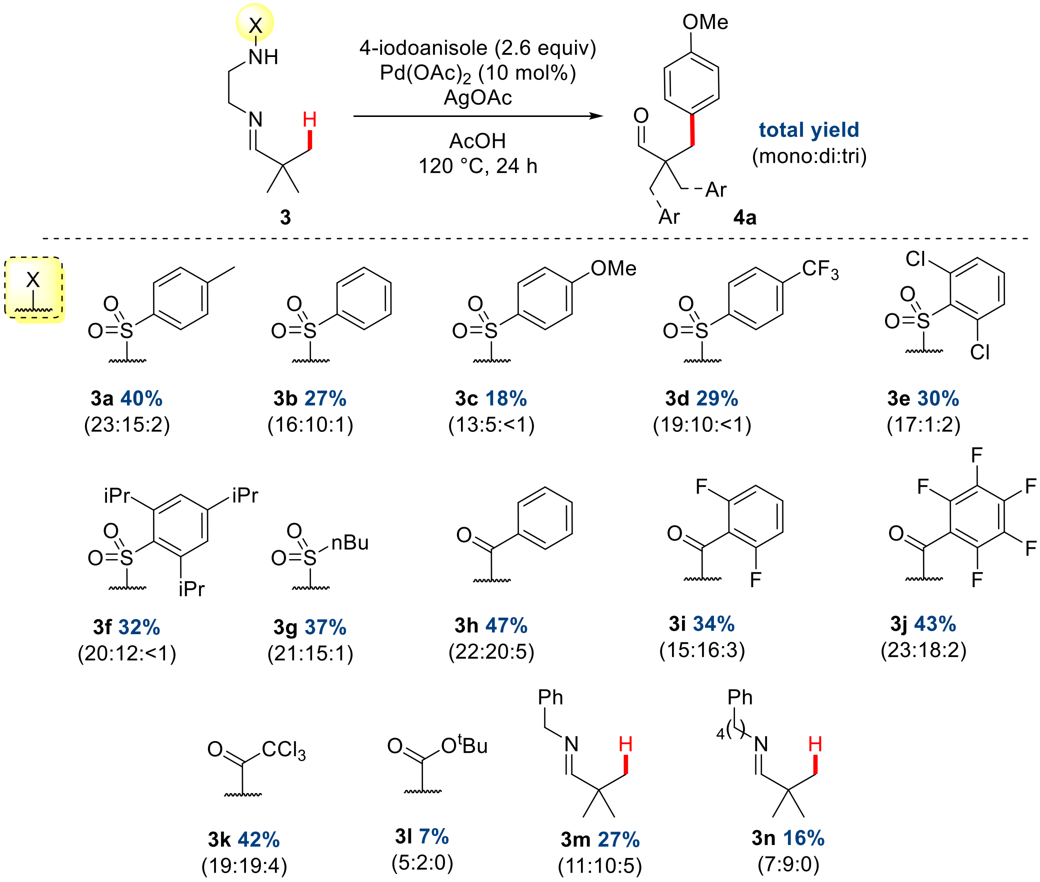


Entry	Solvent	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	none	13	3	0	16
2	toluene (1 M)	trace	0	0	trace
3	toluene (2 M)	trace	0	0	trace
4	dioxane	trace	0	0	trace
5	AcOH	21	16	1	38

Table 3.2: Solvent screen for imine arylation (0.4 mmol scale). [a]Yields determined by [1]H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Trace yields were seen with toluene as a solvent, even when used at high concentrations (Table 3.2, Entries 2,3). Dioxane was also ineffective. Pleasingly however, when using acetic acid, the yield was increased dramatically to 38%. Importantly, the use of the acidic solvent assisted in hydrolysis of the imine enabling a facile filtration through silica to be used as the work-up for further experiments.

With the enhanced yield from the improved solvent system, the reactivities of the library of directing groups could be compared. All synthesised imines were hence subjected to the arylation conditions (Scheme 3.4).



Scheme 3.4: Arylation of imines. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Surprisingly, each imine synthesised was able to promote the arylation to some extent, even the two examples which could only coordinate through the imine nitrogen (**3m** and **3n**), however, these yields were lower compared to the bidentate systems. For both the amide and sulfonamide containing imine series, no definite trends in yield were observed when changing the sterics and electronics of the aromatic ring, possibly suggesting that the secondary binding centre may be labile, so that these effects play a less significant role. The Boc carbamate **3l** gave a very low yield, which could be attributed to Boc-deprotection under the acidic reaction conditions. Generally, the amide examples gave an improved yield compared to the sulfonamides, but this came at a consequence of a more complex mixture of aldehyde products, as seen in the representative examples of the crude ^{1}H NMR spectra (Figure 3.2).

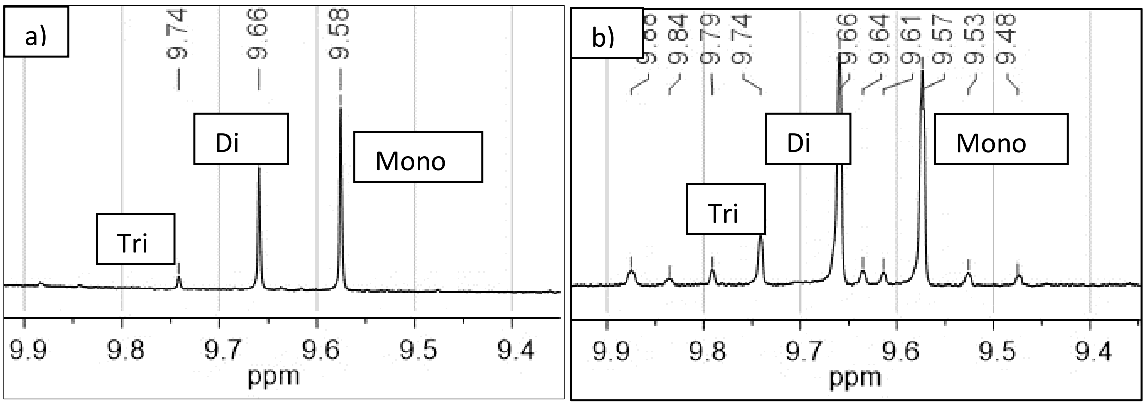
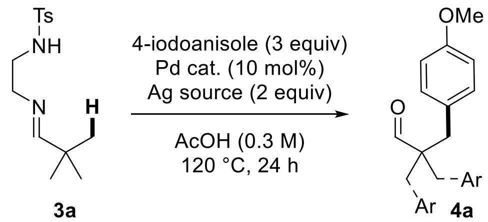


Figure 3.2: Aldehyde regions of imine arylation in the ^{1}H NMR of the crude reaction mixture using a) *N*-{2-[(*E*)-(2,2-dimethylpropylidene)amino]ethyl}-4-methylbenzene-1-sulfonamide **(3a)** and b) 2,2,2-trichloro-*N*-{2-[(*E*)-(2,2-dimethylpropylidene)amino]ethyl}acetamide **(3k)**

As well as the distinct mono, di and triarylated aldehyde signals as labelled, the imino-amide directing group (**3k**, Figure 3.2b) shows many additional aldehyde signals. These peaks were likely to represent products that had additionally reacted on the new benzylic sites of each (mono-, di- and tri-) arylated product. In contrast the sulfonamide (**3a**, Figure 3.2a) was selective for arylation at the methyl groups. This effect was also the case for all other amide and sulfonamide imines. As a result, the best sulfonamide directing group (*N*-tosylethylenediamine, **3a**) was selected for further studies.

Alternative palladium and silver sources were investigated in the form of palladium pivalate and silver trifluoroacetate (Table 3.3).



Entry	Pd catalyst	Ag source	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	$Pd(OAc)_2$	AgOAc	21	16	1	38
2	$Pd(OAc)_2$	AgTFA	18	18	7	43
3	$Pd(OPiv)_2$	AgOAc	20	16	2	38
4	$Pd(OPiv)_2$	AgTFA	20	18	5	43

Table 3.3: Investigation of palladium catalyst and silver source, 0.2 mmol. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The use of silver trifluoroacetate with palladium acetate gave a marginally higher proportion of di- and triarylated products, and a slight improvement in yield. Palladium pivalate gave a comparable result to palladium acetate using either silver source. AgOAc continued to be used to maximise the yield of monoarylation.

When dissolving the pivaldehyde imine in deuterated acetic acid and observing the resultant ^{1}H NMR, it was found that almost 50% of the imine was hydrolysed into the amine and aldehyde components or a hydrolysis intermediate (Figure 3.3).

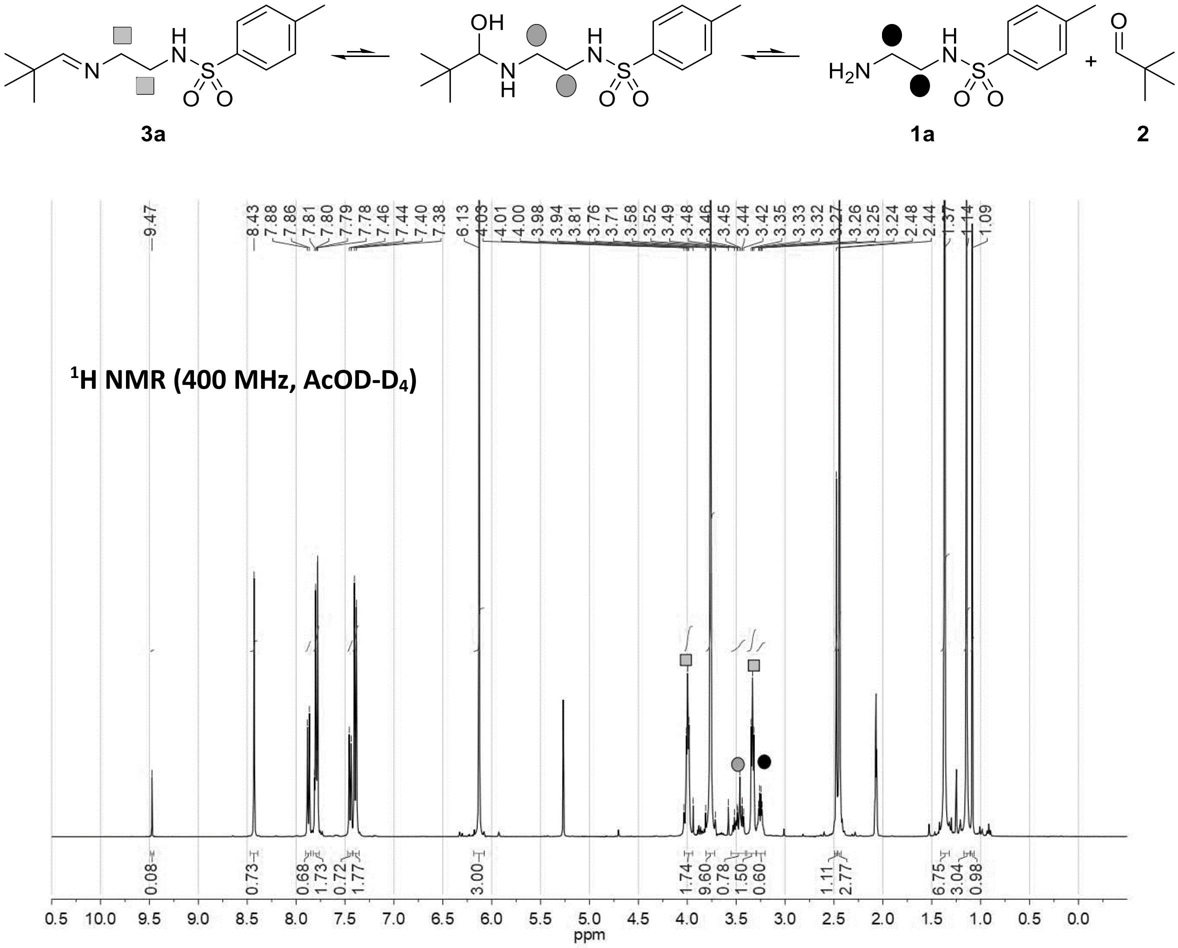


Figure 3.3: Hydrolysis of the *N*-tosylethylenediamine pivaldehyde imine **3a** in AcOD-D_4

Conversely, combining a 1:1 mixture of amine **1a** and pivaldehyde **2** in deuterated acetic acid gave an 8% conversion to the imine (Figure 3.4).

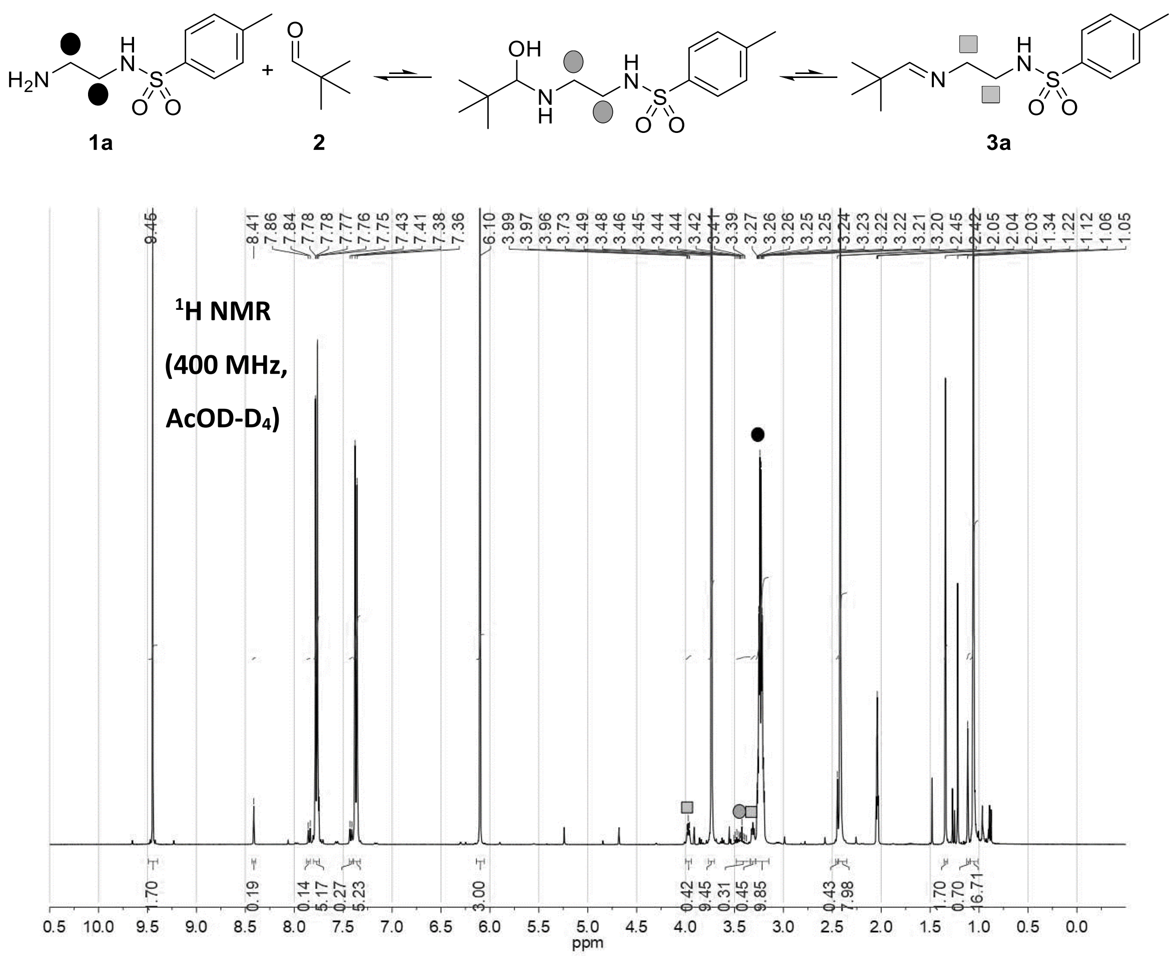
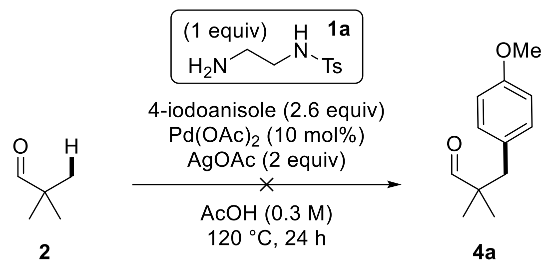


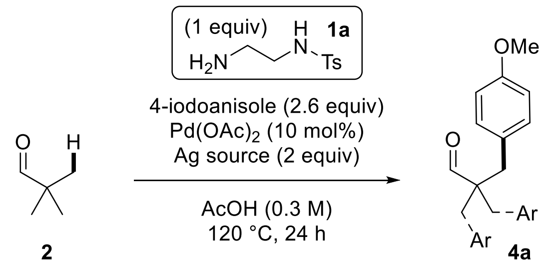
Figure 3.4: Formation of the *N*-tosylethylenediamine pivaldehyde imine **3a** in AcOD-D4

As small amounts of imine could be formed by simply combining the aldehyde and amine in the reaction solvent, this displayed the potential to realise a *transient* imine directing group. Encouraged by this, a 1:1 mixture of the pivaldehyde **2** and *N*-tosylethylenediamine **1a** were used in place of the pre-formed imine under the arylation conditions (Scheme 3.5).



Scheme 3.5: Trace yields of aldehyde products for direct arylation of pivaldehyde

Unfortunately, under the conditions used for the imine arylation, only trace amounts of aldehyde product was observed for the direct aldehyde arylation. In hope to see some improved reactivity, alternative silver sources were investigated (Table 3.4).

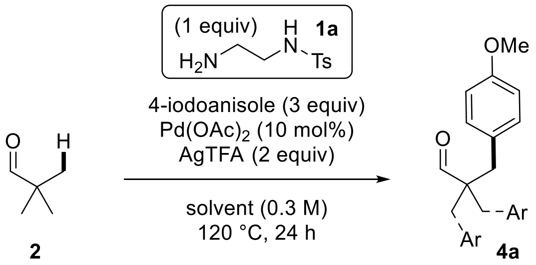


Entry	Ag source	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	AgOAc	Trace	0	0	Trace
2	Ag_3PO_4	2	0	0	2
3	Ag_2SO_4	2	0	0	2
4	AgTFA	15	11	3	29
5	AgF	2	0	0	2

Table 3.4: Investigation of silver source, 0.2 mmol. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Although a very slight improvement in yield was shown with silver sulfate, phosphate and fluoride, product formation was dramatically increased when switching to silver trifluoroacetate (Table 3.4, Entry 4). Interestingly however, under the imine arylation conditions AgTFA gave an almost identical yield to AgOAc (Table 3.3, Entry 2). This could potentially be attributed to the formation of more electrophilic [PdTFA] species, which enhances the binding of the imine. This effect is more dramatic for the transient system due to the inherent lower concentration of imine as illustrated by the NMR experiments (Figures 3.3 and 3.4).

After achieving a yield of 29% with only one change from the initial conditions, alternative solvents including solvent mixtures were tested (Table 3.5).



Entry	Solvent	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	AcOH	15	11	3	29
2	HFIP	5	3	0	8
3	DMSO	0	0	0	0
4	Toluene	0	0	0	0
5	*t*BuOH	0	0	0	0
6	DCE	2	0	0	2
7	TFA	0	0	0	0
8	PivOH	11	6	2	19
9	$CH_3CH_2CO_2H$	9	4	Trace	13
10	HCO_2H	0	0	0	0
11	Cl-AcOH	8	3	Trace	11
12	TCA	Trace	0	0	Trace
13	HFIP:AcOH (3:1)	19	14	6	39
14	HFIP:AcOH (1:1)	20	13	3	36
15	HFIP:AcOH (1:3)	20	13	3	36
16	DCE:AcOH (3:1)	11	0	0	11
17	*t*BuOH:AcOH (3:1)	Trace	0	0	Trace
18	Toluene:AcOH (3:1)	17	5	3	25
19	Toluene:AcOH (1:1)	15	6	Trace	21
20	Toluene:AcOH (1:3)	18	5	Trace	23
21	TFA:AcOH (1:9)	15	13	3	31
22	TFA:AcOH (1:3)	20	13	1	34
23	TFA:AcOH (1:1)	14	4	0	18

Table 3.5: Investigation of reaction solvent. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

HFIP gave a low yield of 8% (Table 3.5, Entry 2). DMSO, toluene and *t*BuOH as the reaction solvent failed to form any of the desired product. DCE formed the arylated aldehyde in small quantities (Table 3.5, Entry 6). Although none gave an improvement in yield compared to acetic acid, some alternative acid solvents did show some product formation (Entries 7-12).

Neat TFA or TCA formed no arylated product as the conditions were likely too acidic and caused degradation of the starting materials. As none of the single solvent systems gave an improved yield compared to acetic acid, solvent mixtures were examined. When mixing acetic acid with non-polar solvents DCE and toluene, arylation could be achieved but these systems were not as effective as acetic acid alone (Table 3.5, Entries 16, 18-20). Using HFIP as a co-solvent, the yields were increased with the best ratio for maximum monoarylation when using a 1:1 mixture. Comparable yields were achieved when using AcOH:TFA solvent mixtures however the milder HFIP:AcOH system was brought forward through the optimisation. HFIP is known to form hydrogen-bonding cages which can enhance the acidity of other acids[104] which may be why the yield was improved and also comparable to using the stronger acid (TFA).

An NMR experiment was conducted to observe the effect of the new solvent system (AcOH:HFIP, 1:1) on the concentration of imine in solution (Figure 3.5).

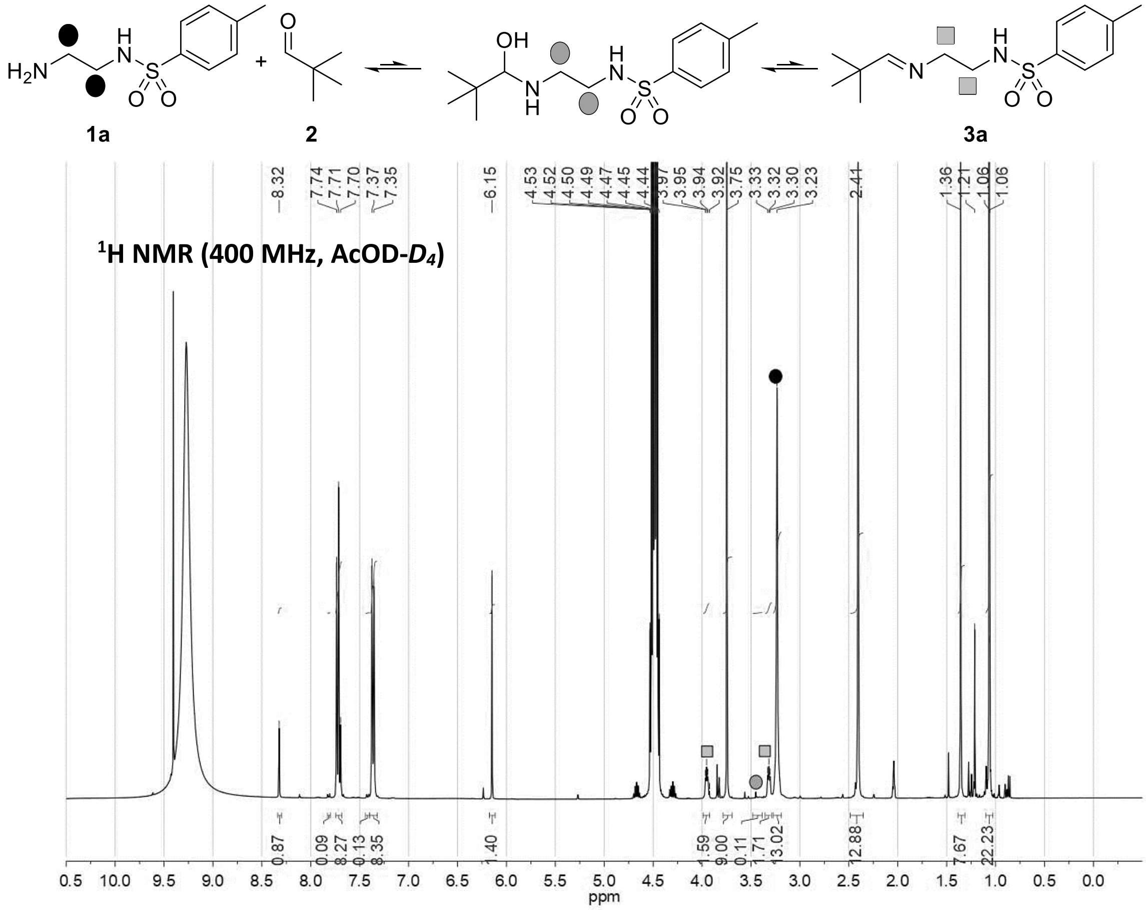
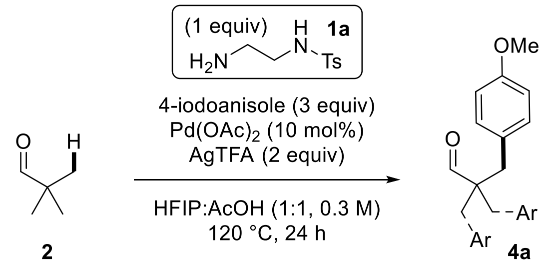


Figure 3.5: Formation of the *N*-tosylethylenediamine pivaldehyde imine **3a** in AcOD-D$_4$:HFIP (1:1)

The presence of HFIP as a co-solvent resulted in the conversion from aldehyde to imine to be increased from 8% (in deuterated acetic acid) to 22%. This strongly suggests HFIP assists the reaction by increasing the concentration of the active imine species.

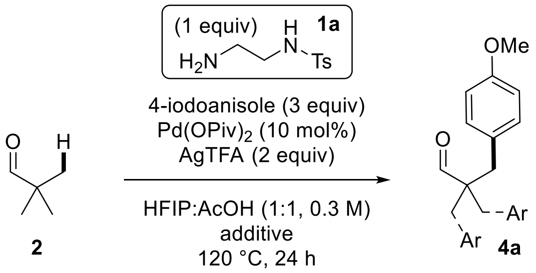
Next, the palladium source was investigated (Table 3.6).



Entry	Pd source	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	$Pd(OAc)_2$	20	13	3	36
2	$PdCl_2$	19	13	4	36
3	$Pd(OPiv)_2$	23	17	7	47
4	$Pd(TFA)_2$	20	12	5	37

Table 3.6: Effect of palladium source. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Palladium chloride and palladium trifluoroacetate gave similar yields to palladium acetate. When switching to palladium pivalate, a 10% increase in yield was reached (Table 3.6, Entry 3). Additives were examined at this stage, however none gave an improved yield (Table 3.7).

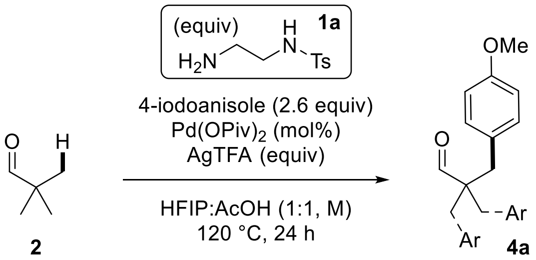


Entry	additive (equiv)	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	none	23	17	7	47
2	$Mn(OAc)_2$	20	11	4	35
3	PivOH	20	13	4	37
4	MesCOOH	23	13	4	40
5	H_2O	18	12	5	35
6	DMSO	24	14	5	43
7	DMSO (0.6)	22	15	4	41
8	Pyrrolidine	17	6	1	24
9	Benzoquinone (1)	0	0	0	0

Table 3.7: Additive screen. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Design of experiment (DOE) studies were used in an attempt to improve the yield of the reaction (Appendix 1). No improved yield was predicted by the software in the ranges of equivalents used for the reaction components examined. The most important factors that affect the product yield was determined to be the equivalents of silver and the solvent concentration, as well as the combination of these factors working together. The amount of palladium catalyst and directing group was found to only have a small impact on product yield.

To confirm the observations made in the DOE investigation, optimisation reactions were carried out by varying the equivalencies of the individual components investigated in the DOE study: AgTFA loading, concentration, TDG (amine **1a**) and catalyst loadings (Table 3.8).



entry	Ag (equiv)	Conc (M)	TDG 1a (equiv)	Pd loading (mol %)	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	**2**	0.3	1	10	25	16	7	48
2	**1.5**	0.3	1	10	16	14	7	37
3	**1**	0.3	1	10	14	7	trace	21
4	**3**	0.3	1	10	20	21	10	51
5	2	**0.1**	1	10	22	16	3	41
6	2	**0.2**	1	10	23	18	6	47
7	2	**0.4**	1	10	23	18	8	49
8	2	**0.5**	1	10	19	18	10	47
9	2	**1.0**	1	10	18	16	8	42
10	2	**2.0**	1	10	10	10	6	26
11	2	0.3	**0.75**	10	25	15	9	44
12	2	0.3	**0.5**	10	22	17	12	51
13	2	0.3	1	**7.5**	20	16	8	44
14	2	0.3	1	**5**	17	9	3	19

Table 3.8: Variation of continuous reaction parameters. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The results confirmed how an increased AgTFA loading has a large positive effect on yield, as suggested in the DOE. The increase in yield appears to be linear but does begin to tail off at 2 equivalents. Higher amounts of di- and triarylated product were also formed as the amount of AgTFA was increased.

Surprisingly, small changes in concentration did not have as large an impact on yield as expected, only when going to very concentrated 2 M there was a significant change in yield. At lower concentrations the yield is marginally decreased with little change in selectivity of the different products. The yield peaks at 0.4 M but this is largely due to more di- and triarylated product. The amount of triarylated species increases linearly up to 0.5 M but then decreases alongside all the other products at higher concentrations.

Next the non-dominant factors identified from the DOE (DG and catalyst loading) were examined to understand if lower loadings could be tolerated (Entries 11-14). The results showed that there was a higher tendency towards triarylated products when using lower quantities of directing group, although it is well tolerated and can give increased total yields. This could be due to less imine formation of the starting material so the arylated imine species can re-cyclometallate and react further. The loading of catalyst appears to give a more significant contribution to yield than the DOE would suggest, with 5 mol% giving only a 19% total yield. 7.5% however, was well tolerated.

A profile of how the percentage yield of the aryl iodide and arylated products changes over the course of the reaction was obtained from multiple discrete experiments conducted at different time points (Figure 3.6).

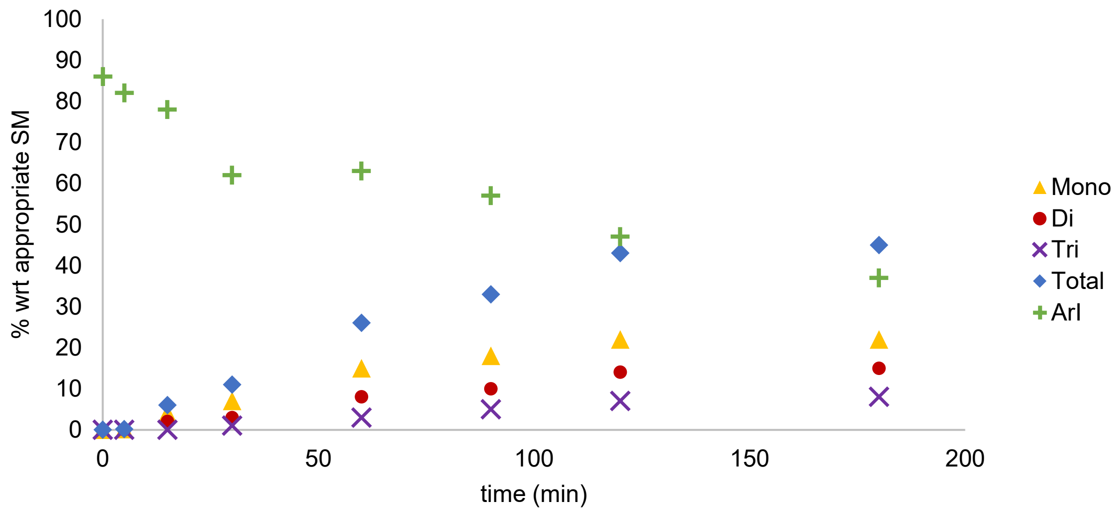
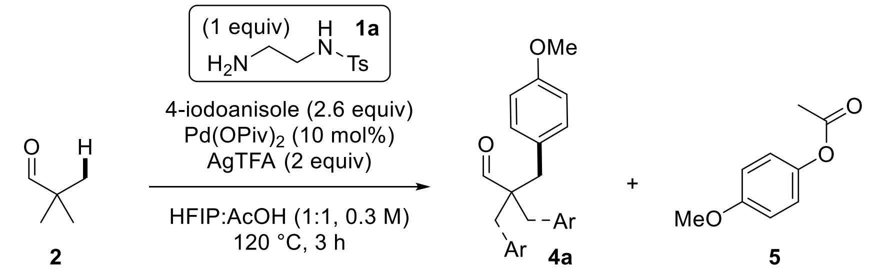


Figure 3.6: Reaction profile for tertiary amine arylation

The graph shows how the amount of 4-iodoanisole decreases as the amount of the arylated products increase. As pivaldehyde is volatile, the amount of this starting material could not be accurately observed. The reaction does not increase in yield after 3 h which could possibly be due to formation of an inactive palladium species. The amount of mono-, di- and triarylated products seems to be at the same ratio at each time point, suggesting that formation of the higher arylated species occurs without the arylated imine leaving the catalytic cycle.

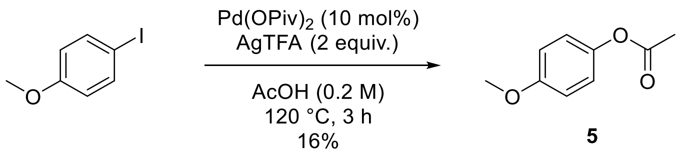
4-Methoxyphenyl acetate **5** (and small amount of 4-methoxyphenol from hydrolysis of this species) was identified as a side-product in the reaction, formed from an unwanted C–O reductive elimination pathway. The formation of **5** was investigated by a series of control reactions (Table 3.9).



Entry	Reaction	total yield 4a (%)[a]	ArOAc 5 (%)[a]	ArI remaining (%)[a]
1	No DG	0	7	17
2	No aldehyde	0	4	79
3	No DG or aldehyde	0	5	15
4	No DG, aldehyde or Pd	0	0	87
5	No DG, aldehyde or Ag	0	trace	75
6	No DG, aldehyde, Pd or Ag	0	0	87

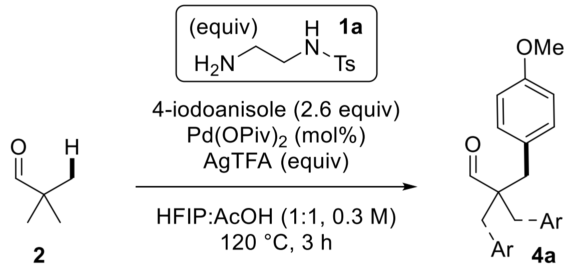
Table 3.9: Investigation of formation of O-acetyl by-product **5**. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

4-Methoxyphenyl acetate **5** could be formed in absence of aldehyde and directing group (Table 3.9, Entries 1-3). When no amine is present the amount of recovered aryl iodide is largely diminished, suggesting that amine-Pd complexes reduce unwanted side reactions with the aryl iodide. The acetoxylated aryl species could also be formed in the absence of silver in small amounts, but the palladium was required. It was concluded that the formation of **5** was therefore a palladium catalysed process, assisted by silver. As this transformation from aryl iodide to aryl-acetoxy using palladium catalysis is currently unprecedented, an attempt to form the acetylated species preferentially was conducted (Scheme 3.6). A low (16%) yield was achieved with 10 mol% $Pd(OPiv)_2$ and 2 equivalents of AgTFA. This reaction was not further investigated.



Scheme 3.6: Formation of ArOAc species

With a shorter reaction time (3 h), the loadings of directing group and catalyst were re-explored, this time changing both equivalencies concurrently (Table 3.10).

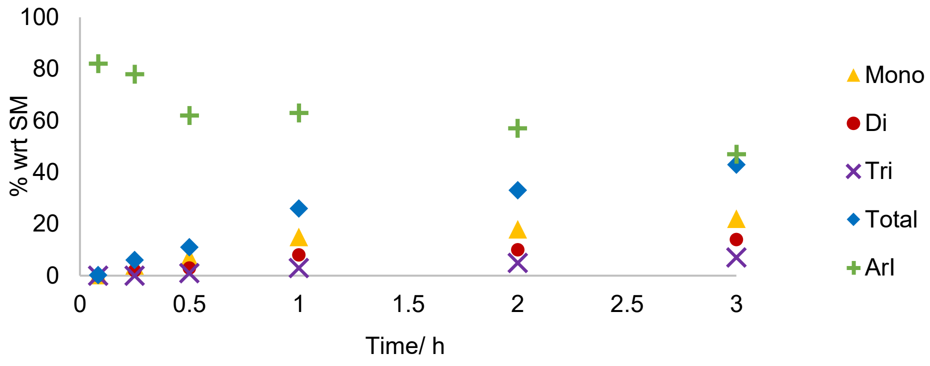


Entry	Pd (mol%)	DG (equiv)	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	10	1	22	16	8	46
2	10	0.5	15	11	5	31
3	7.5	1	21	13	6	40
4	7.5	0.5	24	16	7	47
5	5	0.5	22	15	8	45
6	2.5	0.25	18	11	6	35
7	2.5	0.15	18	11	5	34
8[b]	2.5	0.15	19	11	5	35

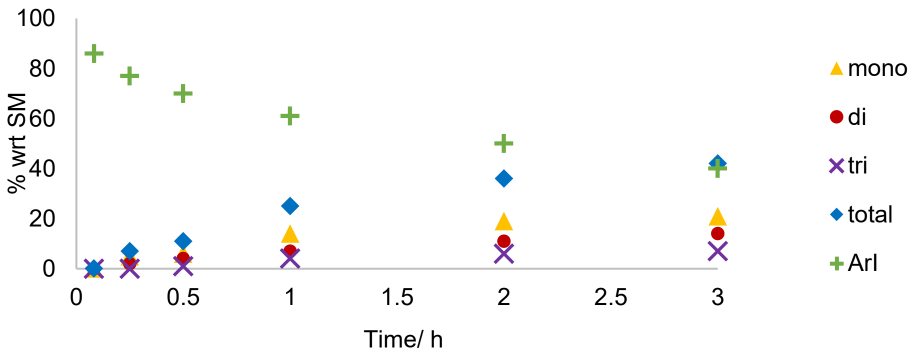
Table 3.10: Reducing the loadings of $Pd(OPiv)_2$ and *N*-tosylethenediamine **1a**. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard [b]6 h.

When using loadings of only 5 mol% catalyst and 0.5 equivalents of DG, similar yields to the higher loading experiments could be obtained. Reducing the amount of catalyst to 2.5 mol% was less tolerated, giving a 35% yield with both 0.25 and 0.15 equivalents of DG, even with an increased reaction time (Entries 6-8).

The effect of the reaction rate upon reducing the amounts of the directing group and catalyst was investigated by obtaining a new reaction profile and comparing with the previous results (Figure 3.7).



a) 10 mol% Pd(OPiv)$_2$, 1 equiv DG

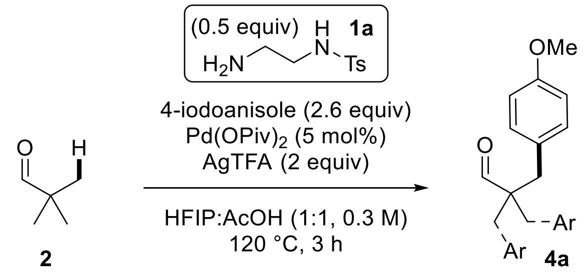


b) 5 mol% Pd(OPiv)$_2$, 0.5 equiv DG

Figure 3.7: Reaction profiles at different Pd and TDG loadings

The profiles of these reactions were astoundingly similar, with what appears to be no increase in rate of reaction when more catalyst and directing group is used. This may be due to limited solubility of the catalyst at increased loadings, or a zero order in Pd. Reagent spiking experiments showed that the addition of extra palladium catalyst, TDG or both once the reaction had reached completion at 3 h, did not result in improved yields.

At this stage additives were again examined, to stabilise palladium intermediates along the catalytic cycle (Table 3.11).



Entry	Additive (equiv)	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	none	22	18	8	46
2	DMSO (0.3)	28	18	9	55
3	DMSO (1)	29	19	8	56
4	DMSO (2)	31	19	7	57
5	H_2O (1)	15	8	4	27
6	KF (0.3)	15	9	5	29
7	KF (1)	14	8	5	27
8	LiCl (0.3)	21	15	8	44
9	LiCl (1)	21	12	6	39
10	DMF (1)	27	18	10	55
11	DMA (1)	24	15	8	47
12	TBAC (1)	9	2	1	12
13	DMPU (1)	22	15	9	46

Table 3.11: Additive screen. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

It was found that one equivalent of DMSO as an additive could improve the yield to 56%. Increasing or decreasing the amount of DMSO had no advantage (Table 3.11, Entries 2, 4). DMF had a similar effect (Table 3.11, Entry 10). When water was present (Table 3.11, Entry 5) the yield was decreased, potentially due to hydrolysis of the imine prior to arylation. Sources of F^- and Cl^- did not increase the yield (Table 3.11, Entries 6–9). DMA and DMPU additives were well tolerated but gave no improvement in yield. TBAC hindered the reaction.

The role of DMSO was investigated by comparing the reaction profiles with and without the additive (Figure 3.8).

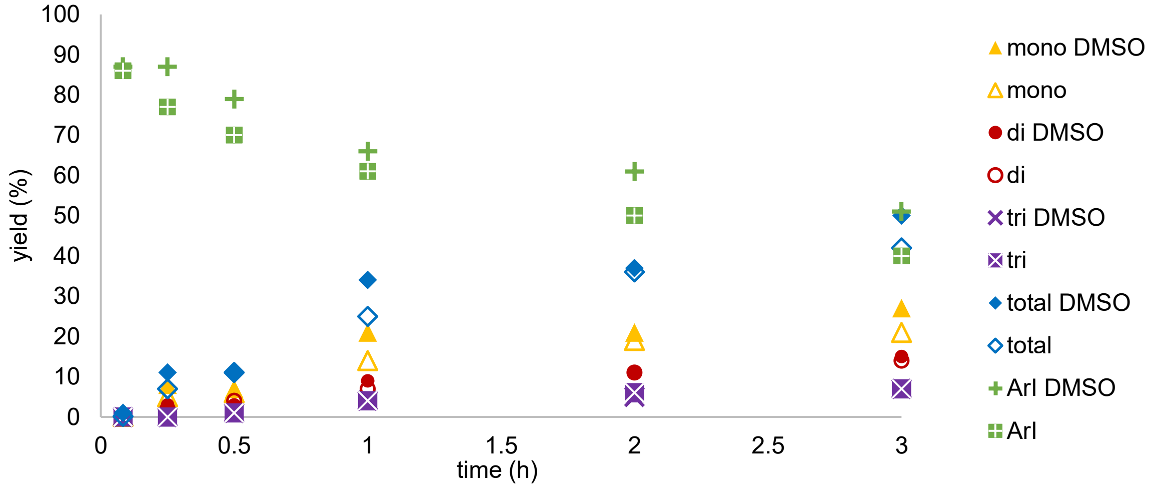


Figure 3.8: Reaction profile comparing conditions with and without the DMSO additive

The improved yield with the DMSO could potentially be explained by the initial reduced breakdown of the aryl iodide (despite an increased yield) meaning that the additive may be reducing the abundance of unwanted side reactions between the aryl iodide and palladium such as protodehalogenation or biaryl formation.

The use of AgTFA in place of AgOAc appeared to have a dramatic effect on the success of the reaction, despite the high concentration of acetic acid. This phenomenon was investigated by using AgOAc as the silver source and adding increasing amounts of trifluoracetic acid as an additive (Figure 3.9).

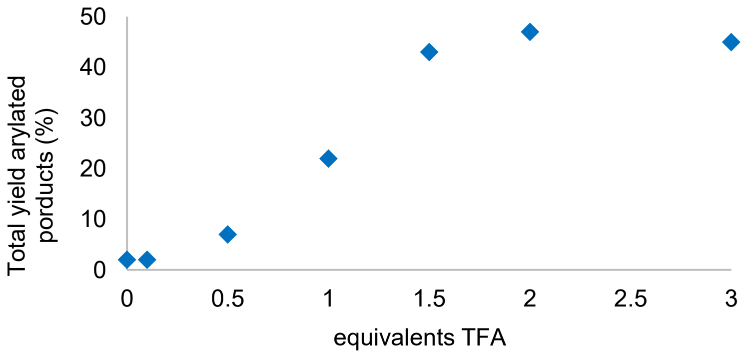
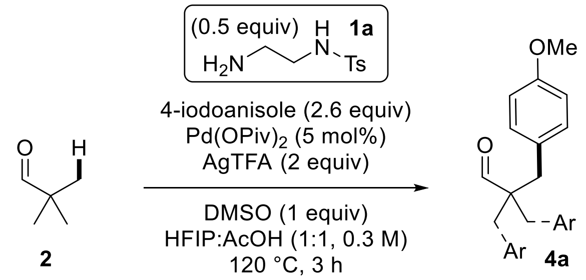


Figure 3.9: Effect of TFA concentration when using 2 equivalents of AgOAc

A positive trend in yield with the amount of TFA added was observed, which plateaued after 2 equivalents. This experiment highlighted the potential to use cheaper AgOAc as a silver source to give comparable yields to AgTFA when using free TFA as an additive.

With an ideal additive selected (DMSO), a final set of experiments (changing the loading of aryl iodide, silver source, temperature and concentration) was conducted (Table 3.12).

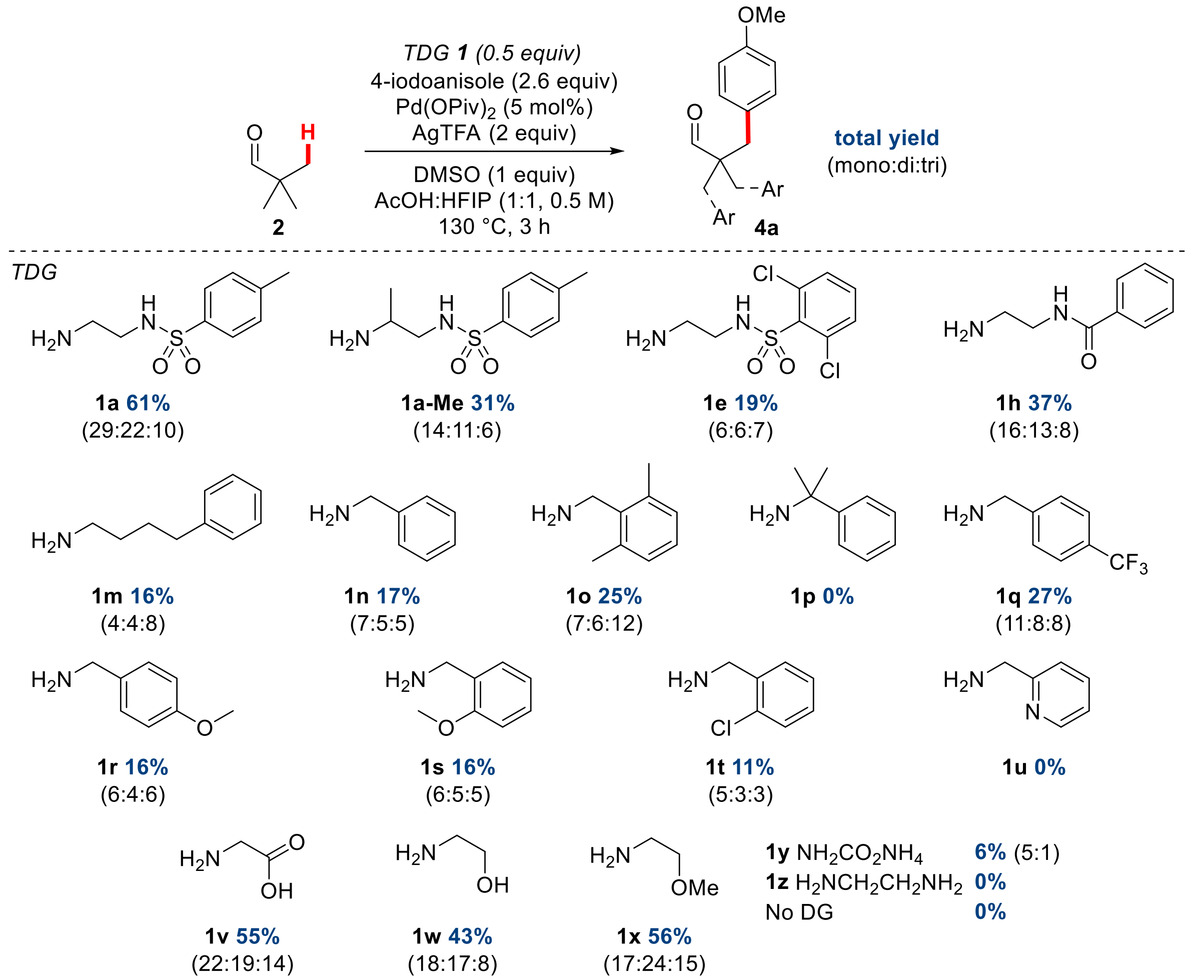


Entry	Description	yield 4a-mono (%)[a]	yield 4a-di (%)[a]	yield 4a-tri (%)[a]	total yield (%)[a]
1	Control	**29**	**19**	**8**	56
2	4 equiv. ArI	26	17	8	52
3	3 equiv. Ag	28	18	10	57
4	0.1 M	27	18	8	53
5	0.5 M	29	21	9	59
6	130 °C	29	19	8	57
7	0.5 M + 130 °C	30	23	10	61
8	3 equiv. Ag + 0.5 M	21	14	8	43

Table 3.12: Variation of reaction parameters. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Higher equivalents of aryl iodide or silver did not have a significant impact on product yield. Increasing both the concentration and temperature appeared to be advantageous (Table 3.12, Entries 5,6). Combining these changes gave an increased yield of 61% by ^1H NMR (Table 3.12, Entry 7). A higher silver loading with an increased concentration gave a decreased yield.

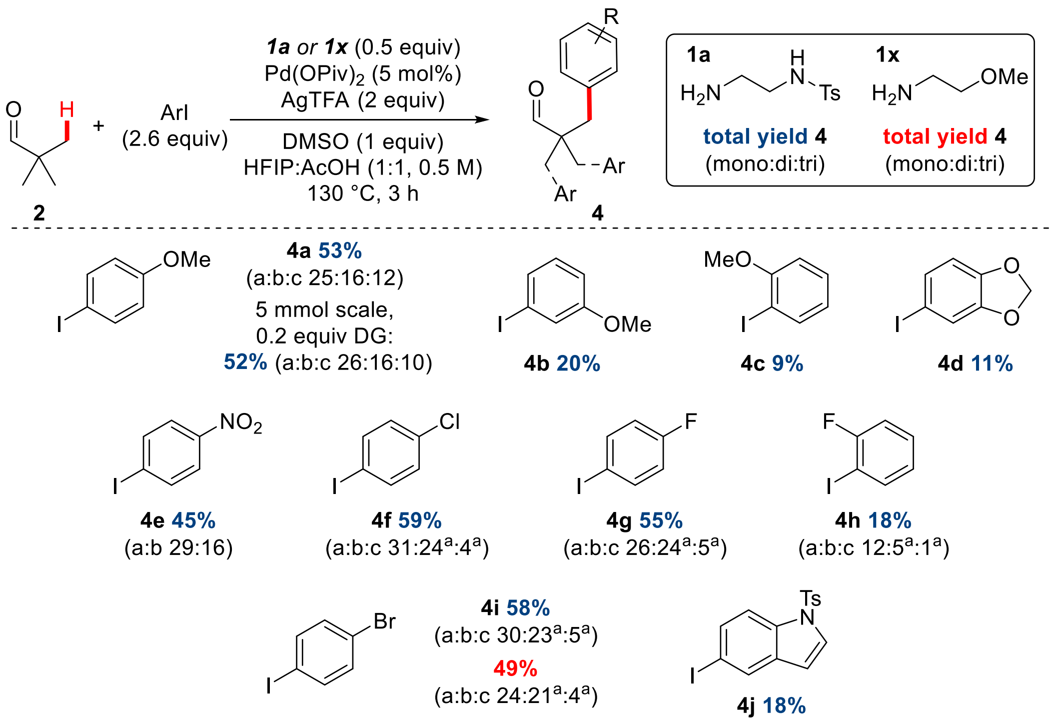
With the optimised reaction conditions, the structure of the (now transient) directing group was investigated, by using alterative amines to *N*-tosylethenediamine **1a** (Scheme 3.7). Both bidentate and monodentate transient directing groups were tested, as well as some examples with oxygen-based secondary binding sites.



Scheme 3.7: Transient directing groups for direct C–H arylation of pivaldehyde. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Hindering imine formation by putting a methyl group adjacent to the amine (**1a-Me**) led to a reduced yield of 31%. Bulky 2,6-dichlorosulfonamide **1e** was less effective that the tolyl, as was the previously highly active phenyl amide **1h**. Monodentate transient imines could promote the reaction in lower yields (**1m-r**). From the series of benzylamines tested, the most effective were hindered **1o** and electron poor **1q**. Coordinating 2-methoxy or 2-chloro substituents on the benzylamine (**1s**, **t**) did not lead to an increased product yield through chelation. Picolylamine **1u** coordinated strongly to the catalyst in its free amine form, leading to full inhibition. Some oxygen-based secondary binding groups were also investigated (**1v-x**). Under these conditions, Yu's glycine **1v**[80] could promote the reaction in good yields with a slightly higher tendency to form di- and triarylated products compared to *N*-tosylethylenediamine **1a**. Unexpectedly, simple amino alcohol **1w** and amino ether **1x** could also promote the reaction in good yields, and like the acid there was a slightly higher tendency to form the higher arylated products. Interestingly, a simple NH imine formed from an ammonia source (ammonium carbamate, **1y**) could also promote the reaction in low yield. Like the picolylamine, ethylenediamine **1z** resulted in competitive catalyst coordination, deactivating the reaction. Crucially when no amine is present, the free aldehyde was unable to promote any amount of arylation.

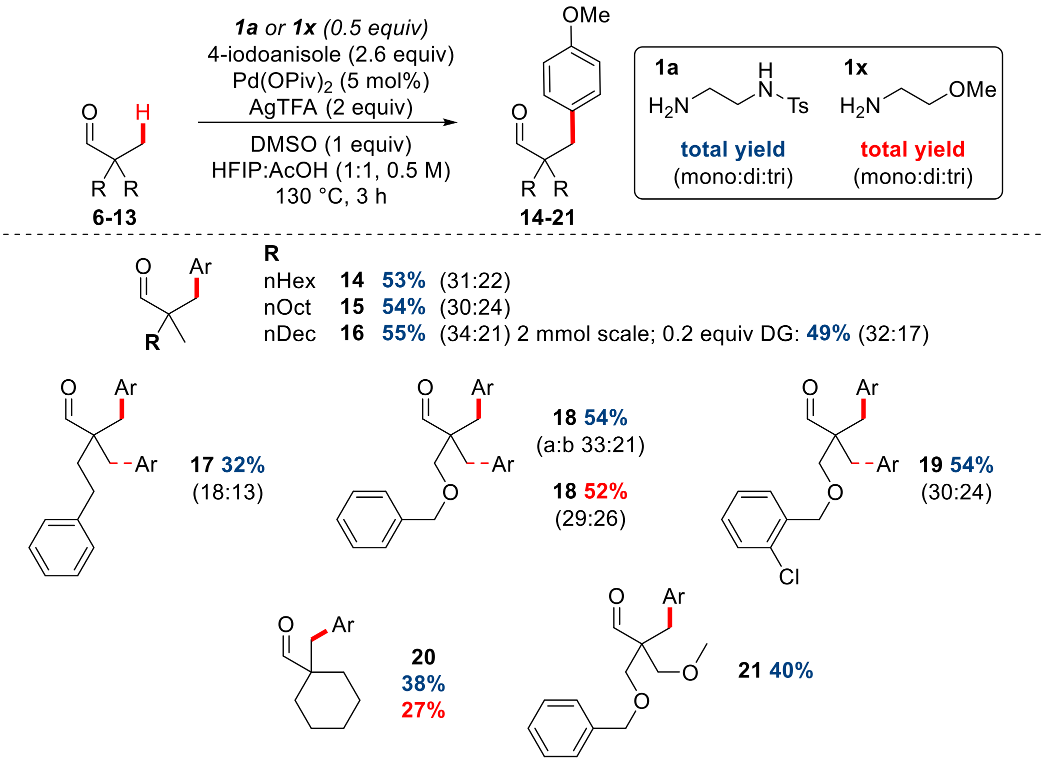
With the best directing groups (**1a** and **1x**) the scope of the reaction was investigated, starting with the aryl iodides (Scheme 3.8).



Scheme 3.8: Direct C–H arylation of pivaldehyde with aryl iodides, 0.4 mmol scale. [a]Isolated as a mixture of di- and triarylated products

For 4-iodoanisole, the products **4a** (**4a-mono, 4a-di, 4a-tri**) were isolated in a 53% total yield with separation of the mono-, di- and triarylated species by column chromatography. The reaction using this substrate was amenable to a larger (5 mmol) scale using only 0.25 equivalents of the directing group, affording the products in comparable yield. Walking the methoxy substituent around the ring to the *meta-* and *ortho*-positions led to sequentially lower yields, highlighting the limitation of steric hinderance of the aryl iodide (**4b-c**). The electron poor (and largely insoluble) 4-nitroiodobenzene formed the arylated aldehyde products (**4e**) in 45% yield. *para*-Halo-substituted aromatic groups were all installed in good yields (**4f-g, i**). For these examples, due to the less significant polarity changes, the di- and triarylated products were isolated as a mixture. 2-Fluroiodobenzene gave a higher yield than the 2-iodoanisole, reflecting the lower steric influence of the fluoro group. For 4-bromoiodobenzene the reaction was also demonstrated using methoxy ether TDG **1x**, which gave a slightly lower yield with more di- and triarylation, as expected. *N*-Tosyl indole could be incorporated in 18% yield of the monoarylated product **4j-mono**.

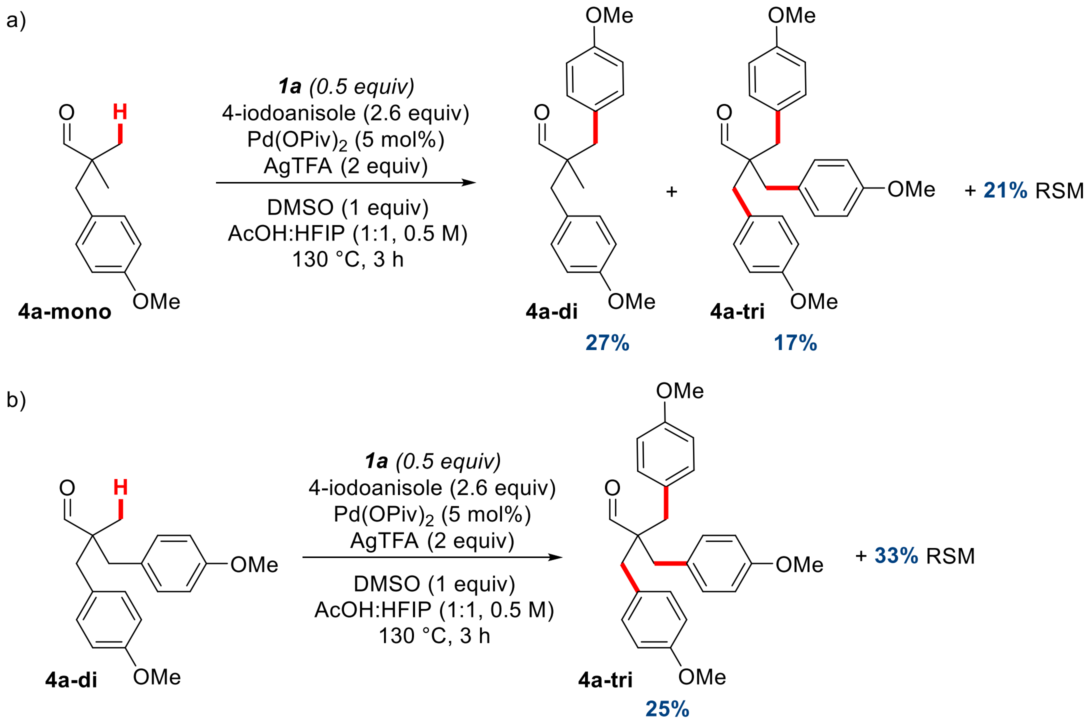
The aldehyde scope was also investigated (Scheme 3.9).



Scheme 3.9: Direct C–H arylation of various aldehydes using 4-iodoanisole, 0.4 mmol scale

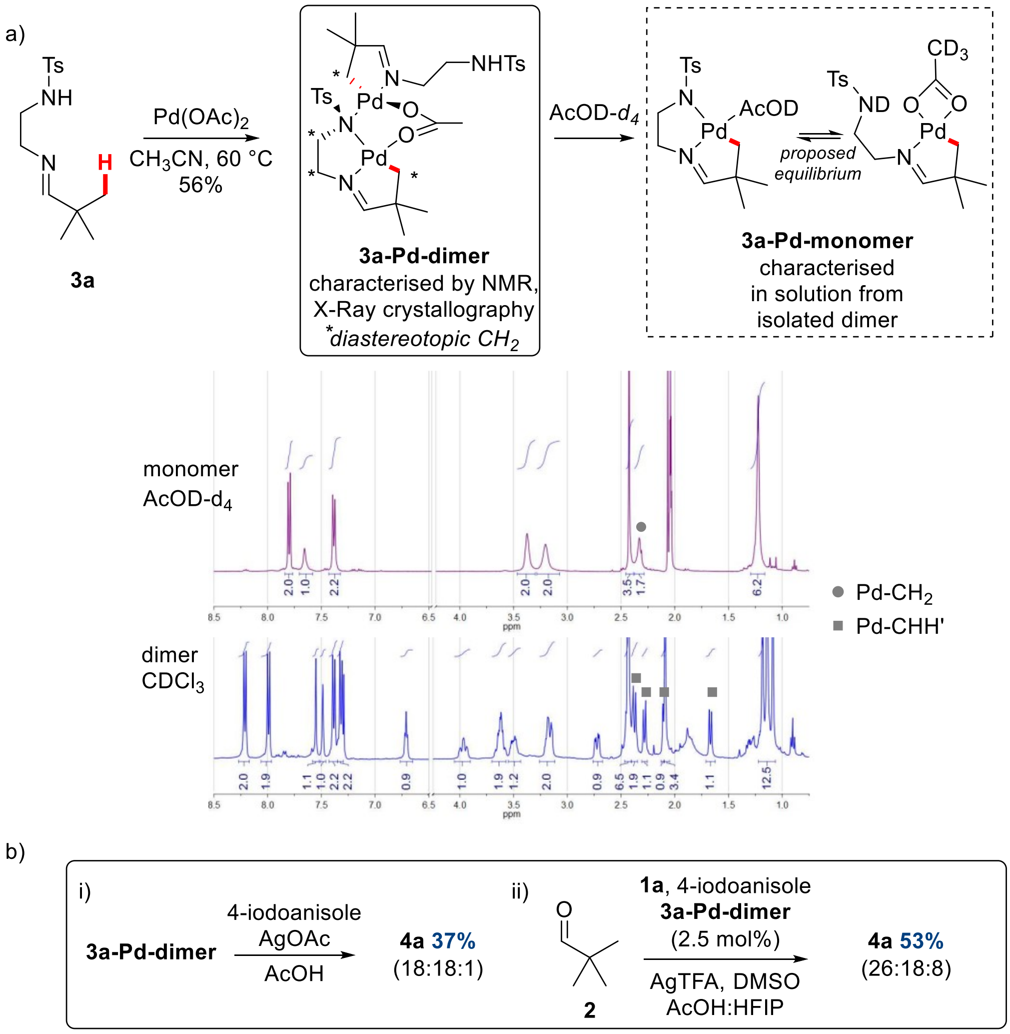
Altering the length of the R group on the aldehyde had little effect on the yield of the reaction (**14-16**). For product **16**, the reaction was also shown to be scalable, with a lower loading of amine **1a** required. The reaction was tolerant of coordinating ether and bis-ether functional groups. Again the simple TDG **1x** was used which produced arylated products **18** and **20** in good yields.

When using the mono- (**4a-mono**) and diarylated (**4a-di**) pivaldehyde products as substrates in the reaction, further arylation readily occurred (Scheme 3.10). This suggests that as well as continuing around the catalytic cycle, the arylated imines can be hydrolysed, re-formed and re-enter the cycle. In both these reactions, the mass recovery is poor (around 50%). This feature has been apparent across the whole project and is most likely a result of unwanted oxidation pathways (to the acid) or removal of insoluble complexes during the silica filtration work-up.



Scheme 3.10: Further arylation of the arylated products **4a-mono** and **4a-di.** Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

For further understanding of the reaction mechanism, a palladacycle was formed from heating pre-formed imine **3a** with $Pd(OAc)_2$ in acetonitrile for 4 h (Scheme 3.11a). Following a simple workup (dissolve the residue in toluene, filtration through Celite and evaporation) an unusual and unsymmetrical palladium dimer **3a-Pd-dimer** was formed. The structure was unambiguously assigned by single crystal X-ray diffraction (Figure 3.10). Each Pd centre demonstrated a different potential binding mode of the optimal imine directing group, either monodentate or bidentate. This observation was of interest, as the lability of the secondary binding site was previously implied by the lack of trend on modification of this site's properties in the imine arylation experiments (Scheme 3.4). The structure also contained an unusual sulfonamide N-bridge, and there are limited examples of this type of ligand in the literature.[105–107] Dissolving the dimer in deuterated acetic acid led to simplification of the NMR, from formation of a monomeric species, which was characterised in solution. Due to the broad acetate and ethylene DG backbone signals, there is a likely equilibrium between chelation of the DG or the acetate, which may have a beneficial effect on intermediates in the catalytic cycle. **3a-Pd-dimer** was an active substrate under the imine arylation conditions and a highly active catalyst under the aldehyde arylation conditions (Scheme 3.11b). This supports that related cyclometalated species are present in the catalytic cycle.



Scheme 3.11: Palladacycle formation experiments. Arylation yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Conditions for bi) **32-Pd-dimer** (0.04 mmol), 4-iodoanisole (2.6 equiv), AgOAc (2 equiv), AcOH (0.3 M), 120 °C, 24 h, bii) Pivaldehyde (0.2 mmol), **1a** (0.5 equiv), 4-iodoanisole (2.6 equiv), **3a-Pd-dimer** (2.5 mol%), AgTFA (2 equiv), DMSO (1 equiv), AcOH:HFIP (1:1, 0.5 M).

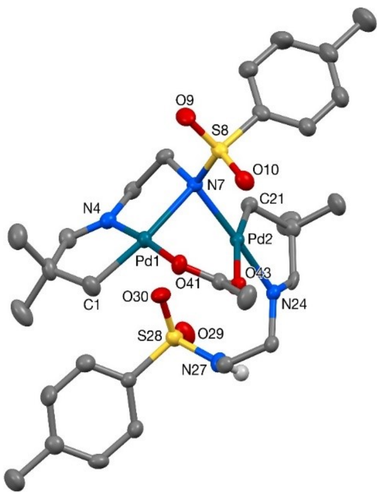


Figure 3.10: Crystal structure of **3a-Pd-dimer** showing alternate binding modes of the directing group

Formation of the palladacycle was observed *in situ* by ^{1}H NMR in deuterated acetonitrile at 60 °C (Figure 3.11).

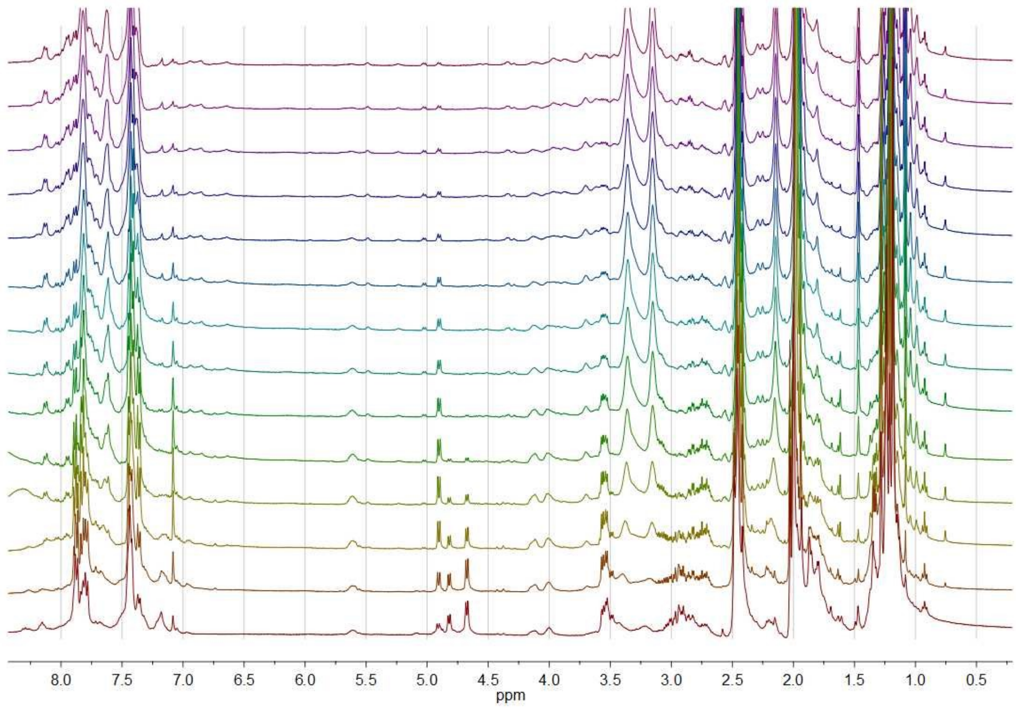
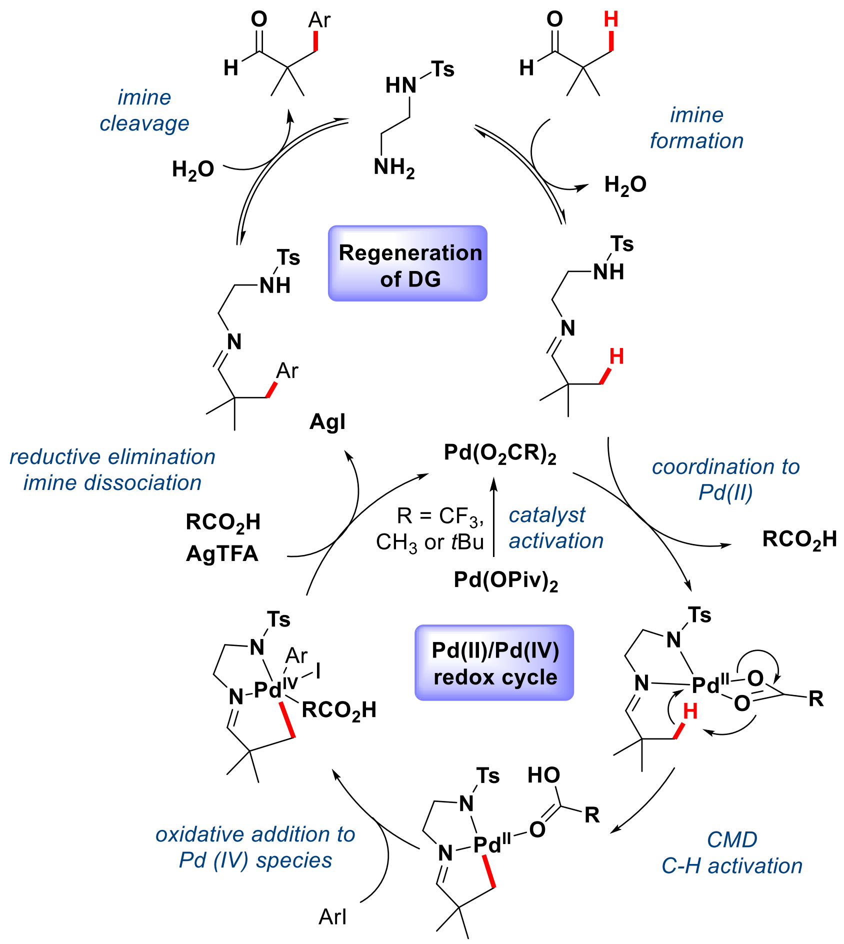


Figure 3.11: ^{1}H NMR spectra of cyclometalation of **3a** by palladium acetate in 5-minute increments for the first 60 minutes (bottom to top)

The experiment showed rapid coordination of the catalyst to the imine and gradual cyclometalation, to give the simplified signals of a palladacycle monomer (CH_2's of the ethylene diamine chain at 3.12 and 3.36 ppm and Pd-CH_2 at 2.17 ppm). This cyclometalation occurs progressively at 60 °C reaching maximum conversion after 80 minutes. The gradual disappearance of the broad signal at 5.6 ppm may correspond to the deprotonation and binding of the sulfonamide N. Sharp peaks between 4.5–5.0 ppm may be indicative of a coordinated, charged intermediate Pd species prior to this deprotonation.

Based on these findings, a proposed catalytic cycle for the tertiary aldehyde arylation is given in Scheme 3.12.



Scheme 3.12: Proposed catalytic cycle for direct arylation of tertiary aldehydes with a TIDG

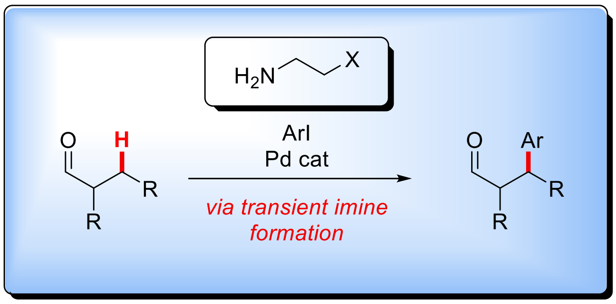
Under the reaction conditions, the aldehyde condenses with the catalytic amount of amine additive to form the active imine directing group. This coordinates to an activated (loss of pivalate and replaced most likely with TFA) Pd^{II} catalyst with deprotonation of the sulfonamide nitrogen. This complex can undergo redox neutral CMD, affording a palladacycle monomer, the structure of which is supported by the palladacycle studies. To this, oxidative addition of the aryl iodide generates a Pd^{IV} aryl intermediate which reductively eliminates. Dissociation of the catalyst gives the arylated imine. The role of the silver in this case is to abstract the iodide from the palladium and provide a new TFA ligand for palladium. The arylated imine is hydrolysed *in situ* to furnish the arylated aldehyde product and regenerate the *N*-tosylethylenediamine TDG.

In conclusion, direct Pd-catalysed arylation of tertiary aldehydes was realised, using simple and catalytic *N*-tosylethenediamine **1a** or 2-methoxyethan-1-amine **1x** to form transient imine directing groups. The scope of both the aldehyde and aryl iodide were explored, and mechanistic details were supported through stoichiometric Pd experiments and NMR studies. For a concise account of this project, see: *Chem., Sci.,* **2017**, 4840.[108]

3.2 Methylene $C(sp^3)$–H Arylation of Secondary Aldehydes

Under the conditions optimised for the tertiary aldehydes (Section 3.1), poor mass recovery and only trace arylation was observed when using secondary aldehydes. This was likely due to the relatively harsh reaction conditions employed (strong acid, 130 °C). A second limitation was the chemoselectivity for β-methyl C–H bonds, with methylene positions being inert to the C–H arylation.

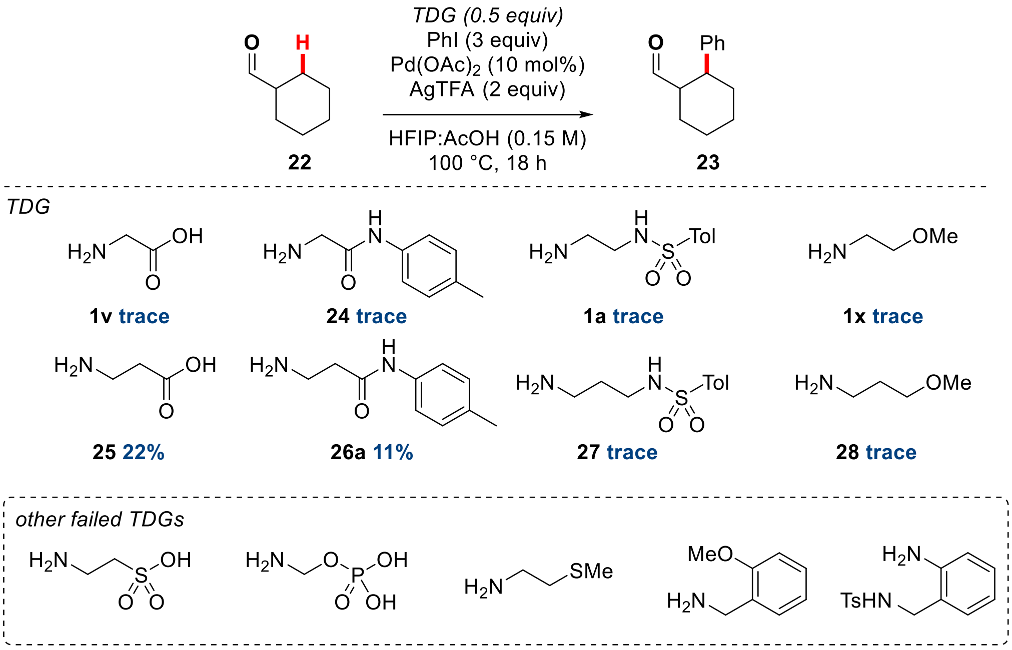
The next stage of the project was to overcome these limitations to enable i) arylation of more unstable secondary and potentially primary aliphatic aldehydes and ii) improved reactivity to realise methylene C–H activation (Scheme 3.13).



Scheme 3.13: Aim: methylene C–H functionalisation of secondary aldehydes

As Ge had observed low reactivity with cyclohexanecarboxaldehyde when using β-alanine as a TDG,[84] alternative directing groups would be tested using this aldehyde as the model substrate (Scheme 3.14). Milder reaction conditions were used (lower concentration and temperature) in efforts to improve the mass recovery.

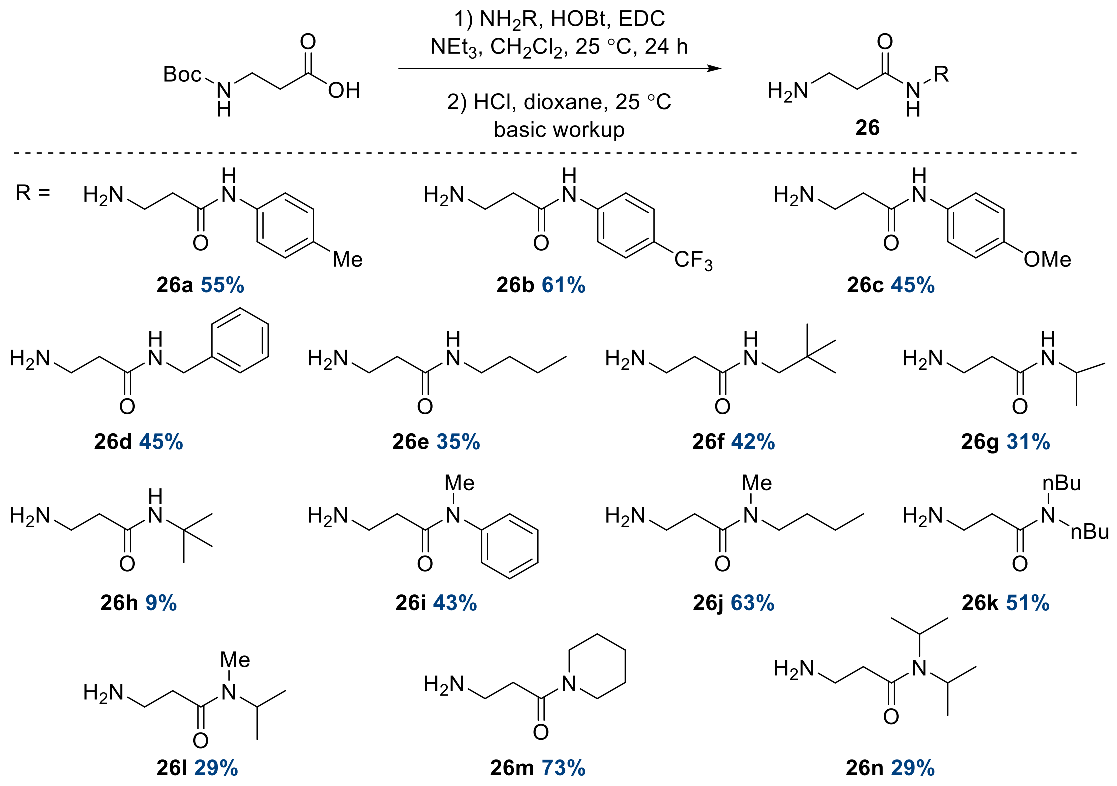
Directing groups were selected to explore a variety of secondary binding groups. Additionally, direct comparisons of 5- and 6-membered chelates were provided for amino acid, amino amide, sulfonamide and methyl ether examples. Yu has demonstrated how increasing the chelation from 5- to 6-membered rings may facilitate the functionalisation of methylene groups by minimising steric repulsion for both ligand-assisted and transient imine $C(sp^3)$–H functionalisations.[89,109]



Scheme 3.14: Initial screen of directing groups for the methylene β-C–H arylation of cyclohexanecarboxaldehyde. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

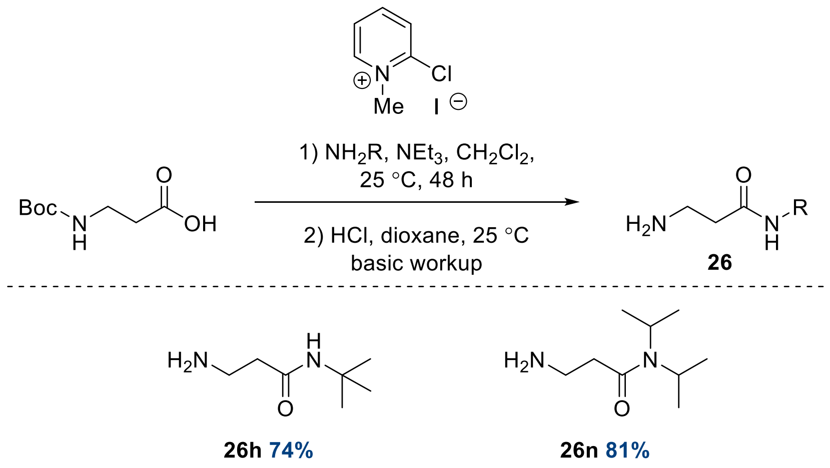
Iodobenzene was selected as the coupling partner as the product was known in the literature for comparison. It was found that under these conditions only β-alanine **25** and an amide analogue **26a** were capable of promoting the methylene C(sp^3)–H arylation of cyclohexanecarboxaldehyde **22**. The equivalent acid (glycine, **1v**) or amide (**24**), which would form a smaller 5-membered chelate, did not form significant amounts of the arylated product **23**. A sulfonic acid (taurine) and phosphoric acid were tested, as well as some selected aromatic examples and a simple thioether, but all failed to form the desired product. The reactivity of amide **26a** was a key result as this enabled the investigation of other amide analogues of β-alanine, to formulate a more effective TDG.

A library of β-alanine amides was synthesised in two steps from *N*-Boc-β-alanine (Scheme 3.15).



Scheme 3.15: Synthesis of amino-amide directing groups

Yields for the amide products were variable and related to the low reactivity of the hindered amines. *tert*-Butyl **26h** and diisopropyl **26n** amides were formed in improved yields with an alternative amide coupling agent (Scheme 3.16).



Scheme 3.16: Synthesis of amino-amide directing groups with 2-chloro-1-methylpyridinium iodide

The library of β-alanine amides **26a-n**, primary amide **29**, as well as a benzyl derivative of the DIPA amide (**30**) were tested under the arylation conditions. These conditions were improved from the initial directing group screen and used a lower temperature, 0.25 equivalents of the directing group and a longer reaction time. Each transient directing group led to arylation of cyclohexanecarboxaldehyde **22**, forming both monoarylated aldehyde **23-mono** and diarylated aldehyde **23-di**. An aqueous work-up was required to remove acetic acid and allow more accurate calculation of the yields by ^{1}H NMR using the aldehyde signals of the products (**23-mono:** δ = 9.42 ppm(d) and **23-di:** δ = 9.26 ppm (d)). Data has been compiled into a graph for easier comparison of total yield, with the monoarylated product yield shown in blue and diarylated product yield in red (Figure 3.12). Each bar represents the average of two experiments, where the results were within 5% yield.

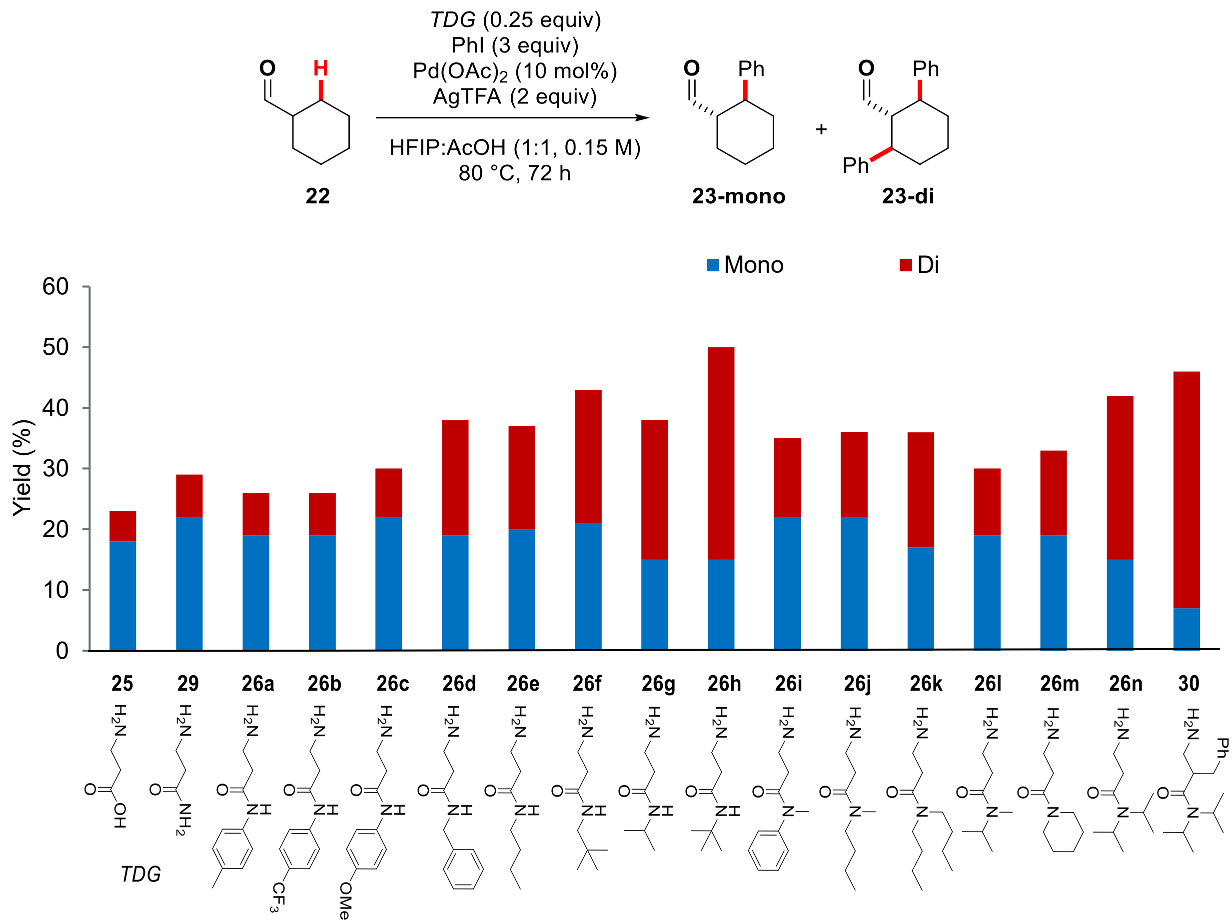


Figure 3.12: Screen of β-alanine derivatives for the methylene β-C–H arylation of cyclohexanecarboxaldehyde. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Under the improved conditions, the original hit amino amide **26a** resulted in a higher total yield of the arylated products than β-alanine **25**. Primary amide **29** also gave good yields. The highest total yield of **23** was achieved using *tert*-butyl amide **26h** as the TDG. Aliphatic secondary amides (**26d-h**) gave generally improved total yields compared to the aromatic amides (**26a-c**). More hindered aliphatic amides were more effective. Interestingly, tertiary amides could also promote the arylation (**26i-n**). Again, more hindered examples gave improved yields of **23**, with the best tertiary amide being diisopropylamide **26n**. The reactivity of the tertiary amides provides evidence for O- over N-chelation, with a neutral secondary binding group. This provided novelty over existing methods which use acids as anionic chelating groups.[i] An analogue of the DIPA amide TDG, substituted at the α-position of the amide with a benzyl group (**30**),[89] was synthesised. Benzyl derivative **30** gave a high total yield with a large ratio of diarylation.

Both mono- and diarylated species were determined to be the *trans* stereoisomers by careful consideration of the observed multiplicities and *J* values for the C*H*CHO and C*H*CH$_2$Ph protons in the ^{1}H NMR spectra (Figure 3.13).

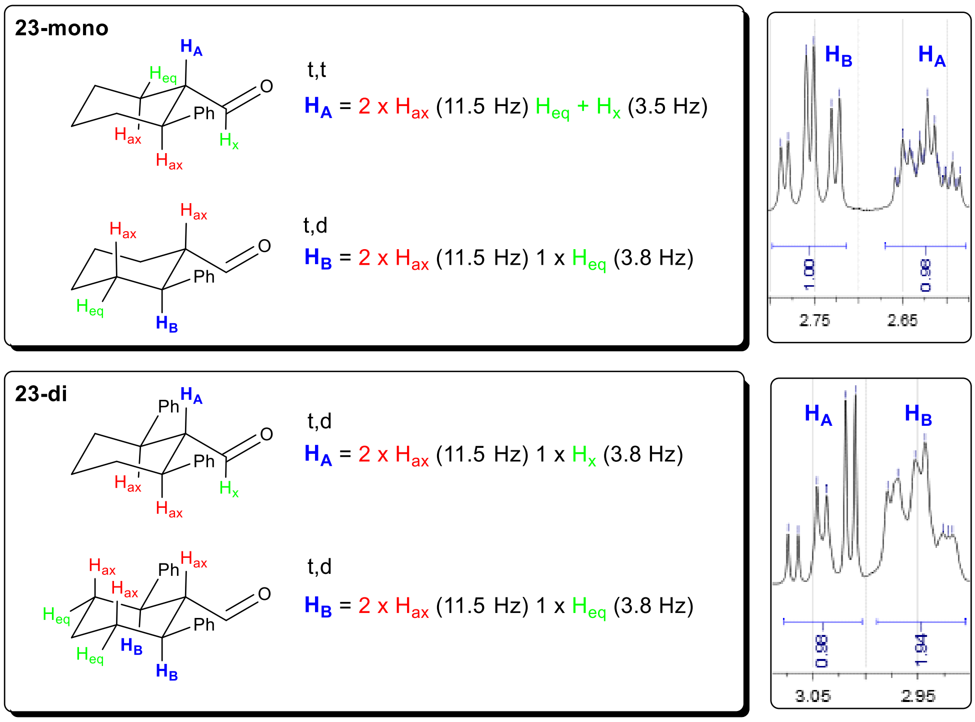


Figure 3.13: *Trans* determination of the arylated products

On the monoarylated species, the C*H*CH$_2$Ph signal (H_B) is more downfield, this switches in the diarylated species due to the additional neighbouring benzylic centre deshielding the C*H*CHO (H_A) position. The multiplicities of both H_A and H_B signals for both the mono- and diarylated species is consistent with the proposed *trans*-geometry. The *cis*-diastereomers

[i] Yu later published an example of an amino-tertiary amide directing group, showing chelation of the carbonyl oxygen through X-ray crystallography, see reference 83.

would observe significantly different splitting patterns. In Ge's aldehyde study, a *cis*-geometry of the monoarylated product **23-mono** is proposed by NOE NMR.[84] The spectra obtained by Ge was identical to those obtained here however, so there is contradiction in the proposed diastereoselectivity. Although the *trans*-species are the major products, some unknown aldehydes are present in the ^{1}H NMR spectra of the crude reaction mixtures. Although not isolated and characterised, these signals may correspond to small amounts of the *cis*-diastereomers of the arylated products. Additionally, the presence of α-β-unsaturated aldehydes is likely, as many of the unknown aldehydes have an absence of splitting of the aldehydic C–H.

The change in total yield of the arylated products over time when using β-alanine **25**, *tert*-butyl amide **26h** and DIPA amide **26n** were investigated (Figure 3.14). These experiments were carried out by discrete reactions following a filtration through silica.

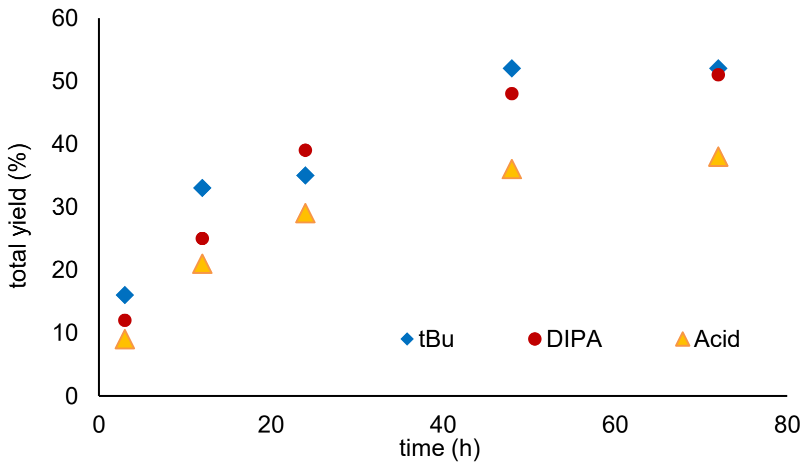


Figure 3.14: Rate of formation of arylated cyclohexanecarboxaldehyde products **23** using *tert*-butyl amide **26h** (blue), DIPA amide **26n** (red) and β-alanine **25** (yellow)

The reaction is sluggish, slowly progressing over the 72 h range tested. The rate of formation of the arylated products for the amides **26h** and **26n** were similar, and notably higher than when using the amino acid **25**.

The formation of the mono- and diarylated products over time was also monitored for each of these TDGs (Figure 3.15).

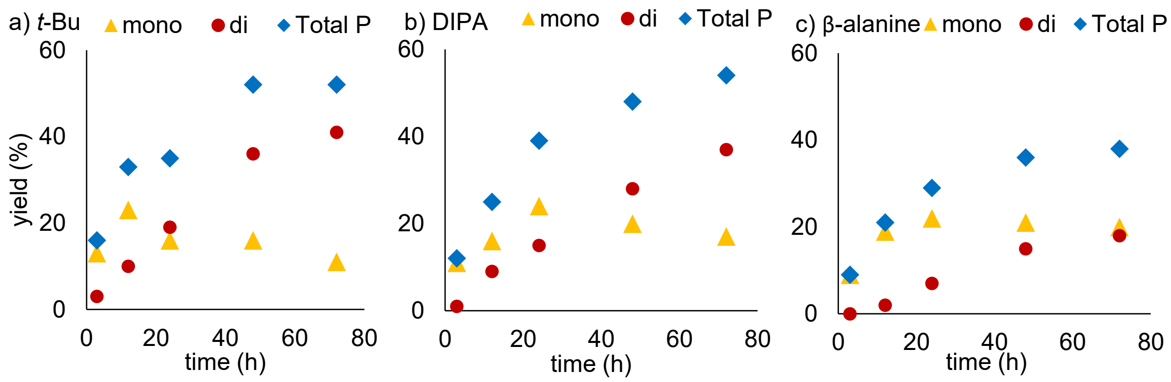
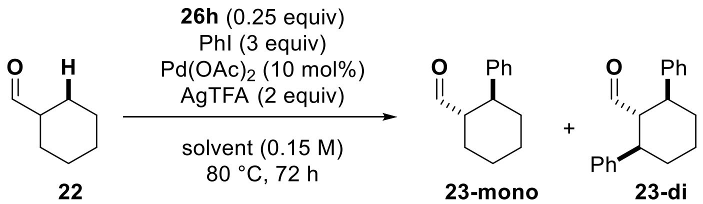


Figure 3.15: Reaction profile with select directing groups a) *t*-Bu amide **26h,** b) DIPA amide **26n** and c) β-alanine **25**

In the tertiary aldehyde study, the mono-, di- and triarylated products are formed at essentially equal rates (see Figure 3.6). For each case here, it appears that the monoarylated product is formed first, reaching a maximum at 12 h for the *tert*-butyl amide (a) and 24 h for the DIPA amide (b) and amino acid (c). The monoarylated product **23-mono** is then gradually converted to the diarylated species **23-di** over time. Both amide directing groups (graphs a and b) reached similar final total yields in these experiments, however the ratio of diarylation was higher for *tert*-butylamide **26h**. Arylation of the aldehyde using β-alanine (c) was slower, reaching a lower total yield and equal amounts of the mono- or diarylated products at 72 h. In each case, conversion from **23-mono** to **23-di** appears to continue over time, so that the total number of arylations may continue to increase beyond the 72 h time tested. As the *tert*-butyl directing group **26h** gave the highest total yield when comparing the amides, optimisation was conducted using this TDG. Firstly the solvent was investigated (Table 3.13).



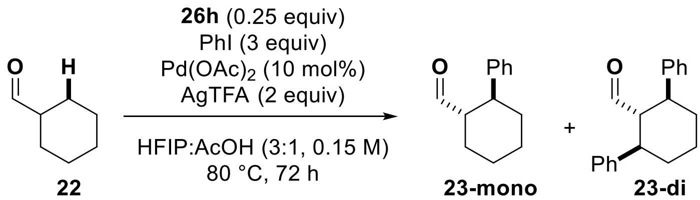
22 **23-mono** **23-di**

Entry	Description	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	1:1 (HFIP:AcOH)	15	35	50
2	1:3 (HFIP:AcOH)	21	19	40
3	3:1 (HFIP:AcOH)	11	40	51
4[b]	3:1 (HFIP:AcOH)	9	39	48
5	5:1 (HFIP:AcOH)	10	37	47
6	AcOH	15	2	17
7	HFIP	20	3	23

Table 3.13: Solvent screen. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]With DIPA amide **26n**.

Changing the ratio of HFIP:AcOH impacted the yield of **23**. Generally larger proportions of HFIP gave higher total yields and more diarylation up to when a 3:1 ratio was used, which gave the best total yield of 51%. DIPA amide **26n** gave a similar yield under these conditions (Table 3.13, Entry 4). As seen in the tertiary aldehyde arylation (Section 3.1) either AcOH or HFIP alone gave lower arylation yields than the mixtures.

A selection of additives was then investigated (Table 3.14).

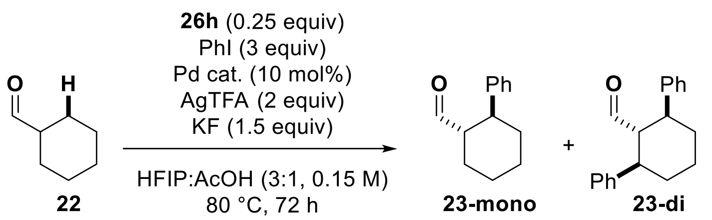


Entry	Additive (equiv)	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	None	11	40	51
2	DMSO (1)	6	37	43
3	DMF (1)	9	37	46
4	H_2O (0.5)	12	37	49
5	H_2O (1)	9	44	53
6	H_2O (2)	10	39	49
7	KF (0.5)	11	38	49
8	KF (1)	9	45	54
9	KF (1.5)	14	44	58
10	KF (2)	11	42	53
11	PivOH (0.5)	13	34	47
12	MesCOOH (0.5)	13	33	46

Table 3.14: Additive screen. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Although beneficial for the tertiary aldehyde arylation (see Section 3.1), DMSO and DMF led to a slight drop in yield in this case (Table 3.14, Entries 2,3). Water was very well tolerated, with a slight improvement in yield when adding 1 equivalent (Table 3.14, Entry 5). Potassium fluoride also led to improved yields, and at 1.5 equivalents a 58% yield could be achieved (Table 3.14, Entry 9). This additive was therefore retained for further optimisations. The presence of bulky acids PivOH or MesCOOH led to a slight drop in yield (Table 3.14, Entries 11-12).

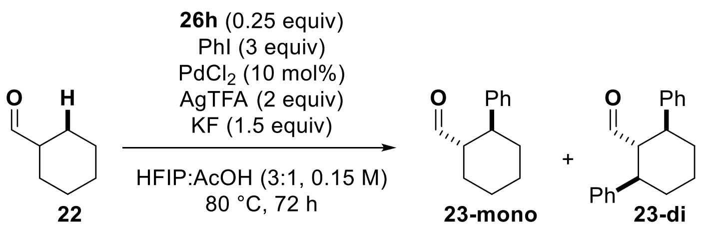
The palladium source was then explored (Table 3.15).



Entry	Pd pre-catalyst	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	$Pd(OAc)_2$	14	44	58
2	$PdCl_2$	19	38	57
3	$Pd(OPiv)_2$	14	42	56
4	$Pd(TFA)_2$	11	42	53

Table 3.15: Pre-catalyst screen. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Palladium chloride gave a comparable yield to palladium acetate and a slightly cleaner crude reaction mixture, so it was selected as the optimal pre-catalyst. Morpholine, dioxane and HCl were tested as additives in conjunction with the potassium fluoride (Table 3.16).

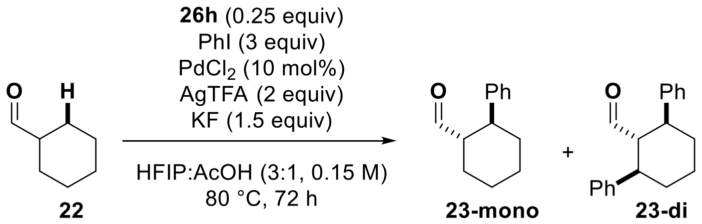


Entry	Additive (0.5 equiv)	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	none	19	38	57
2	Morpholine	9	26	35
3	Dioxane	19	25	44
4	HCl_{aq} (37%, 3 drops)	22	9	31

Table 3.16: Additives screen. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Morpholine and dioxane were investigated as additives with the aim to break up potentially inactive Pd aggregates, but both led to reduced yields. Although with HCl the yield was decreased, good mono-selectivity was observed.

As a total yield of ~60% had been reached, the selectivity of the reaction was then investigated. The aim was to reach maximum yields of either the mono- *or* diarylated products, to form synthetically useful quantities of these desirable building blocks. To improve mono-selectivity, the strategy was to use the aldehyde in excess, change the solvent system and to use toluene as an additive, which could potentially pull the more lipophilic arylated products out of the polar reaction media (Table 3.17). When using the aldehyde in excess, the iodobenzene became the limiting reagent which was used in the same quantity (0.20 mmol) as the aldehyde was used in all prior experiments, so that all other reagents were used in the same amounts.



Entry	Change from conditions	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	none	19	38	57
2	Aldehyde in excess (1.5:1)	30	11	41
3	Aldehyde in excess (1.2:1)	28	16	44
4	Aldehyde in excess (1.2:1), 9:1 HFIP:AcOH	19	24	43
5	Toluene additive (0.1 mL)	15	45	60
6	Toluene additive (0.2 mL)	10	36	46
7	Toluene additive (0.05 mL)	17	45	62
8	Xylene additive (0.1 mL)	12	50	62
9	Xylene additive (0.05 mL)	14	41	55
10	Xylene additive (0.025 mL)	6	38	44
11	trifluorotoluene additive (0.05 mL)	13	46	59
12	Heptane additive (0.05 mL)	8	37	45

Table 3.17: Optimisation for mono- or diarylation, 0.2 mmol scale. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

With the aldehyde in excess, improved mono-selectivity was achieved and a 30% yield of the monoarylated product **23-mono** could be reached using 1.5 equivalents of cyclohexanecarboxaldehyde **22**. A similar monoarylation yield was obtained when 1.2 equivalents of aldehyde was used, though more diarylation occurred over the 72 h reaction time. With 1.2 equivalents of aldehyde, a 9:1 HFIP:AcOH solvent system switched the selectivity back to diarylation (Table 3.17, Entry 4). Interestingly (with PhI in excess), when adding a small amount of toluene, an improved yield was observed, with a high proportion of diarylation (Table 3.17, Entry 5). Increasing the amount of toluene was detrimental but lowering the volume to 0.05 mL increased the yield further (Table 3.17, Entry 7). Other non-polar co-solvents were also tested. Xylene in place of toluene gave a 50% yield of **23-di** (Table

3.17, Entry 8). Use of less xylene (0.05 mL,Table 3.17, Entry 9) decreased the yield and selectivity. Trifluorotoluene gave a similar result to toluene at 0.05 mL (Table 3.17, Entry 10). Heptane decreased the yield compared to when no additive was present.

To again consider how the concentration of the products changed over time, a reaction profile was conducted in the presence of 0.1 mL xylene (Figure 3.16).

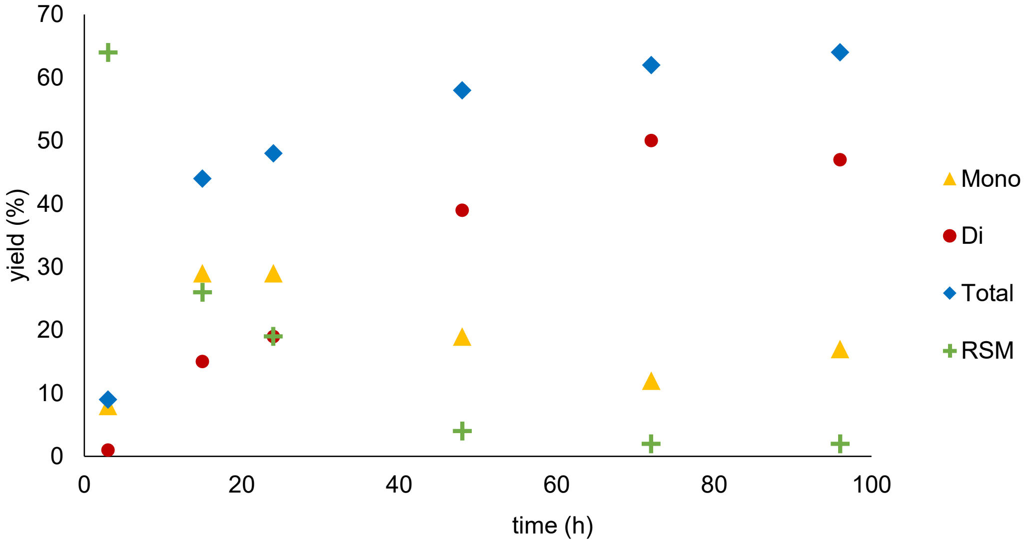
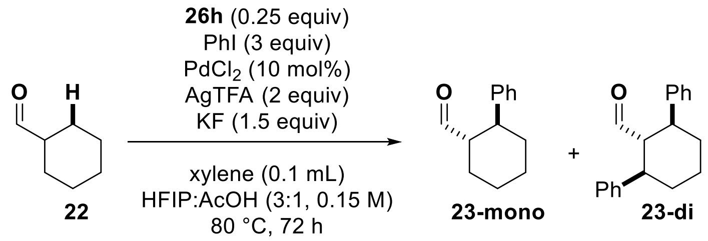


Figure 3.16: Reaction profile in the presence of 0.1 mL xylene

As observed previously (see Figure 3.15) following maximum amount of monoarylation (29%, at 15 h), **23-mono** is gradually converted to **23-di**. Similar yields were observed for both 72 and 96 h.

To improve the yield of **23-di** further, additional alterations to the reaction conditions were attempted (Table 3.18).

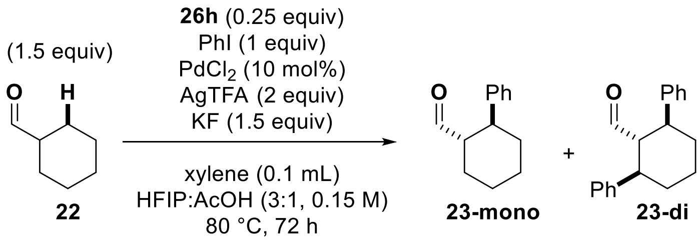


Entry	Change from conditions	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	none	12	50 (6)[b]	62
2	$Pd(OAc)_2$	4	37	41
3	No KF	25	38	63
4	5 equiv PhI	7	36	43

Table 3.18: Optimisation for diarylation. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield, 0.4 mmol.

Previously, $Pd(OAc)_2$ was shown to be more selective for diarylation (Table 3.15, Entry 1). Although good selectivity was observed, a lower yield of the diarylated product was achieved using $Pd(OAc)_2$. Interestingly, omitting KF gave a high total yield but also poorer di-selectivity (Table 3.18, Entry 3). Use of higher equivalents of iodobenzene gave good selectivity but a lower final quantity of **23-di**. With the optimum conditions on a larger scale, an isolated yield of the diarylated product was obtained. Separation from the **23-mono** was highly problematic; therefore the isolated yield of the clean diarylated product is low with coelution occurring even using slow gradients during column chromatography.

Use of the xylene additive formed more of the diarylated product, not because it was more selective, but as the system had improved reactivity. Hence, when trying to improve the monoarylated yield, this additive was again used. For these experiments, the aldehyde was used in 1.5 equivalents, with iodobenzene as the limiting reagent, to maximize the amount and selectivity of monoarylated product **23-mono** (Table 3.19).



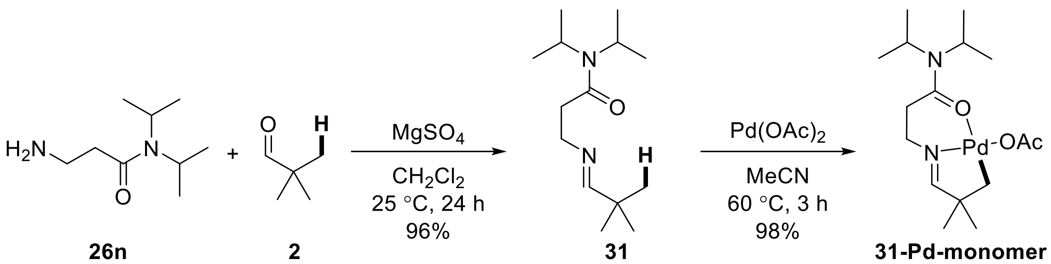
Entry	Change from conditions	yield 23-mono (%)[a]	yield 23-di (%)[a]	total yield (%)[a]
1	none	31	8	37
2	no KF	33	11	44
3	No KF, 2.0 equiv **22**	39 (4)[b]	10	49

Table 3.19: Optimisation for monoarylation. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield, 0.4 mmol.

With the xylene additive and the aldehyde in excess, the monoarylation yield was 31%, with the best observed mono-selectivity. Omission of the KF gave a similar yield of monoarylation, but also more diarylation. With no KF and a higher equivalent of aldehyde, a yield of 39% monoarylation was achieved. The monoarylated compound was isolated in low yield as separation from **22** and **23-di** was problematic.

Both cyclobutanecarboxaldehyde and tetrahydropyran-4-carbaldehyde were tested as substrates using both the mono- and diarylation conditions. Product formation was not observed for either example.

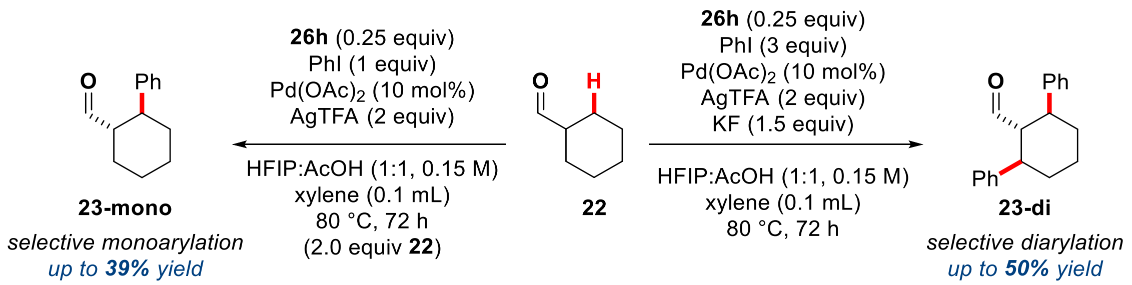
To understand the coordination modes of the optimal directing group, experiments with stoichiometric palladium were conducted. Attempts to form the imine or any palladacycle species with cyclohexanecarboxaldehyde were unsuccessful, complicated by the enolizable α-proton. Therefore pivaldehyde **2** was used, with tertiary DIPA amide **26n** (to show O chelation) and the imine and related palladacycle could be formed in good yields (Scheme 3.17).



Scheme 3.17: Pivaldehyde imine palladacycle formation

The crude palladacycle **31-Pd-monomer** was isolated in high yield following a simple work-up of diluting the reaction mixture with toluene, filtration through Celite and evaporation of the solvents. Attempts to further purify the crude material or grow crystals for XRCP analysis by slow evaporation or vapour diffusion techniques to provide definitive proof of the O-chelation were unsuccessful. Analysis of 2D NMR spectra of the crude (COSY, HMBC, DEPT-HSQC) elucidated a monomeric species containing one acetate ligand. Many of the signals are broad, suggesting that the directing group is chelated, or perhaps labile. The low chemical shift (2.25 ppm) of the cyclometalated CH_2 was indicative of a neutral species.

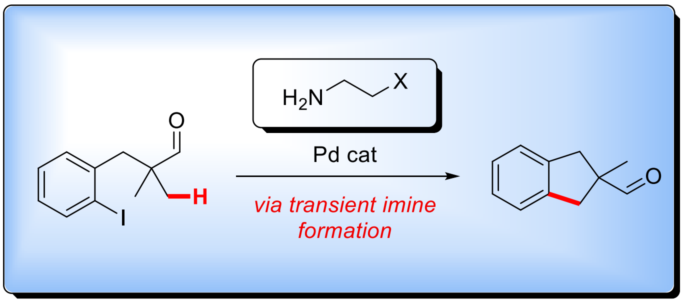
Methylene C(sp^3)–H arylation of secondary aldehydes has been developed. In comparison to the tertiary aldehyde arylation study (Section 3.1), milder conditions and a 5,6-metallacyclic system with β-amino amide transient directing groups enable functionalisation of these less stable, more challenging substrates. The amino amide is thought to coordinate through the carbonyl oxygen. Most hindered alkyl secondary or tertiary amides give higher total yields by promoting coordination through O over N. Selective mono- or diarylation of cyclohexanecarboxaldehyde has been achieved by modifying the reaction conditions (Scheme 3.18). A palladacycle of a pivaldehyde imine using a tertiary β-amino amide directing group has been isolated. Further work will improve the mono- and diarylation yields, before conducting aryl iodide and aldehyde scope.



Scheme 3.18: Selective mono- or diarylation conditions of cyclohexanecarboxaldehyde **22.** Max yields quoted are by ^{1}H NMR

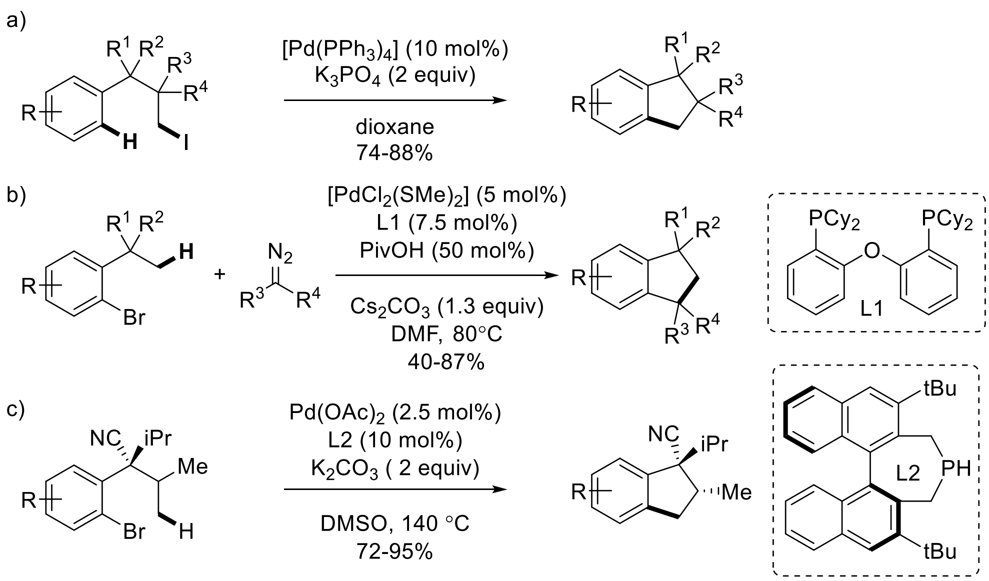
3.3 Intramolecular Annulation for Indane Synthesis

Indanes are a bicyclic ring system, consisting of a fused benzene and cyclopentane. Indane derivatives have shown important biological activities.[110] It was envisaged that an intermolecular variant of the tertiary aldehyde arylation (Section 3.1) would enable a step-efficient route to such structures (Scheme 3.19).



Scheme 3.19: Formation of indanes through intramolecular C–H arylation with a transient imine directing group

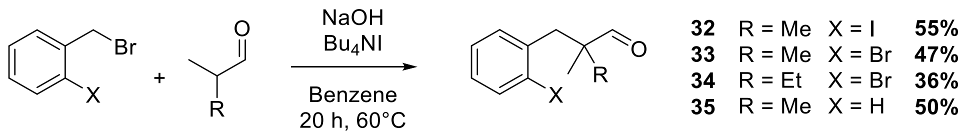
Indane synthesis has previously been achieved through intramolecular C–H functionalisation by a variety of research groups using different strategies (Scheme 3.20).



Scheme 3.20: Indane synthesis through intramolecular C–H arylation

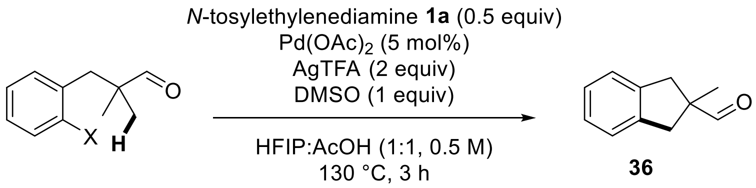
Alexanian showed that oxidative addition to unactivated alkyl iodides could promote proximal $C(sp^2)$–H activation and cyclisation to form substituted indanes (Scheme 3.20a).[111] Oxidative addition to an Ar–Br bond can also enable activation of $C(sp^3)$–H bonds. Martin combined an oxidative addition, $C(sp^3)$–H activation, and carbenoid insertion for Pd^0/Pd^{II} catalysed indane formation (Scheme 3.20b).[112] Baudoin developed an efficient enantioselective annulation using phosphine ligand L2 with low loadings of $Pd(OAc)_2$ (Scheme 3.20c).[113] In these methods the regioselectivity is determined by the intramolecular nature of the reaction (see Section 1.1) whereas the transient imine approach would be directing group assisted C–H activation.

The starting material **32** could be synthesised in one step from commercial materials by a phase transfer catalysed enolate addition reaction. Aryl-bromide (methyl **33** and ethyl **34** examples) and a C–H substrate **35** were also synthesised using this method (Scheme 3.21).



Scheme 3.21: Single-step synthesis of annulation substrates

Starting materials **32**, **33** and **35** were subjected to the tertiary aldehyde arylation conditions (Table 3.20).

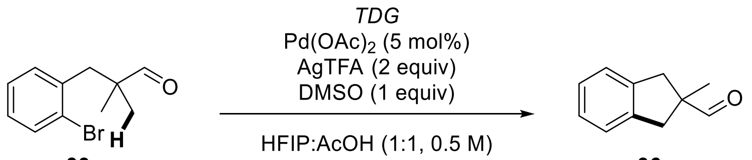


Entry	X	RSM (%)[a]	yield 36 (%)[a]	yield acid (%)[a]
1	I (**32**)	0	38	29
2	Br (**33**)	82	20	0
3	H (**35**)	89	0	0

Table 3.20: C(sp^3)–H annulation with I, Br and C–H substrates. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Iodo substrate **32** cyclised to form indane aldehyde **36** in the highest yield, as anticipated. The recovery of the starting material, however, was low as oxidation to the carboxylic acid occurred, observed in the ^1H NMR of the crude reaction mixture. Pleasingly, the bromide substrate **33** could also be cyclised in a lower yield, but with good recovery of the SM, making it an excellent substrate for further optimisation. This is the first example of transient imine directed C(sp^3)−H arylation with aryl bromides. The C–H substrate (**35**) was not cyclised by dual C–H activation under these conditions or in the presence of external oxidants.

Cyclisation of the bromide substrate was attempted with alternative directing groups and conditions (Table 3.31).



33 **36**

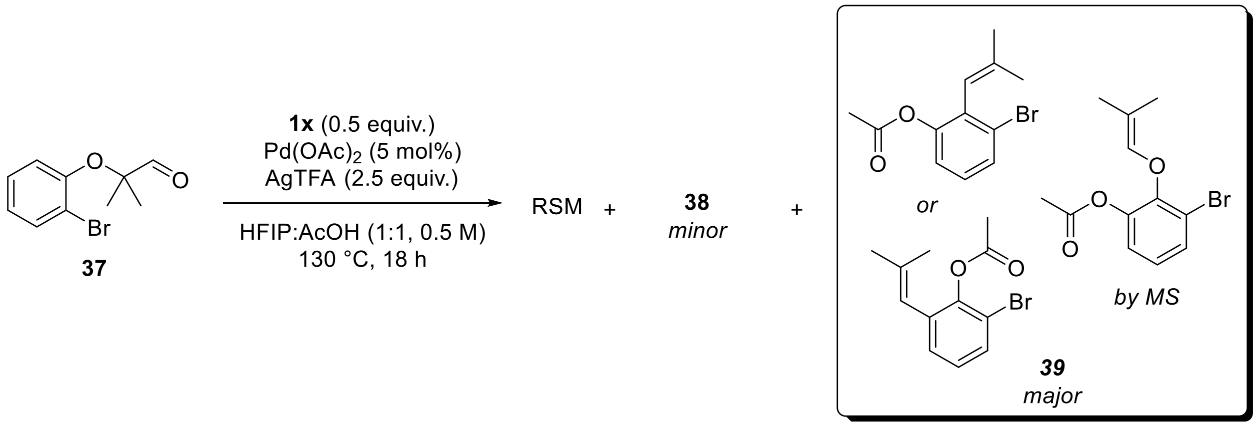
Entry	TDG (equiv)	Change from conditions	RSM (%)[a]	yield 36 (%)[a]
1	*N*-tosylethylenediamine **1a** (0.5)	-	83	27
2	Benzylamine **1n** (1)	-	86	9
3	$NH_2CH_2CH_2OMe$ **1x** (1)	-	58	31
4	$NH_2CH_2CH_2OMe$ **1x** (1)	No DMSO	33	46
5	$NH_2CH_2CH_2OMe$ **1x** (1)	AcOH as solvent	74	12
6	$NH_2CH_2CH_2OMe$ **1x** (1)	0.2 M	57	14
7	$NH_2CH_2CH_2OMe$ **1x** (0.5)	-	53	35
8	$NH_2CH_2CH_2CH_2OMe$ **28** (0.5)	-	51	25
9	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv)	23	53
10	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (3 equiv)	19	55
11	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, 1 M	30	44
12	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, 2 M	21	50
13	$NH_2CH_2CH_2OH$ **1w** (0.5)	No DMSO	55	24
14	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, $Pd(OAc)_2$ (10 mol%)	16	48
15	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv), 1 M	24	42
16	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, (HFIP:AcOH, 9:1, 1 M)	24	45
17	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, (HFIP, 1 M)	40	26
18	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv) *per*-F-*t*BuOH:AcOH	29	38
19	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv) Aryl *iodide* **32**	0	43
20	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv) 110 °C	50	9
21	$NH_2CH_2CH_2OMe$ **1x** (0.5)	No DMSO, Ag (2.5 equiv) Pre-stir 1 h	26	45
22	$NH_2CH_2CH_2OMe$ **1x** (0.25)	No DMSO, Ag (2.5 equiv)	26	47 (41)

Table 3.21: Optimisation table for annulation reaction. [a]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses.

A longer reaction time was chosen for these optimisations due to the presence of unreacted starting material in the crude reaction mixtures, which gave a slightly improved yield of 27%

using *N*-tosylethenediamine **1a**. One equivalent of monodentate benzylamine **1n** as the directing group led to a reduced yield of 9% (Table 3.21, Entry 2). An improved yield was seen using methoxy directing group **1x**, which also showed success in the tertiary aldehyde arylation study (see Section 3.1). Further optimisations were therefore conducted using this simple amine. Positively, omitting the DMSO gave a 10% improvement in yield (Entry 4). The HFIP co-solvent was again advantageous for this substrate and using AcOH alone reduced the yield by more than 20% (Table 3.21, Entry 5). Dilution to 0.2 M also caused a large drop in yield (Table 3.21, Entry 6). Reducing the equivalents of the directing group gave a slight increase in yield (Table 3.21, Entry 7). An alternative DG **28** (Table 3.21, Entry 8) with a one carbon increase in backbone length led to a 10% reduction in yield. Subsequent experiments excluded DMSO and use only 0.5 equivalents of methoxyethylamine TDG **1x** (Table 3.21, Entries 9-22). Increasing the amount of AgTFA to 2.5 or 3 equivalents gave an 8 or 10% increase in yield respectively. Using a 1 M concentration did not improve the yield however increasing the concentration further to 2 M led to a 4% improvement to 50% product. A TDG with an alcohol as the secondary binder **1w** led to a 24% yield (Table 3.21, Entry 13). Doubling the catalyst loading to 10 mol% gave a similar yield as 5 mol% (Table 3.21, Entry 14). When using both a higher concentration and higher silver loading, no improvement in yield was observed (Table 3.21, Entry 15). A higher ratio of HFIP at the higher concentration did not affect the product yield (Table 3.21, Entry 16). Use of HFIP as the only solvent reduced the yield by half. Replacing HFIP with another strong H-bond donor/acceptor, perfluoro-*t*-butanol, caused a slight drop in yield. Use of the aryl iodide starting material **32** was, under these conditions, not beneficial (Table 3.21, Entry 19). A lower temperature of 110°C resulted in a dramatic drop in yield to under 10%. Pre-stirring the reaction mixture at room temperature had no effect. Pleasingly lowering the amount of directing group to only 0.25 equivalents was well tolerated, and under these conditions the product could be isolated in 41% yield.

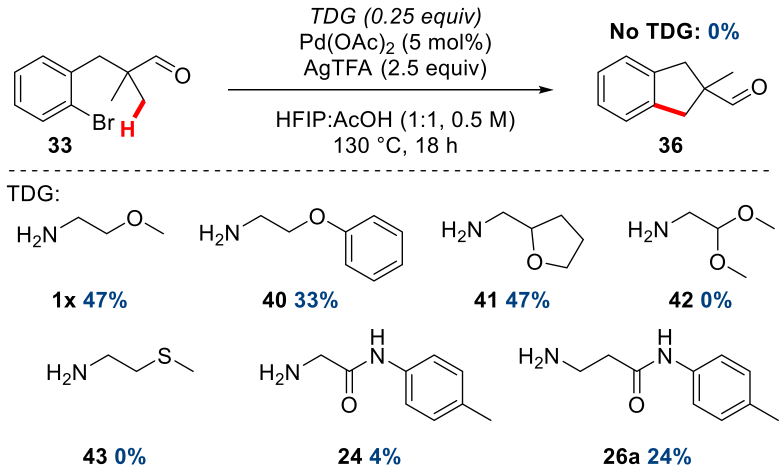
An alternative O-linked substrate **37** (synthesised from the relevant phenol and 2-bromo-2-propanal) was subjected to the reaction conditions to form the dihydrobenzofuran scaffold using this novel strategy (Scheme 3.22).



Scheme 3.22: Attempted arylation of O-linked substrate **37**

Unfortunately, no cyclisation product was present in the crude [1]H NMR. Instead, two other products (one minor, one major) were isolated alongside the unreacted starting material. 2D NMR was used to determine the structures. The minor product appeared to be a 1,2,3 trisubstituted aromatic although may have contained some impurities and so was not assigned. The major product was also difficult to analyse, although it was clear that it contained an alkene signal, acetate and three (1,2,3 substituted) aromatic signals. After extensive analysis of the chemical shifts and 2D NMR data, the structures in Scheme 3.22 were proposed. However, the mass spec gave a molecular ion peak of 284.0048. This is consistent with a formula of $C_{12}H_{13}O_3Br$ which contains an additional O atom, which could be between the alkene and aromatic, however the chemical shifts in the ^{1}H NMR for the terminal methyls on the alkene contradict this, as they are significantly more upfield compared to the expected values. Following this result, the O-linked substrates are unlikely to be pursued further, as any heteroatom on this position is likely to facilitate unwanted ortho C(sp^2)–H activation.

Additional directing groups were investigated using the aryl bromide substrate **33** including alternative ethers, a thioether and amino acid derivatives (Scheme 3.23). A control reaction in absence of directing group was also conducted.



Scheme 3.23: Screen of transient directing groups for C–H annulation. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

No reaction occurred in the absence of amine, ruling out both an intramolecular selectivity mechanism (c.f. examples in Scheme 3.20) as well as any potential monodentate direction by the aldehyde. Changing the sterics and electronics of the ether oxygen by changing from a methyl to a phenyl group resulted in a slightly decreased yield. For commercial THF ether **41**, the yield was consistent with methoxy amine **1x**. Amino acetal **42** was ineffective, potentially due to self-condensation under the reaction conditions, or the high binding affinity of the amino acetal to the catalyst, causing deactivation. Thioether amine **43** was unreactive, possibly due to catalyst coordination or instability under the reaction conditions. Analogous with the secondary arylation (Chapter 3.2), β-amino amide derivative **26a** showed greatly increased yield compared to the α-amino amide **24**. However, this increase in chelate size was not advantageous with the optimal methoxy secondary binding group (see Table 3.21, Entry 8), where one carbon homologation of the backbone led to a 10% drop in yield.

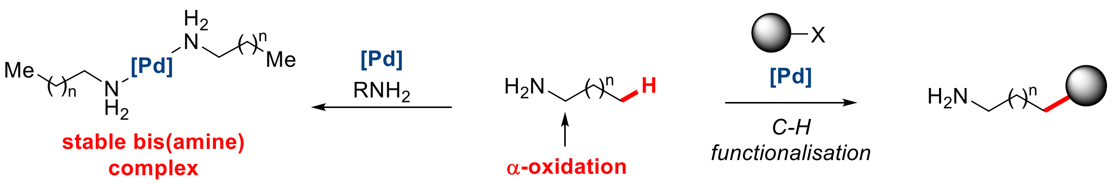
Indane synthesis can be achieved through C(sp^3)–H activation using a transient *endo*-imine directing group, through subsequent intramolecular oxidative addition and reductive elimination steps. The intramolecular aldehyde substrates can be formed in a single step from commercial starting materials. The product aldehydes are highly fragrant, and may have applications in the perfume industry.[114] Future investigations will be to improve the yield with further optimisation, including testing additional silver or other metal salts, carboxylate additives, palladium pre-catalysts, and a higher temperature. Further optimisation of the continuous reaction parameters, perhaps through a DOE approach, may also lead to improved yields. Finally, novel indane aldehydes will be synthesised and collaborations sought to identify odour properties for industrial application of the products.

3.4 Direct C(sp^3)–H Arylation of Primary Amines

3.4.1 C(sp^3)–H Functionalisation of Amines

Amines are present in a multitude of natural products as well as pharmaceuticals, with a large range of biological activities. Due to their huge importance, the ability to form and derivatise amines in a step-efficient and divergent manner would be extremely desirable and C–H functionalisation can provide a potential solution.

Palladium has been shown to be a highly active and versatile catalyst for both C(sp^2)–H and C(sp^3)–H functionalisation across a range of substrates.[115] The major challenge faced with the use of Pd catalysis for C–H functionalisation of free amines is the avoidance of stable bis(amine) palladium complexes, which are formed as a result of the high affinity of palladium to amine ligands.[91] A second challenge is avoiding unwanted α-oxidation of the amine by palladium (Scheme 3.24).[92,93]



Scheme 3.24: Bis(amine) complex formation and α-oxidation: challenges for the palladium catalysed C(sp^3)–H functionalisation of amines

There are three key approaches for overcoming these challenges, to enable selective C(sp^3)−H functionalisation of amines (Figure 3.17).

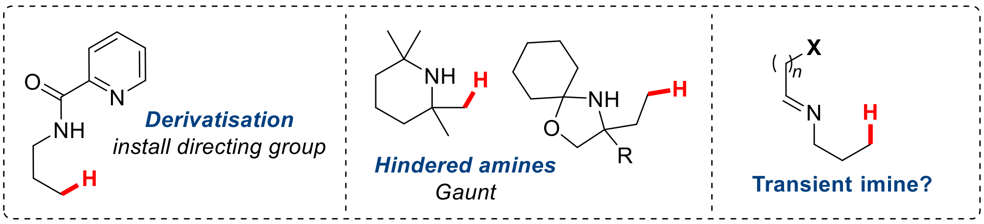


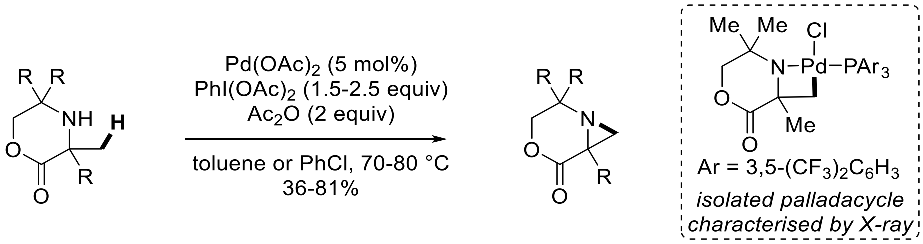
Figure 3.17: Strategies for C(sp^3)–H functionalisation of amines

The binding ability of the nitrogen atom can be altered by derivatisation, which can also act to form new bidentate directing groups (DGs).[116] However, this is a stepwise process for DG installation and removal, resulting in reduced efficiency of the overall C–H functionalisation, and so techniques to use free amines directly would be beneficial. Although the transient imine approach as described previously in Section 1.4 is one potential method, the binding affinity of the free amine can also be exploited as a monodentate directing group, which will be discussed here. Free amine directing groups have successfully been used to direct *ortho*-C(sp^2)–H functionalisations,[10] however C(sp^3)–H functionalisations are much rarer. Much of the relevant literature is from the Gaunt group, using highly substituted amines.

3.4.2 Free Amine Directed C(sp^3)-H Functionalisation

In 2014, Gaunt published the seminal example of using an unprotected aliphatic amine as a directing group for C(sp^3)–H activation.[117] Palladium catalysed aziridination (Scheme 3.25) and carbonylation (Scheme 3.27) reactions using cyclic, hindered secondary amines were demonstrated. Unlike the traditional 5-membered, kinetically favoured palladacycle, formed using the typical directing groups as described in Section 1, these systems proceeded through a highly unusual 4-membered palladacycle. These were the first examples of a 4-membered Pd-cycle and the structure of the proposed intermediates were confirmed by X-ray crystallography.

In the aziridination reaction (Scheme 3.25) the presence of a lactone was required, otherwise acetoxylation occurred preferentially. It was suggested that the carbonyl on the lactone tunes the reactivity of the Pd(IV) intermediate from oxidation of the cyclometalated species by diacetoxyiodobenzene. The C–H activation step favoured the two methyl groups neighbouring the lactone carbonyl due to a slight stereoelectronic preference. Unusually, a substrate where one of the reactive centres was an ethyl group resulted in palladacycle formation only on the methyl centre to make the 4-membered palladacycle, despite possible C–H activation on the ethyl group, which would form the kinetically preferred 5-membered ring system.



Scheme 3.25: Catalytic aziridine formation of hindered amines

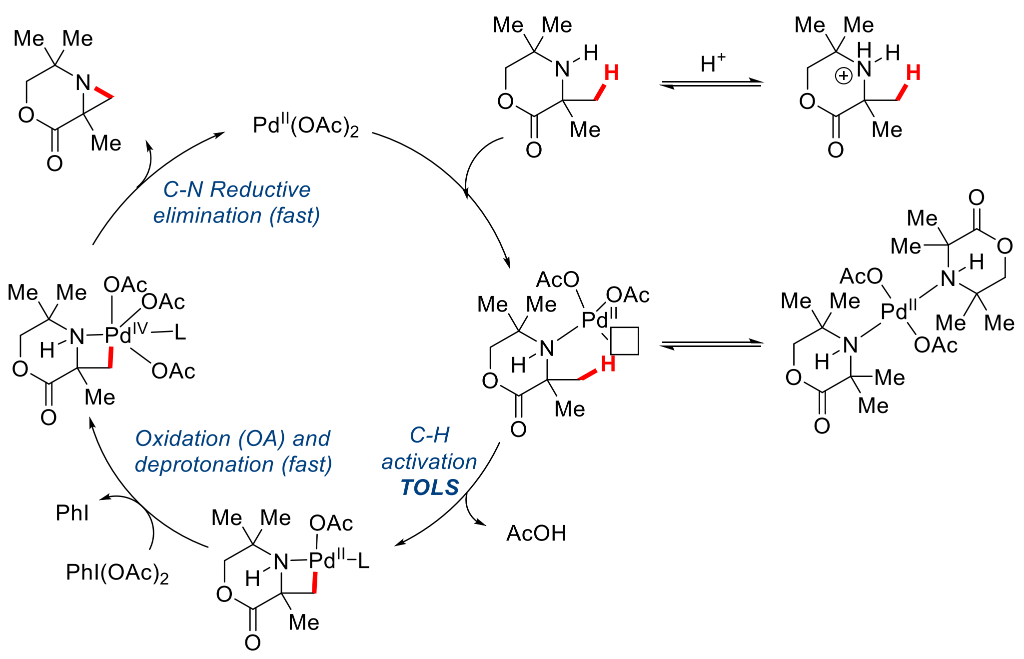
In the reaction scope, substituents other than methyl were well tolerated, even those containing alkyl halides, esters and protected nitrogen groups with many examples undergoing aziridination in 70-80% yield. The 4-membered palladacycle could also be formed on methylene centres, forming the aziridine products in lower yields. Most restrictive however was the need for fully substituted carbons at either side of the secondary amine, with no reaction occurring on less substituted secondary amines. This could be to reduce formation of unreactive bis(amine) palladium complexes.

A comprehensive study of the reaction mechanism for the aziridination reaction was conducted with both experimental and computational studies.[118] It was found that the rate of aziridination increased over time (autoinduction), and “same excess” experiments (for further discussion on “same excess” as used in this thesis, see Section 3.4.3)[119] suggested this was due to a negative rate dependence of the amine starting material. Initial rates experiments showed a zero order in oxidant, suggesting the turn over limiting step (TOLS) was prior to oxidation, which was determined by a high KIE and first order in catalyst to be the C–H activation step. Evidence for the bis(amine) complex as an off-cycle intermediate was gained by comparing the reactivities of two amines, one with greater steric hindrance than the other, hence a less stable bis(amine) complex. The more hindered amine reacted significantly faster, as it enabled a more favourable equilibrium shift to the monomeric amine species with the active vacant site that enables C–H activation.

Kinetics-led optimisation of the reaction conditions was performed based on these results, leading to the addition of moderate amounts of acetic acid which meant that using only 1 mol% of palladium gave an 87% yield of aziridine product on a gram scale. Acetic acid assisted the reaction by protonating the amine, which lowers the concentration of free amine resulting in less bis(amine) complex formation. At high concentrations of acetic acid however, the product degraded. The role of the acetic anhydride in accelerating the reaction using the initial conditions (Scheme 3.25) was found to be due to the removal of water, the addition of which led to reduced yields.

DFT studies showed that a CMD mechanism was likely for the C–H activation step and confirmed the lower energy transition states for C–H activation on the methyl groups closer to the lactone, consistent with the observed regioselectivity.

A detailed catalytic cycle was proposed as a result of these studies (Scheme 3.26).

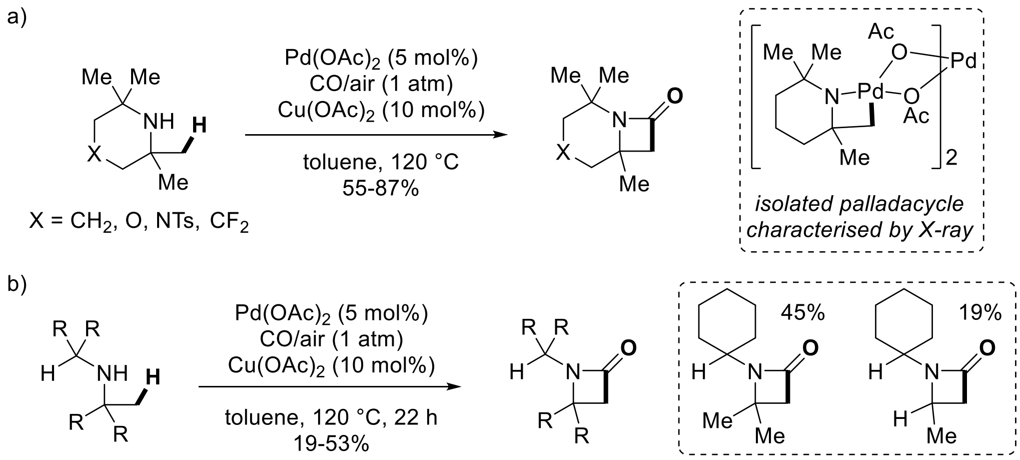


Scheme 3.26: Catalytic cycle for the aziridination of hindered secondary amines

Firstly, the free amine (from a pool of the protonated species), coordinates the Pd^{II} catalyst, forming a monomeric species. This can either go through turnover-limiting CMD C–H activation or form an inactive bis(amine) complex, which is more favourable with less hindered amines. After CMD, oxidation by bis(acetoxy)iodobenzene affords a Pd^{IV} species which undergoes C–N reductive elimination to form the aziridine and regenerate Pd^{II}.

This aziridination work was also translated into a flow process, to form 0.77 g of clean aziridine product per hour.[120] Additionally, a study in early 2017 within the Gaunt group developed this 4-membered Pd-cycle aziridine formation into the first enantioselective de-symmetrising Pd(II)/Pd(IV) process using chiral anionic-BINOL-phosphoric acid ligands.[121] Very recently, Gaunt has also shown that ethyl-morpholinone substrates using alternative, tosylate containing hypervalent iodine reagents could form a 5-membered palladacycle and reductively eliminate to form azetidines.[122]

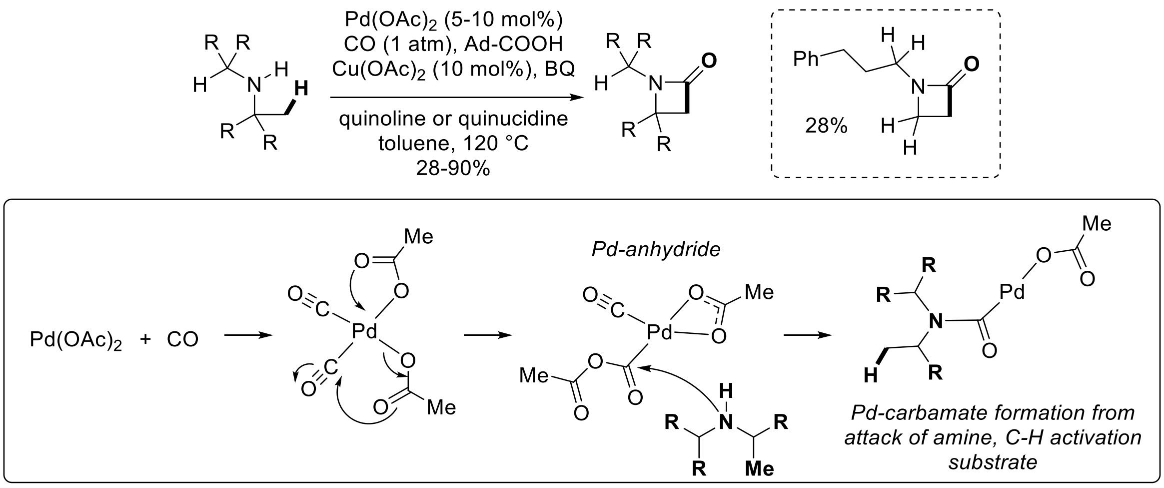
Carbonylation was also demonstrated, to form 4-membered lactams on TMP (2,2,6,6 tetramethylpiperidine) and heterocyclic amine derivatives (Scheme 3.27a), as well as some linear amines (Scheme 3.27b).[117] Stoichiometric studies again showed the formation of a 4-membered palladacycle as a dimeric species, directly characterised by XRCP. The reaction is thought to proceed through a Pd(0)/Pd(II) redox cycle.



Scheme 3.27: Lactamisation of bulky amines by C(sp^3)–H carbonylation

When using linear substrates, amines with one tertiary and one quaternary α-carbon, as well as two tertiary α-carbons could be used, in sequentially lower yields due to the higher stability of the relevant bis(amine) Pd complexes (Scheme 3.27b).

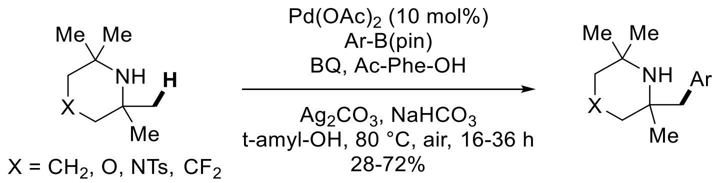
Carbonylation to form β-lactams using a different mechanistic approach (proposed as attack of the amine on a Pd-anhydride species to form a Pd-carbamate) led to a much broader scope of amines, including less substituted and pharmacologically relevant compounds (Scheme 3.28).[123]



Scheme 3.28: Pd catalysed C(sp^3)–H carbonylation through trapping of Pd-anhydride species with an amine

The substrate scope was excellent, with many functional groups including heterocycles, esters and thioethers well tolerated. Crucially, the reaction worked on unhindered amines, and an amine with two secondary α-carbons could undergo lactamisation in synthetically useful yield.

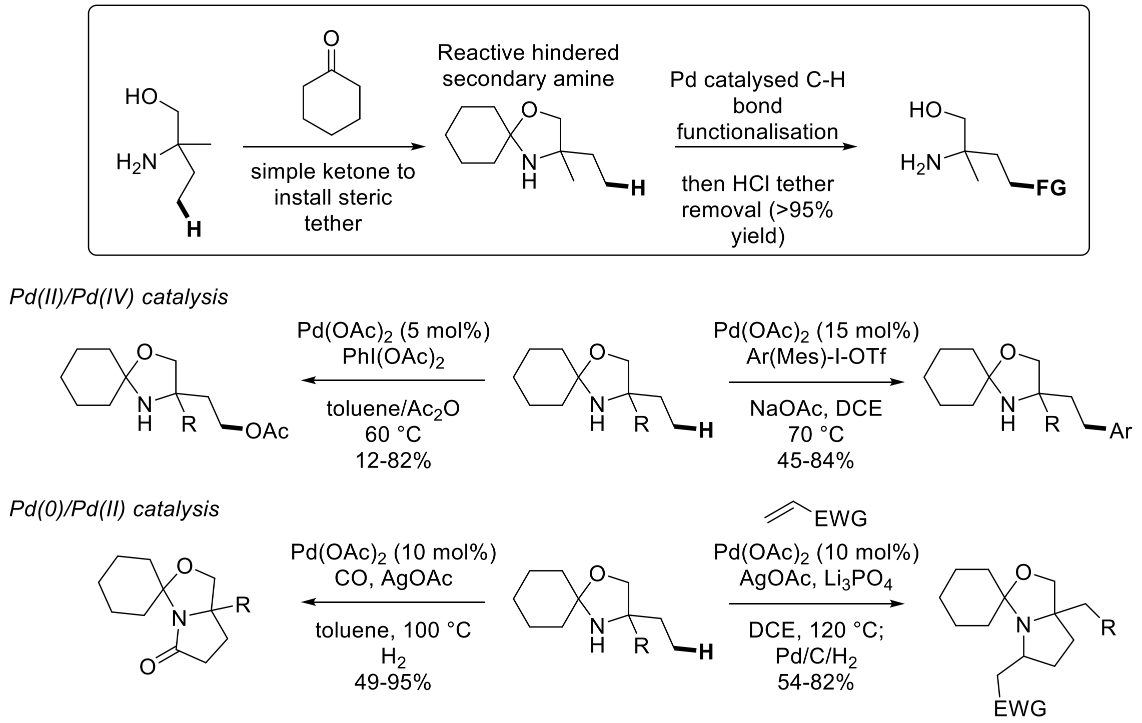
Pd(0)/Pd(II) catalysed arylation could be achieved on tetramethylpiperidine (TMP) derivatives using arylboronic esters coupling partners and an acyl-amino acid ligand (Scheme 3.29).[124]



Scheme 3.29: Arylation of hindered amines with Pd(0)/Pd(II) catalysis

The amine scope was modest with 8 examples of varied heterocycle derivatives. Linear amines, and those without both α-carbons fully substituted were not tolerated. Interestingly the lactone substrate used in the aziridination studies was unreactive. Various arylboronic esters could be used with varied functionality to form the arylated TMP products in good yields. Chiral N-acetylated amino acid ligands could be used to reach up to 60% *ee* using a reduced reaction temperature of 60 °C, a promising start for further development of an enantioselective process.

Functionalisation of primary amine derivatives could be achieved using a “steric tether” approach (Scheme 3.30).[125] The tether, derived from simple ketones and readily available bulky amino alcohol substrates could be used to mediate the formation of the unreactive bis(amine) complexes and allow various functionalisations to take place *via* a 5-membered palladacycle. The steric tether could be removed easily and in high yields by treatment of the products with aqueous HCl.

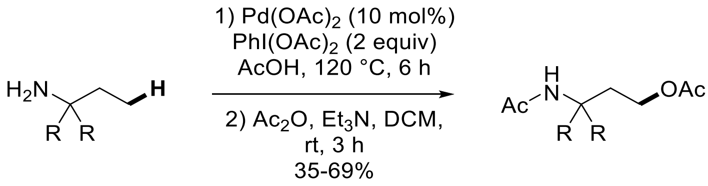


Scheme 3.30: C(sp^3)–H Functionalisation of primary amines using a steric tether approach

Pd(II)/Pd(IV) catalysis could be used in acetoxylation and arylation reactions with diacetoxyiodobenzene and diaryliodonium salts, respectively. Pd(0)/Pd(II) redox cycles were also investigated, and carbonylations and alkenylations (alkenylation products underwent aza-Michael additions to form pyrrolidines) were also optimised. For the carbonylation and alkenylation, the reaction mixtures were directly hydrogenated to force any undesired β-hydride elimination side-products to the saturated systems. Interestingly, cyclopalladation to the 4-membered palladacycle seen in the previous studies[117,118,124] was not observed in any case using the sterically tethered amino alcohol.

Alkenylation with alkenes, followed by cyclisation to give a pyrrolidine was later described on morpholinone substrates, and it was found that an acyl amino acid ligand enabled the C–H activation step to be reversible and not the TOLS.[126]

In July 2017, Z-J Shi proposed a protonation approach to enable primary amine functionalisation. In this study, protonation of the free primary amine both reduced the formation of stable bis(amine) complexes and increased the stability of the usually reactive primary amine to the oxidative conditions. This enabled the acetoxylation of free primary amines with $PhI(OAc)_2$ under acidic conditions (Scheme 3.31).[127]



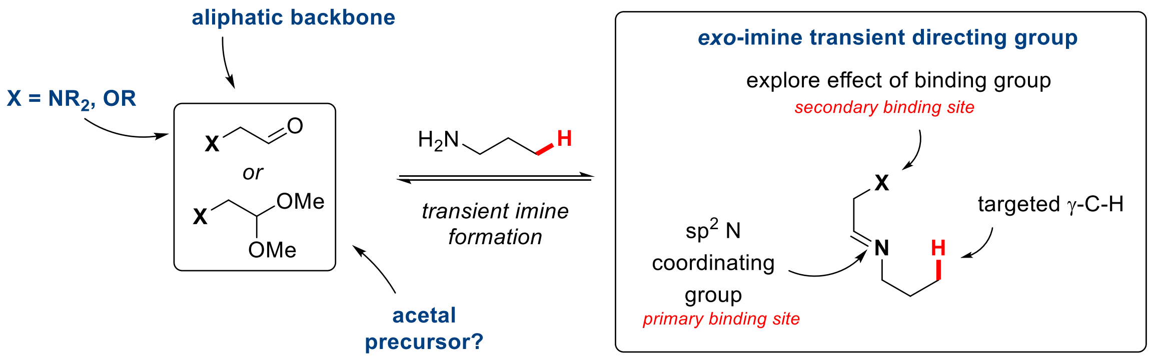
Scheme 3.31: Acetoxylation of free primary amines using a protonation strategy

An off-cycle protonation was also mentioned by Gaunt in the study on the carbonylation of cyclic, bulky secondary amines,[118] and it is very likely to be a feature in all the reactions of free amines listed above that take place under acidic conditions. The model substrate for optimisations contained four potential reactive C–H's (β-, γ-CH_3, γ-CH_2 and δ) and it was found that acetoxylation only occurred at the γ-methyl group, *via* a 5-membered palladacycle.

The scope of the acetoxylation reaction was limited to amines bearing a fully substituted α-carbon, with less than 10% yield achieved with only one methyl group on the α-carbon. Amines with aromatic groups on the α-, β- or γ-positions were also not tolerated, decomposing under the reaction conditions, however distal aromatic and other functionalities were well tolerated. Interestingly, on omission of any acetic anhydride or $PhI(OAc)_2$ only trace *N*-acetylation of the free amine occurred when heating the starting material in acetic acid, but on the γ-C–H acetoxylated product, *N*-acetylation occurred readily.

3.4.3 C(sp^3)–H Arylation of Primary Amines using a Catalytic Alkyl Acetal to form a Transient Directing Group

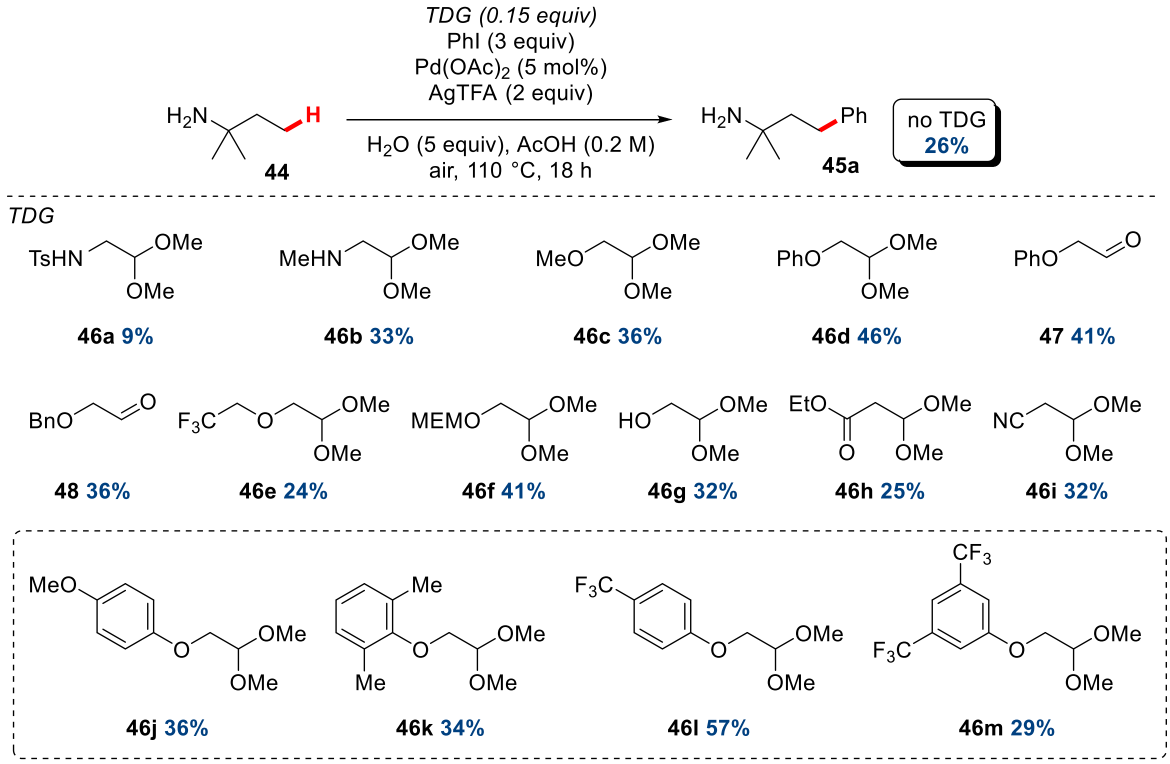
Free amines have been shown to act as suitable monodentate directing groups for C(sp^3)–H functionalisation under certain circumstances. The approach for amine functionalisation in this study however was to use a transient *exo*-imine directing group to promote γ-functionalisation of a wide range of primary aliphatic amines. Previous transient imine directing groups strategies for amine functionalisation have involved the condensation of conjugated or aromatic aldehyde activators (see Section 1.4). The aim of this study was to investigate whether more reactive *alkyl* aldehydes (containing a variety of O and N secondary binding groups) might lead to some improved or different reactivity. The design of the envisaged bidentate imine directing group is shown in Scheme 3.32. The heteroatom (N or O) secondary binding group, attached to the α-position of the imine, would enable the formation of a stable 5,5-palladacycle on activation of the γ-C–H. Due to the instability of these proposed aldehyde TDGs, acetals were employed predominantly at the outset, with many being commercially available.



Scheme 3.32: Design of *exo*-imine transient directing groups for amine arylation

Initial studies for this reaction were performed by MSci student Alex Ou, which are discussed in Appendix 3.[128] Arylation of *tert*-amylamine **44** with iodobenzene was used as the model reaction. This amine was chosen as it was sterically activated and α-oxidation stable. The conditions tested for directing group screening were based on those previously developed,[128] with a lower (5 mol%) catalyst loading. Yields were calculated from the crude ^{1}H NMR spectra with an internal standard following a work up of filtration through Celite.

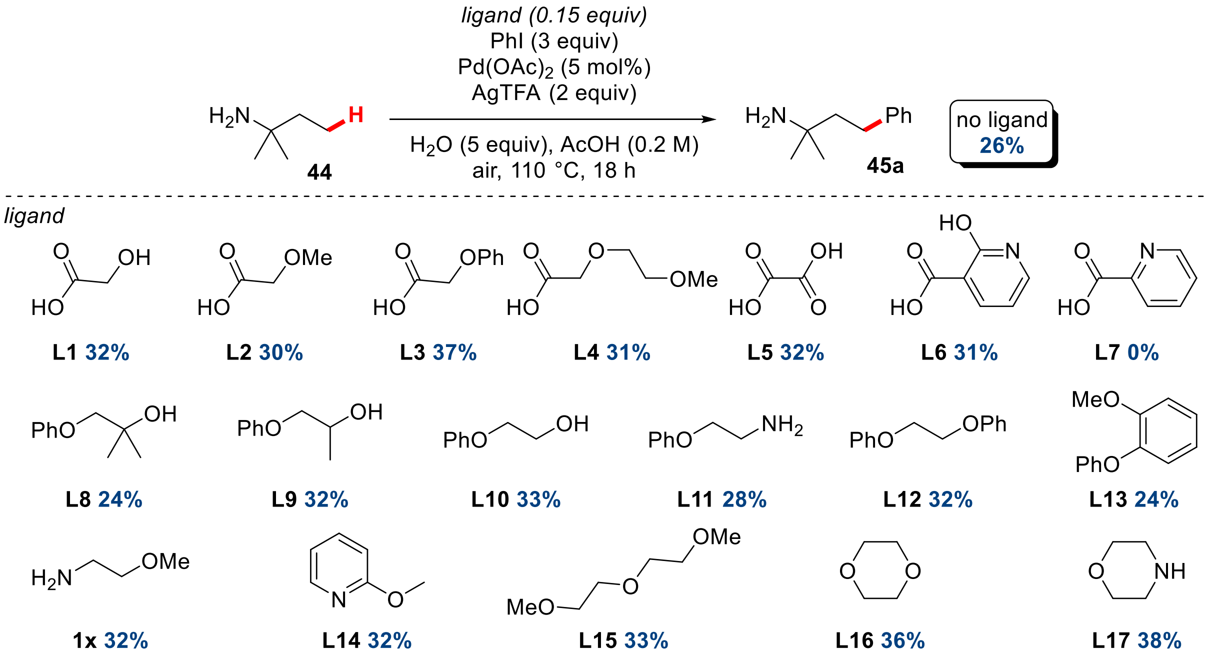
As free amines can promote C(sp^3)–H functionalisation by acting as a monodentate directing group (see Section 3.4.2), the control reaction was carried out in absence of any additive. Arylated amine product **45a** was formed in 26% yield under these conditions. This value is higher than that reported by others;[97] the control was hence repeated on two other occasions (with distilled *tert*-amylamine **44**) and gave consistent results of 26–27% yield. A selection of aldehyde and acetal activators were tested, to improve the yield through a transient imine mechanism (Scheme 3.33).



Scheme 3.33: Screen of TDG's for amine arylation. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

Improved yields for the arylation were achieved when using a selection of acetal or aldehyde additives, suggesting a more productive imine-promoted pathway. In the tertiary aldehyde study (Section 3.1), the *N*-tosyl secondary binding group was optimal. Here however, it caused a decrease in yield compared to the background reaction, with the likely cause too strong coordination of the free additive. A free secondary amine directing group **46b** increased the yield to 33%. Oxygen (ether) secondary binding groups were then explored. While trifluoroethyl example **46e** was ineffective, methoxy ether **46c**, phenoxy ether **46d** and benzyl ether **48** were able to enhance the yield above 35%. The phenoxy ether acetal **46d** gave the optimum yield of 46%, and a comparable yield was observed for the unstable hydrolysed aldehyde **47**, supporting the formation of this species in solution. MEM protected ether **46f** led to a 41% yield of the arylated amine, although its corresponding unprotected alcohol **46g** was less effective. Secondary ester and nitrile binding groups were unsuitable. New aryl ether examples were synthesised from the corresponding phenol and alkyl bromide (**46j–m**). While increased electron density (**46j**) and steric hindrance (**46k**) led to a reduction in product yield, electron poor 4-trifluromethyl derivative **46l** gave the highest yield of 57%. This trend was not continued in less electron rich example **46m**.

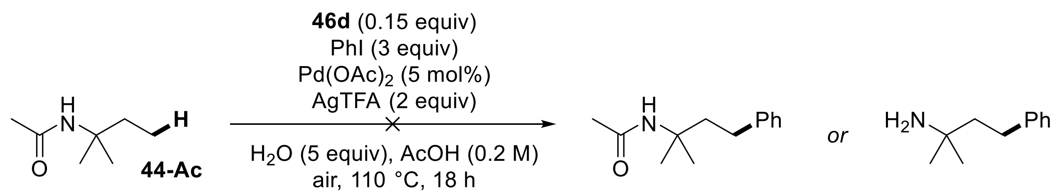
Due to the significance of the background reaction, an alternative strategy was employed to exploit the monodentate amine directing group. Here, a variety of ligands were explored as a potential method of breaking up bis(amine) or other inactive Pd aggregates and promote the free amine directed arylation (Scheme 3.34).



Scheme 3.34: Screen of ligands for amine arylation. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard

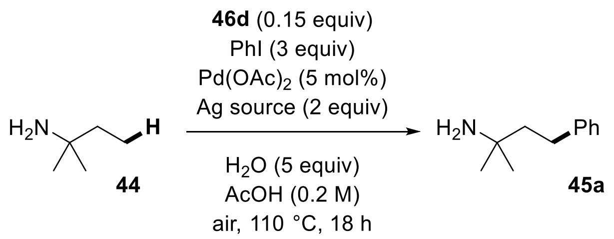
Most ligands were able to enhance the yield of the C–H arylation to a small extent. From the selection of functionalised acids and ethers tested, the highest arylation yields were seen for acid-ether **L3**, dioxane **L16** and morpholine **L17**. Although enhancing the yield with ligands by breaking up inactive Pd-complexes did have some positive effects, a transient imine approach was more efficacious hence ligand-assistance was not further investigated.

The amine was acetylated, and the product was inactive under the arylation conditions (Scheme 3.35). Potential transient acetylation by the acetic acid solvent can hence be ruled out. Although this also provides some evidence for imine formation, acetylation would significantly change the binding properties of the amine, so further investigations were needed.



Scheme 3.35: Acetylated amine was unreactive ruling out a transient *N*-acetyl directing group

The reaction conditions were optimised using commercial phenoxy acetal **46d**. Throughout the optimisation, it was found that the batch of AgTFA had a significant impact on the yield of the arylation. The only results reported in this thesis are those where the AgTFA was optimal and the control reaction gave a result within 5% of the expected value. Firstly, the silver source was investigated (Table 3.22).

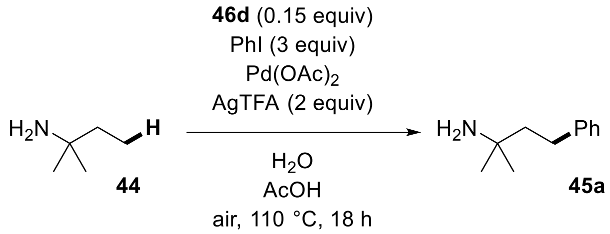


Entry	Ag salt	yield 45a (%)[a]
1	AgTFA	46
2	AgF	20
3	AgOAc	38

Table 3.22: Screen of Ag salts for amine arylation. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Unlike the tertiary aldehyde arylation study (Section 3.1), other silver salts AgF and AgOAc were able to promote the reaction in lower yields. The trifluoroacetate anion is hence less critical to reactivity for the arylation of amines.

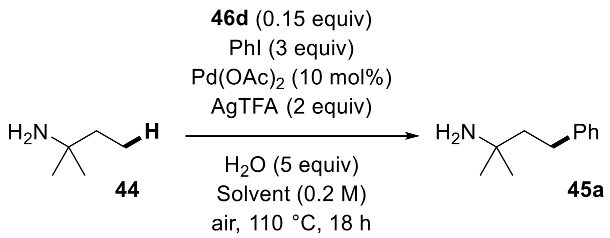
Change in the solvent volume, Pd loading and amount of water were investigated (Table 3.23).



Entry	Catalyst (mol%)	Solvent (M)	Additive (equiv)	yield 45a (%)[a]
1	$Pd(OAc)_2$ (5)	AcOH (0.2)	H_2O (5)	46
2	$Pd(OAc)_2$ (5)	AcOH (0.1)	H_2O (5)	40
3	$Pd(OAc)_2$ (5)	AcOH (0.3)	H_2O (5)	45
4	$Pd(OAc)_2$ (10)	AcOH (0.2)	H_2O (5)	52
5	$Pd(OAc)_2$ (10)	AcOH (0.2)	H_2O (2.5)	50

Table 3.23: Optimisation for amine arylation. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

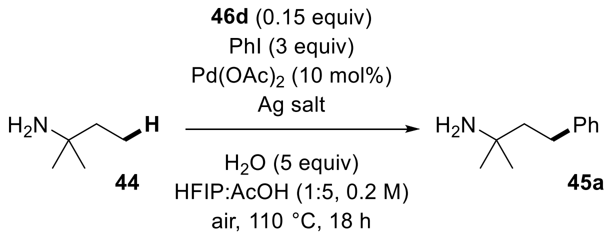
Decreasing the concentration of the reaction led to a slight drop in yield, whereas increasing the concentration to 0.3 M was well tolerated. An improved yield was obtained when doubling the catalyst loading (Table 3.24, Entry 4). With 10 mol% palladium, a similar yield was observed at 5 or 2.5 equivalents of water. HFIP as a cosolvent was then considered (Table 3.24).



Entry	Solvent	yield 45a (%)[a]
1	AcOH (0.2)	52
2	HFIP:AcOH (1:2)	55
3	HFIP:AcOH (2:1)	52
4	HFIP:AcOH (5:1)	49
5	HFIP:AcOH (1:5)	62
6	HFIP:AcOH (1:1)	61
7	HFIP (0.2)	22

Table 3.24: Optimisation for amine arylation, solvent screen. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

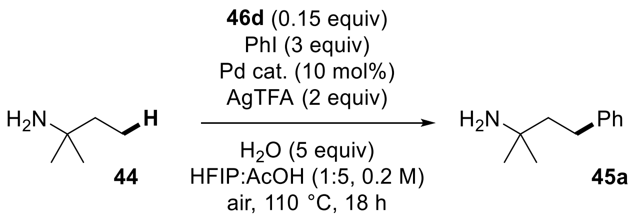
As shown in this thesis, HFIP has been an effective co-solvent for C(sp^3)–H functionalisations with transient imine directing groups. Although ineffective on its own (Table 3.24, Entry 7), when mixing with AcOH, an improved yield of 62% could be obtained with a 1:5 ratio. Generally, a higher proportion of AcOH seemed advantageous. Due to the presence of biphenyl in the reaction from homocoupling of the aryl iodide, some mixtures of AgTFA and AgOAc were used, which has been shown by Yu to reduce the amount of biaryl formation in a related ketone arylation (Table 3.25).[89]



Entry	AgTFA equivalents	AgOAc equivalents	yield 45a (%)[a]
1	2	0	62
2	1	1	52
3	1.5	0.5	58
4	0.5	1.5	53

Table 3.25: Use of silver salt mixtures [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

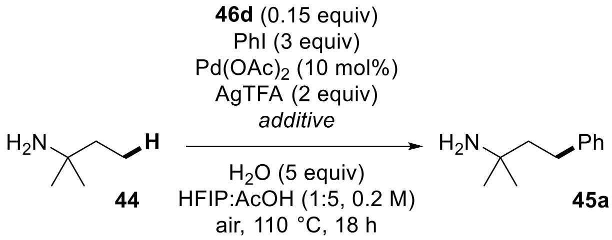
Increasing the proportion of AgOAc to AgTFA caused small detriments in yield. None of the mixtures of silver salts gave an improved yield or discernable difference in biphenyl formation. Next, the Pd pre-catalyst was examined (Table 3.26).



Entry	Pd source	yield 45a (%)[a]
1	$Pd(OAc)_2$	62
2	$PdCl_2$	56
3	$Pd(OPiv)_2$	64 (59)
4	$Pd(TFA)_2$	51

Table 3.26: Pd source evaluation. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses.

Palladium chloride and palladium trifluoroacetate led to slightly reduced yields compared to palladium acetate. When using palladium pivalate however, an improved 64% yield of **45a** (by ^{1}H NMR) was achieved, which was isolated in 59% yield. As the presence of the larger carboxylate anion (pivalate) seemed to assist the reaction, other carboxylates were tested as additives with the cheaper palladium acetate catalyst, as well as some oxidants in the hope to reoxidise any inactive Pd^0 that may be formed (Table 3.27).

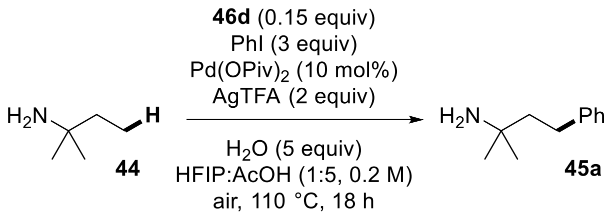


Entry	Additive (equiv)	yield 45a (%)[a]
1	none	62
2	PivOH (0.5)	55
3	MesCOOH (0.5)	55
4	AdCOOH (0.5)	50
5	$Cu(OAc)_2$ (1)	(39)
6	$CuBr_2$ (1)	(16)
7	benzophenone (1)	3

Table 3.27: Carboxylate and oxidant additives. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses.

Carboxylate ligands with various steric properties have been exploited as additives in many C–H functionalisation reactions.[129] In this reaction however, the presence of the carboxylate ligands was not advantageous, causing slight decreases in yield. For the copper salt oxidants, isolated yield values were used due to broadening of the signals in the ^{1}H NMR of the crude reaction mixture. Both salts did not deactivate the reaction but led to a decreased yield. Benzophenone was not tolerated.

A series of control reactions were applied to investigate how the different reaction components effect the yield (Table 3.28).

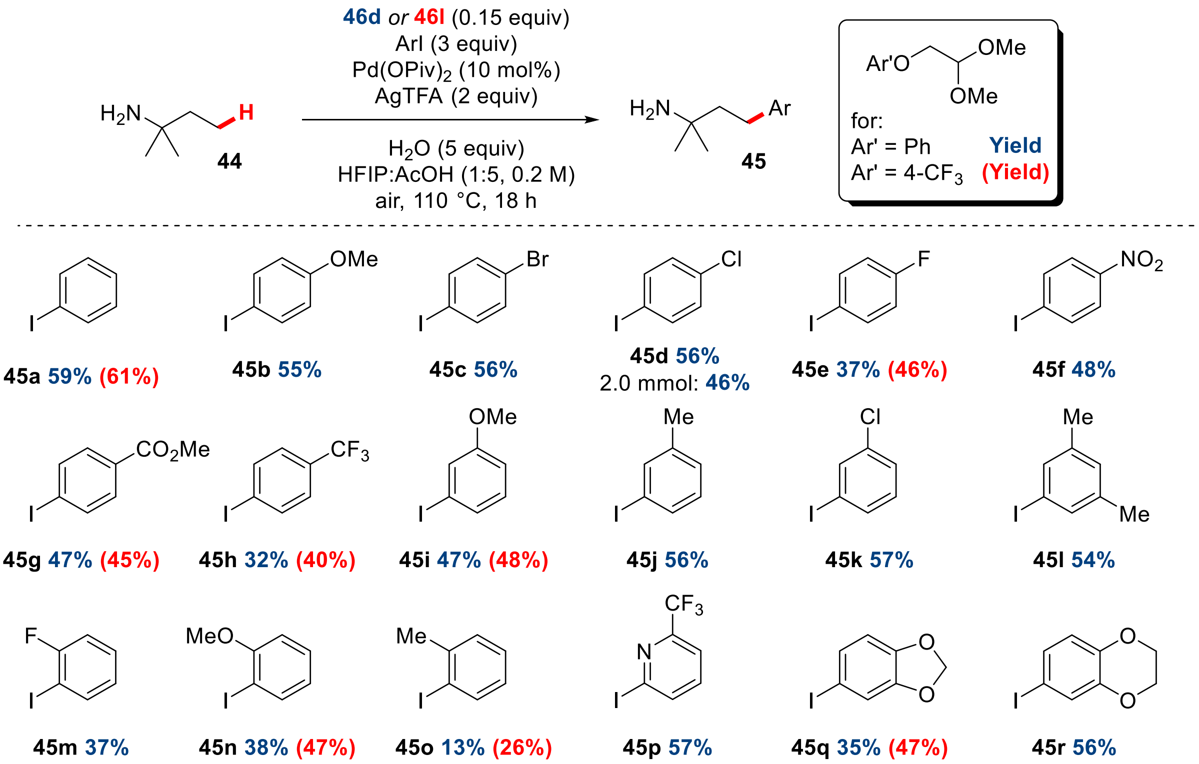


Entry	Change from conditions	yield 45a (%)[a]
1	none	64 (59)
2	90 °C	57
3	130 °C	55
4	no acetal	31
5	no H_2O	47
6	no Pd	0
7	no AgTFA	0
8	AgOAc + TFA (2 equiv)	21
9	CF_3-acetal **46l**	60
10	ligand **L17** (morpholine)	45
11	0.5 equiv **46d**	46
12	1.0 equiv **46d**	23
13	argon	41
14	$[Pd(PPh_3)_4]$	32
15	$[Pd(dppf)Cl_2]$	20
16	no acetal, phenol (0.15 equiv)	30
17	no stirring	54

Table 3.28: Control reactions. [a]Yields calculated by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Changing the temperature had little impact on the yield of the reaction, forming the products in similar yields within the 40 °C range tested. Under the improved conditions, the background reaction directed by the monodentate amine gave an improved (31%) yield, but there was still a marked improvement when using the acetal additive. In the absence of water (Table 3.28, Entry 5), the yield was reduced, indicating the role of the water in either acetal hydrolysis or turnover of the TDG. As expected, no reaction occurred in absence of AgTFA or $Pd(OPiv)_2$. Compared to the tertiary aldehyde arylation study where comparable yields could be achieved when using AgOAc and TFA as an additive, this reaction required AgTFA as the preformed salt to form the product in high yields (Table 3.28, Entry 8). The same yield (21%) was achieved when using different loadings of trifluoracetic acid as an additive in the range of 0.5–3 equivalents, using AgOAc. Notably under these conditions, CF_3-acetal **46l** formed the arylated amine **45a** in the same yield as commercial acetal **46d** (Table 3.28, Entry 9). Morpholine which has previously been identified as capable of improving the yield of the arylation (Scheme 3.34), could also provide some advantage to the yield under these conditions (Table 3.28, Entry 10). Increasing the loading of acetal **46d** led to sequentially lower yields, most likely as a result of coordination of the free acetal or aldehyde to the catalyst (in competition with the imine) causing deactivation. The yield was diminished under an argon atmosphere (a much lower recovery of the starting material was also observed). The role of air in the reaction is not yet understood. A Pd^0 catalyst or pre-catalyst led to lower yields, supporting a Pd^{II}/Pd^{IV} redox cycle. Phenol has been observed as a breakdown product of acetal **46d** in the reaction, which will be discussed later. Phenol itself cannot promote the reaction but does not cause any inhibition (Table 3.28, Entry 16). In the absence of stirring the reaction still progresses in high yields, meaning mass transport is unlikely to be rate determining.

With the optimised reaction conditions in hand, the scope of the reaction was explored using acetals **46d** and **46l**, starting with the aryl iodide (Scheme 3.36). All arylated amine products formed were isolated from a simple acid/base work-up without chromatography.



Scheme 3.36: Scope of aryl iodides for one-pot amine C–H arylation

Para- and *meta*-substituted aromatics were installed in good yields (**45b–k**), improved yields were observed in almost every case using acetal **46l**. Fluorine containing examples (**45e,h**) exhibited slightly lower yields. Compared to other literature examples, even *ortho*-substituted aromatics could be incorporated in moderate yields, including 2-methyl-iodobenzene (an unsuitable coupling partner for Ge),[97] forming arylated amine **45o** in 13% yield, which could be improved to 26% by using acetal **46l**. More complex (hetero)aryl iodides could be used forming products **45p–r** in good yields. Other simple pyridines and *N*-tosyl indole were unsuitable substrates (Figure 3.18), due to *N*-coordination, or in the case of the indole, *N*-deprotection catalysed by the phenol formed from breakdown of the directing group.

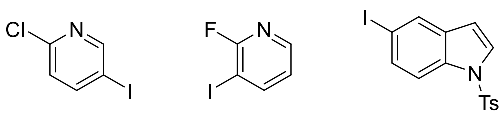
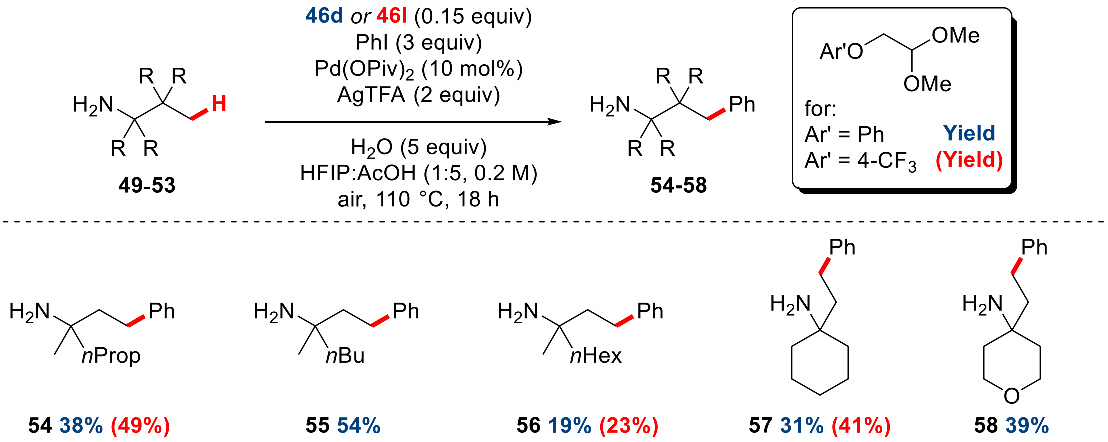


Figure 3.18: Failed aryl iodides

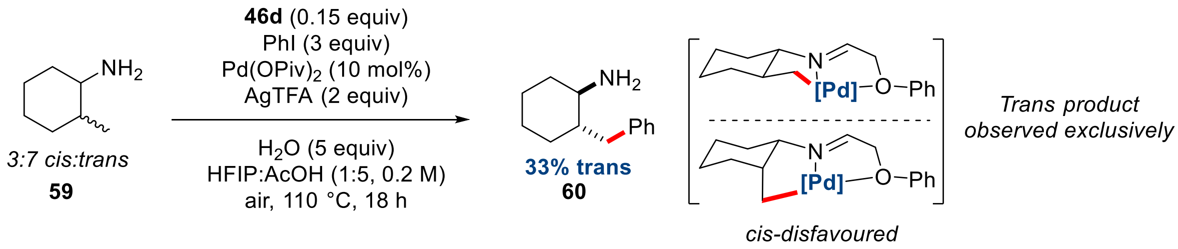
Fully α-substituted amine substrates (formed from a three-step protocol of addition of a Grignard to a ketone, azidation of the tertiary alcohol and reduction by $LiAlH_4$) were arylated (Scheme 3.37).



Scheme 3.37: Arylation of amine substrates

Changing the length of the alkyl group on the α-position of the amine effected the yield of the arylation. While the *n*-butyl group (**55**) was well tolerated, both *n*-propyl (**54**) and *n*-hexyl (**56**) derivatives were formed in reduced yield. With the more reactive acetal **46l**, the *n*-propyl product **54** could be formed in a synthetically useful yield of 49%. The *n*-hexyl product **56** was only formed in 23% maximum yield however, despite using the more active TDG **46l**. This diminished reactivity was likely due to the presence of the charged polar amino head and long aliphatic chain making the amine act like a surfactant in the polar acidic solution, blocking the reactivity. This effect was also likely present in a lower amount for cyclohexyl derivative **57**. The polar oxygen in the THF substrate meant that product **58** was formed in an improved 39% yield with acetal **46d**.

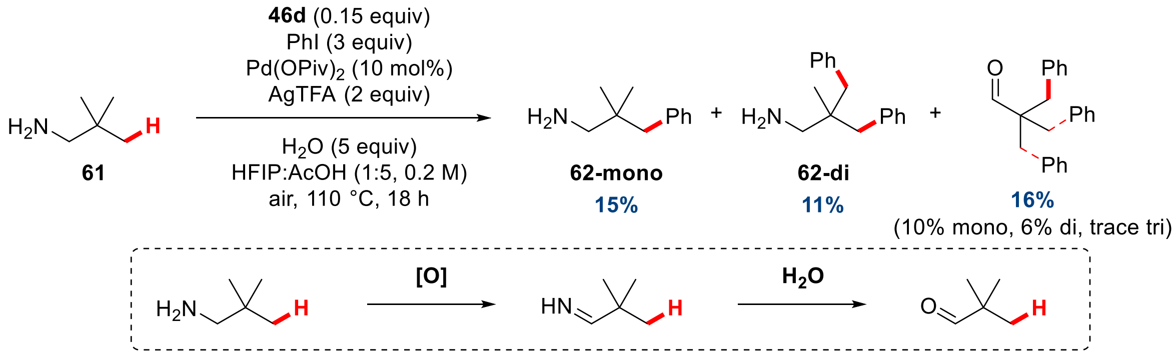
A curious result was obtained when using 2-methylcyclohexylamine **59**. When using acetal **46d** and iodobenzene, the arylation only occurred on the *trans* isomer of the starting material (Scheme 3.38).



Scheme 3.38: Arylation of 2-methylcyclohexylamine

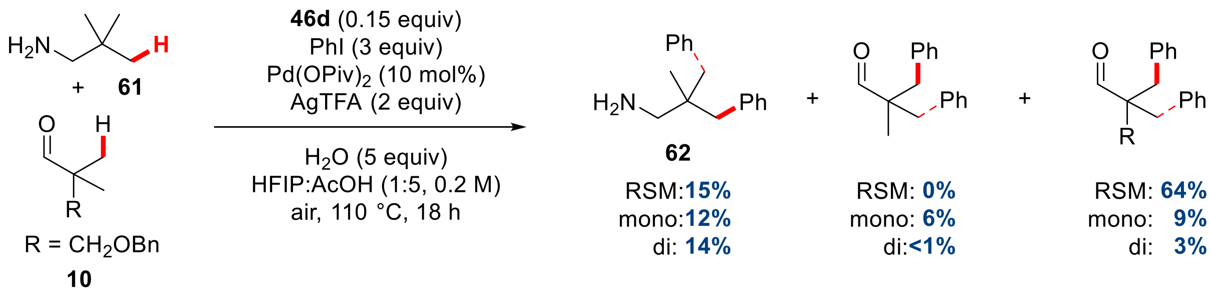
This remarkably high selectivity for this isomer, has most likely arisen due to the higher stability of the *trans*-palladacycle over the *cis*. In contrast, use of Yu's highly active pyridine TDG[98] led to a complex mixture of amine products, containing the *cis*-diastereomer of the arylated product **60**, as well as amines functionalised on the γ-methylene positions.

When using neopentylamine **61** as the substrate, it became apparent that α-oxidation[130] was occurring by the observation of pivaldehyde products in the crude ^{1}H NMR of the reaction mixture (Scheme 3.39). These products arose in absence of the directing groups, affirming that the formation of these aldehydic species occurred from α-oxidation to the imine by palladium[131] or silver,[94] not by isomerisation of the formed imine intermediates.



Scheme 3.39: Oxidation of neopentylamine leading to pivaldehyde products

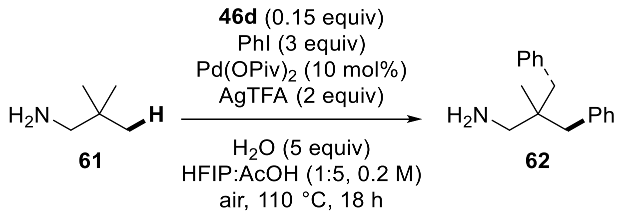
To understand if tertiary aldehydes could be arylated under the amine arylation conditions (opposed to the amine being arylated and subsequently oxidised) a mixture of neopentylamine **61** and tertiary aldehyde **10** was subjected to the amine arylation conditions (Scheme 3.40).



Scheme 3.40: Arylation of neopentylamine **61** in the presence of a second tertiary aldehyde **10**. RSM represents the relevant non-arylated starting material for each product component

The added tertiary aldehyde was arylated under the reaction conditions, suggesting that condensation with neopentylamine **61** formed an active monodentate imine directing group for *aldehyde* arylation.[108] Interestingly, the yields were similar for all products in the absence of acetal, suggesting competitive condensation of the added stoichiometric aldehyde **10** or of the catalytic acetal **46d** with the amine.

The reaction was further optimised for neopentylamine **61** to minimise the occurrence of unwanted oxidation pathways (Table 3.29).

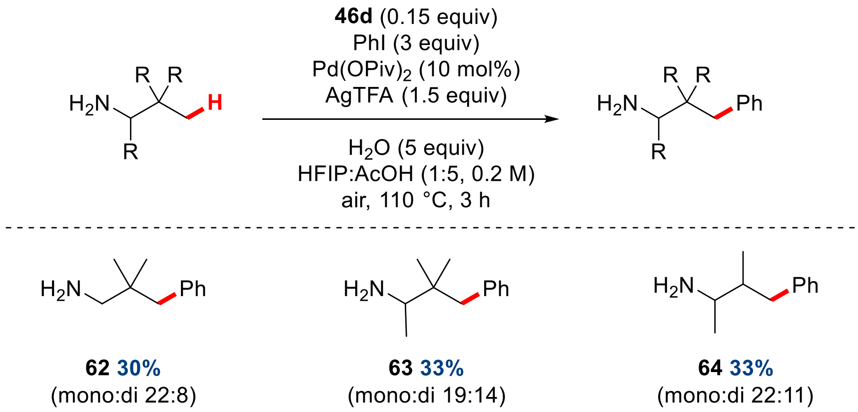


Entry	Change from conditions	yield 62-mono (%)	yield 62-di (%)	yield total (%)	pivaldehyde products (%)
1	none	15	11	26	16
2	90 °C	20	8	28	trace
3	CF_3-acetal **46l**	15	13	28	16
4	3 h	21	9	30	trace
5	5 equiv PhI	12	17	29	10
6	no acetal	14	4	18	23
7	**3 h, 1.5 equiv AgTFA**	**25**	**10**	**35 (30)**	**trace**
8	3 h, 1.5 equiv AgTFA, Ar	13	6	29	trace
9	3 h, 0.1 M	21	12	33	trace
10	3 h, 1.5 equiv AgTFA, 0.1 M	21	11	33	trace
11	3 h, 1.2 equiv AgTFA, 0.1 M	22	10	33	trace

Table 3.29: Optimisation table for neopentylamine **61**. [a]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses.

Reducing the temperature of the reaction led to a large reduction in the formation of the aldehyde products, resulting from a reduction in α-oxidation, leading to an improved yield of the monoarylated product **62-mono** and higher overall yield (Table 3.29, Entry 2). Under these conditions, CF_3-acetal **46l** led to no improvement in product formation. As per lowering the temperature, reducing the time of the reaction to 3 h led to an improved yield with only trace amounts of α-oxidation. For this substrate, effective monodentate direction by the amino group was also apparent, forming the arylated product in 18% yield in absence of acetal. In this case α-oxidation was exacerbated, with a 23% yield of the combination of arylated pivaldehyde products. A reduced reaction time of 3 h was taken forward for further optimisation. Reducing the amount of AgTFA to 1.5 equivalents gave the best yield of 35% by ^{1}H NMR (30% isolated) as a mixture of the mono- and diarylated species. Further changes in the amount of AgTFA and the concentration did not lead to yield improvements (Table 3.29, Entries 8–11).

Additional amines with reactive α-hydrogens were tested under these modified conditions (Scheme 3.41).



Scheme 3.41: Arylation of amines susceptible to α-oxidation under modified conditions

Arylated amines **63** and **64** were formed in 33% total yield each under the modified conditions. In each case, multiple arylation occurred giving a mixture of mono- and diarylated products. Under either set of conditions, amines bearing lower substitution patterns could only be formed in trace yields (Figure 3.19). This is likely to be due to a reduced Thorpe-Ingold effect, increased degrees of α-oxidation to inactive imines, as well as increased bis(amine) complex formation.

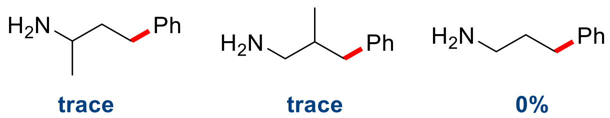
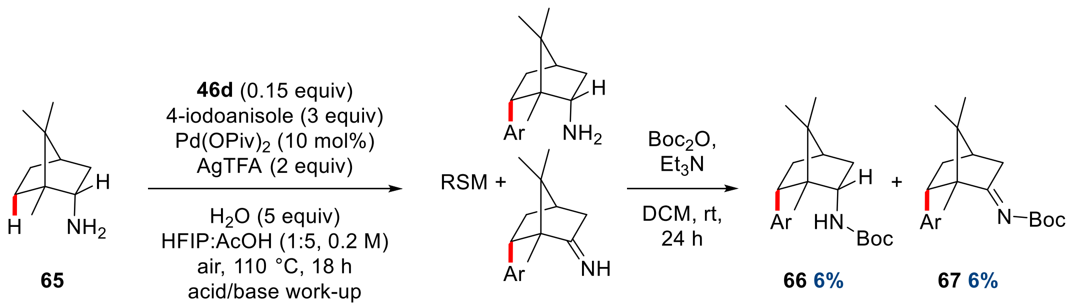


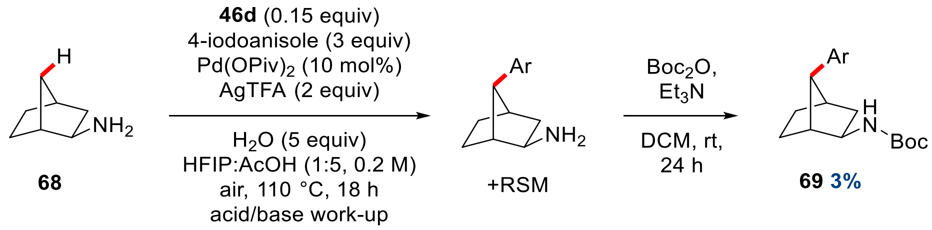
Figure 3.19: Failed amine substrates

Other complex bicyclic amines were also attempted, giving interesting results and supporting the occurrence of α-oxidation. Due to the higher molecular weight of these amines, a Boc-protection of the crude mixture of amines following the arylation and usual acid/base work up was implemented, to enable isolation of the products by column chromatography. Also to assist in the isolation, 4-iodoanisole was used as the coupling partner. α-Oxidation was observed when using (*R*)-(+)-bornylamine (**65**), where due to the steric stabilisation of the imine, it could be isolated as the Boc-derivative in 6% yield (**67**), with a further 6% on the product amine isolated separately (Scheme 3.42). On this highly hindered system, arylation was achieved in low yields on a γ-methylene position, and there was no evidence of arylation at any other C–H bond.



Scheme 3.42: Arylation of (R)-bornylamine to afford α-oxidised product

A very low yield from the arylation of the bridgehead position of *exo*-aminonorbornane **68** was achieved (Scheme 3.43). Notably, with (*R*)-(+)-bornylamine and *exo*-aminonorbornane arylated could be promoted in absence of acetal **46d** under these conditions, in slightly lower yields.



Scheme 3.43: Arylation at bridgehead position of *exo*-aminonorbornane

Based on work by Gaunt using bulky secondary amines for direct C-H functionalisation, including β-positions *via* a 4-membered palladacycle (see Section 3.4.2), some other potential amines, including some anilines, were tested under the reaction conditions (Figure 3.20).

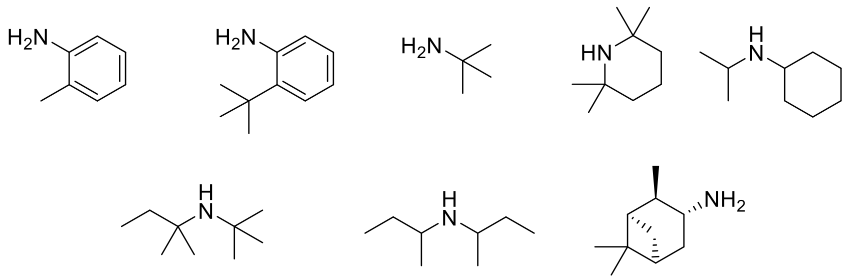
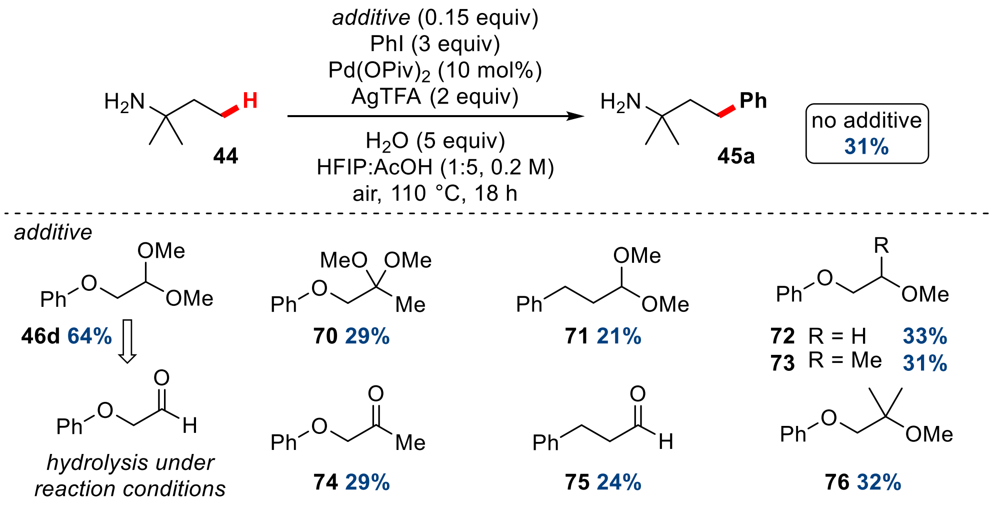


Figure 3.20: Failed amine arylation substrates

None of the bulky secondary or primary amines underwent arylation reactions at the β- or γ-positions except for di-*sec*-butylamine in which arylation could be observed in trace amounts, directed by the amino group. Anilines were not suitable substrates, and no mass recovery was observed following the Celite filtration.

To analyse the important features of the directing group formed using acetal **46d**, a structural comparison using related additives was conducted (Scheme 3.44).



Scheme 3.44: Structural comparison of directing groups

Importantly, the less reactive ketone/ketal derivatives were ineffective, being less reactive to imine formation. Additives with similar binding properties to the acetal, but with no potential for imine formation (**72**, **73** and **76**) could not promote the reaction. When removing the secondary binding oxygen (acetal **71** and aldehyde **75**), the yield compared to the background was decreased. This is potentially due to imine formation occurring, but the monodentate imine formed being a poorer directing group than the free amine.

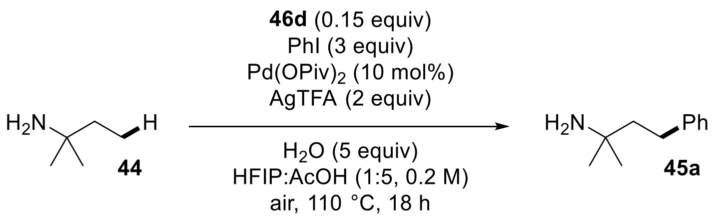
Considerable efforts were put towards formation of palladacycles of the imine and free amine, including with stabilisation by PPh_3 and pyridine ligands. No imine or palladacycle species could be formed or identified by mass spectroscopy or ^{1}H NMR. This difficulty in isolation or identification of these imine species is likely to be indicative of their short-lived transient nature in the reaction.

As formation of any imine species or related palladacycles was unsuccessful, kinetic studies in the form of “different excess” and “same excess” experiments, of Reaction Progress Kinetic Analysis (RPKA), pioneered by Blackmond in 2005,[119] were used, to improve understanding of the reaction.

RPKA is distinct from other forms of kinetic analysis as the progress of the reaction is examined in its entirety, meaning that features of the reaction (for example induction periods, product inhibition) commonly missed with methods such as initial rates, can be identified. In

2012, Blackmond's methods using reaction "excess" were extended to include visual comparisons of concentration profiles without the need for rate data.[132] Burés recently developed mathematical time normalisation techniques to identify orders in catalyst[133] and other reagents, using visual comparison of concentration profiles.[134]

For the amine arylation, the reaction was sluggish in an NMR tube and was largely heterogeneous. As a result, concentration data for each time point was obtained from a discrete, worked-up reaction. Yields were calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Experiments were carried out using the optimised conditions for the amine arylation reaction and the progress monitored by formation of arylated product **45a** (Scheme 3.45).



Scheme 3.45: Conditions used for RPKA experiments

Firstly, a reaction profile was carried out using the standard conditions (Figure 3.21). Concentrations were calculated from percentage yield using the total liquid volume in the reaction, assuming negligible contributions from the solid reagents and acetal ligand. For later experiments, concentration changes with respect to the control were also deemed negligible, due to the significant volume contributions of the solvent.

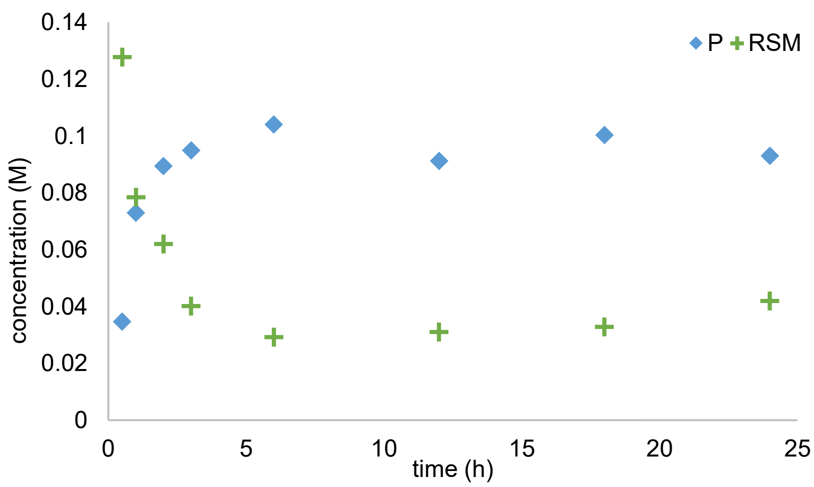


Figure 3.21: Reaction profile for standard arylation conditions. P = product **45a**, RSM = remaining starting material (*tert*-amylamine **44**)

The product is formed rapidly in the early stages of the reaction. The rate of product formation gradually reduces, reaching a plateau at around 3 h. On observing the concentration of the starting material, a smooth curve shows rapid initial consumption of the amine which also gradually plateaus after around 3 h.

The graphical method developed by Burés was employed to determine the order in palladium catalyst.[133] Reaction profiles were obtained at loadings of 5, 7.5, 10 (control) and 15 mol% loadings of $Pd(OPiv)_2$ (Figure 3.22).

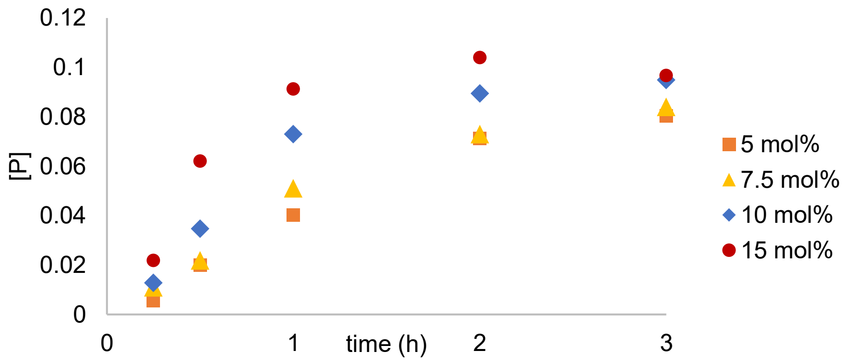


Figure 3.22: Plot of product formation at different $Pd(OPiv)_2$ loadings

The rate of formation of arylated amine **45a** positively correlated to the loading of the palladium catalyst, until ultimately reaching similar final values of conversion. To determine the order in catalyst, the time axis was normalised by changing the x-axis to $t[cat]^x$ (where X = catalyst order) and visually comparing at what value of X the overlay of the curves was best, which corresponded to the order in the reaction (Figure 3.23).[133]

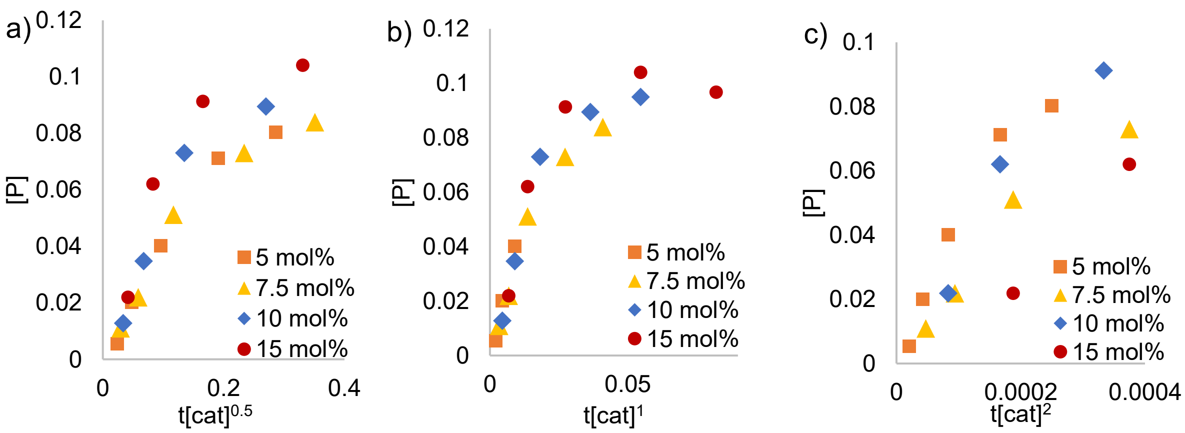


Figure 3.23: Time normalised plots for catalyst orders of a) 0.5, b) 1 and c) 2, showing the reaction to be first order in catalyst due to optimal overlay

The best overlay of all product concentration curves occurs when the catalyst order is set to 1, which is particularly apparent at the most productive stage of the reaction at times less than 1 h. This value is consistent with what would be expected for accepted catalytic cycles with a monomeric Pd catalyst.[19]

Reaction profiles were also obtained varying the catalytic acetal component, at loadings of 5, 15 (control) and 25 mol%, as well as in the absence of acetal (Figure 3.24).

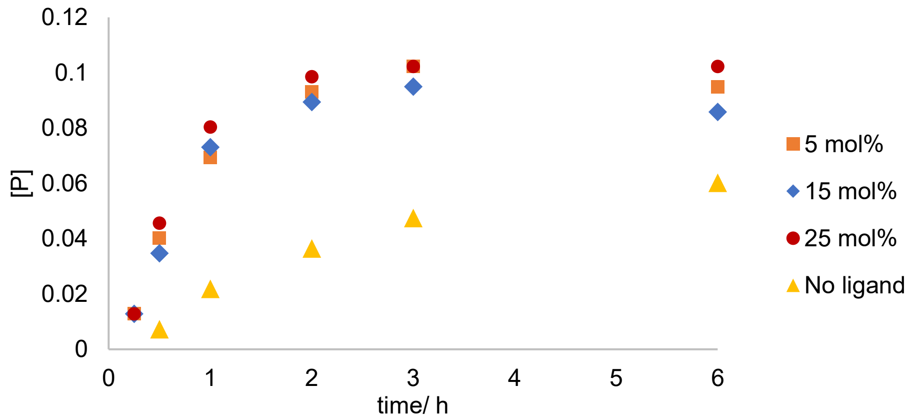


Figure 3.24: Zero order rate dependence on catalytic acetal **46d**

Unlike with the catalyst, the reaction rate is independent on the concentration of the acetal component, even at loadings as low as 5 mol%. This zero order rate dependence may indicate saturation kinetics of acetal **46d** even when used at very low concentrations, i.e. the catalytic cycle of the TDG is fast and does not contain the turnover limiting step. In the absence of the acetal, the rate is distinctly lower, indicating a change in mechanism (to a monodentate amine directing group) when there is no potential for imine formation.

The effects of using CF_3-acetal **46l** and diCF_3-acetal **46m** were also investigated (Figure 3.25).

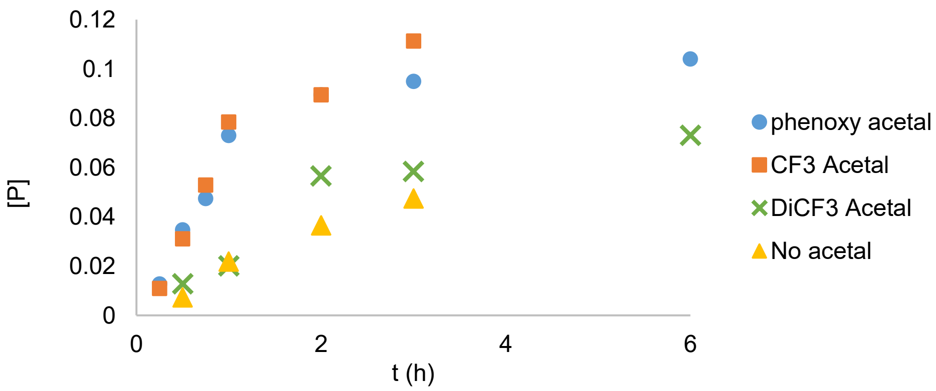
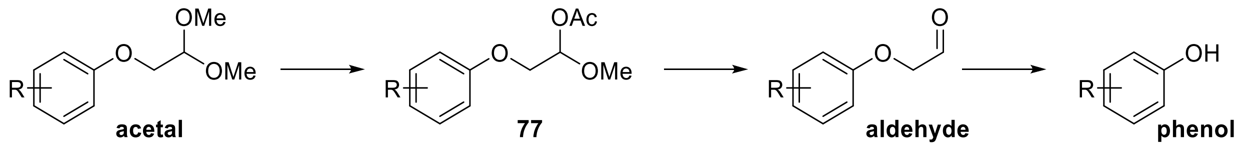


Figure 3.25: Reaction profiles of different acetal activators for the amine C–H arylation

CF_3-acetal **46l** and phenoxy acetal **46d** form the arylated product at the same rate when using *tert*-amylamine **44** and iodobenzene. Di-CF_3 acetal **46m** however, only provides a slight advantage over the reaction in absence of acetal.

It was observed that CF_3-acetal **46l** (and to a greater extent the di-CF_3) had superior stability under the reaction conditions, with a slower breakdown to the respective phenols (Table 3.30). The presence of breakdown species of the acetal could be identified easily from the crude ^1H NMR spectra (Figure 3.26).



acetal **77** **aldehyde** **phenol**

t (h)	Distribution of phenoxy acetal 46d (%)					Distribution of CF_3-acetal 46l (%)				
	acetal	**aldehyde**	***77***	**phenol**	**total**	**acetal**	**aldehyde**	***77***	**phenol**	**total**
0.25	46	11	18	34	109	57	4	9	3	73
0.5	20	8	2	70	100	48	5	16	17	86
0.75	9	3	3	99	114	25	6	12	45	88
1	0	0	0	90	90	17	9	22	53	101

Table 3.30: Proportion of acetal breakdown products during the course of the amine arylation reaction.

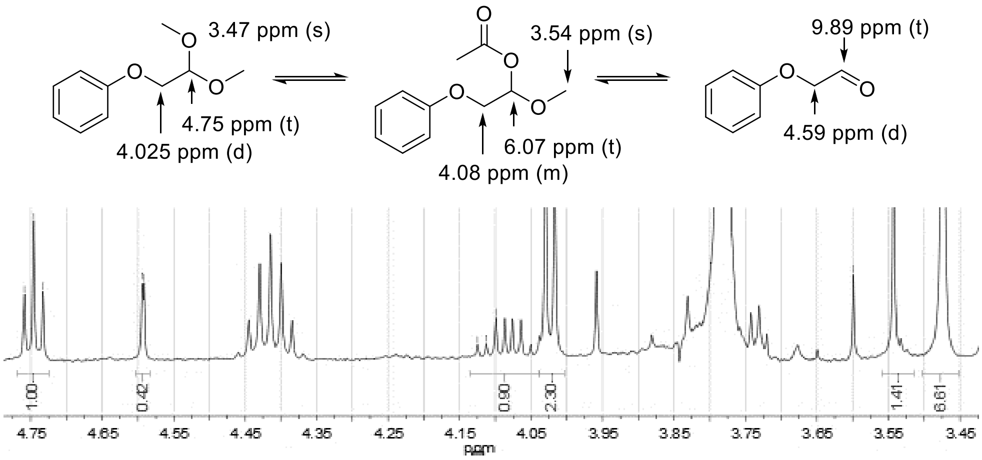


Figure 3.26: Crude ^1H NMR spectra of related acetal signals

It had been identified previously that the acetal can breakdown to the corresponding phenol (which is inactive as a ligand, see Table 3.28, Entry 16). However, addition of further acetal before or during the reaction course did not improve final yields using *tert*-amylamine as the substrate. The improved stability of CF_3-acetal **46l** does not have a marked effect on this particular substrate/aryl iodide system, but in this instance the final yields for the two acetals are similar. It may be the case that other substrate and aryl iodide combinations are arylated at a slower rate, and so the presence of more the stable acetal **46l** can be an advantage, leading to higher final yields.

"Different excess" experiments were conducted where the concentration of a single reactant is changed, and all others are kept constant. The starting concentrations of the amine (Figure 3.27), aryl iodide (Figure 3.28) and silver trifluoroacetate (Figure 3.30) were modified to identify the orders in these reagents (Table 3.31). A third experiment in each series was also conducted using even lower initial concentrations, to investigate any change in reaction orders in more extreme cases.

Experiment	Concentration amine 44	Concentration PhI	Concentration AgTFA
A	0.183 (1 equiv)	0.548 (3 equiv)	0.365 (2 equiv)
B	**0.140** (0.77 equiv)	0.548 (3 equiv)	0.365 (2 equiv)
B2	**0.097** (0.53 equiv)	0.548 (3 equiv)	0.365 (2 equiv)
C	0.183 (1 equiv)	**0.365** (2 equiv)	0.365 (2 equiv)
C2	0.183 (1 equiv)	**0.274** (1.5 equiv)	0.365 (2 equiv)
D	0.183 (1 equiv)	0.548 (3 equiv)	**0.274** (1.5 equiv)
D2	0.183 (1 equiv)	0.548 (3 equiv)	**0.183** (1 equiv)

Table 3.31: Starting concentrations (M) for different excess experiments

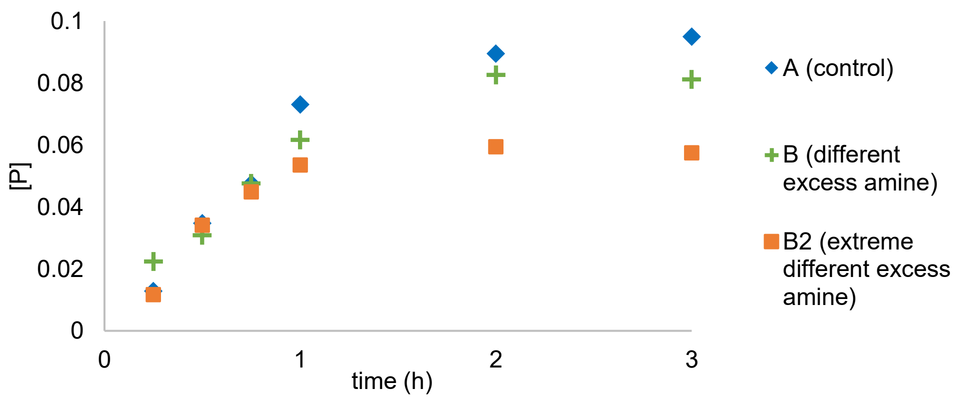


Figure 3.27: Different excess experiment, amine starting material **44**

The rate of product formation when changing the initial concentrations of the amine (B, B2), up to the point of where the conversion to product stops at the different amine concentrations, is the same, even in the extreme case. The rate is therefore independent of the starting amine concentration (zero order in amine **44**). This indicates that the formation of bis(amine) palladium complexes with the starting material is not hindering the reaction.

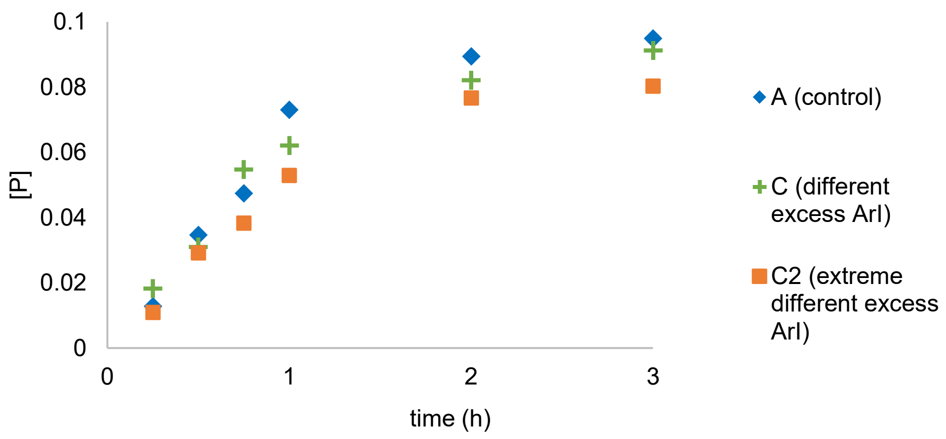


Figure 3.28: Different excess experiment, ArI

The same rate was observed at 2 or 3 equivalents of PhI (A, C). At a lower concentration, using 1.5 equivalents of iodobenzene (C2) there was only a slight drop in rate. The reaction is zero order in PhI under the standard arylation conditions, but at lower concentrations there could be potential for a positive order in aryl iodide.

The effect of the aryl iodide was also investigated by observing product concentration profiles using alternative aryl iodides with different electronic properties (Figure 3.29).

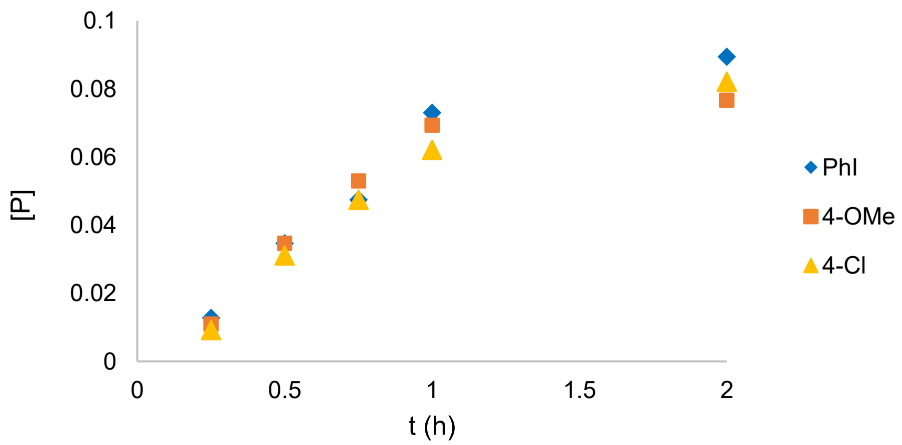
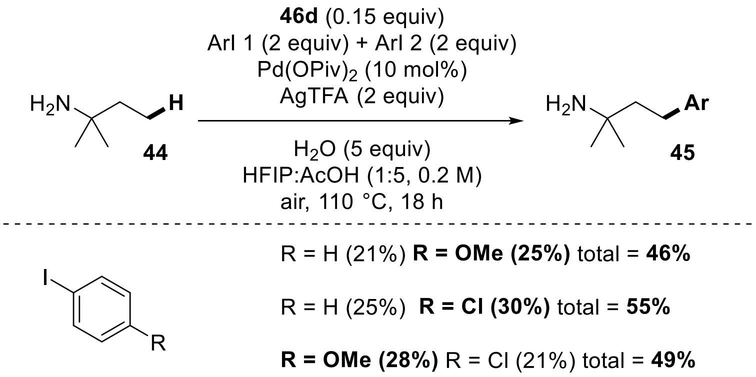


Figure 3.29: Concentration profiles with alternative aryl iodides

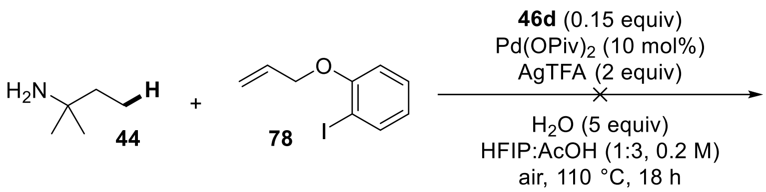
The same rate was observed with iodobenzene, 4-iodoanisole and 4-chloroiodobenzene, providing further evidence of a zero order rate dependence of the aryl iodide. A slower rate was observed with 4-nitroiodobenzene; however, this coupling partner was also highly insoluble. Competition experiments identified some slight preference of products derived from 4-iodoanisole (Scheme 3.46).



Scheme 3.46: Aryl iodide competition experiments

The slight preference for the 4-iodoanisole in these cases may be due to increased pre-coordination with the more electron rich aromatic and the Pd catalyst. Despite this however, the product yield differences between the different aryl iodides are small, supporting that the aryl iodide is not involved in the turnover limiting step.

A final experiment investigating the aryl iodide involved an aryl iodide that can function as a radical trap (**78**). This ortho-substituted aryl group could not be installed onto the *tert*-amylamine substrate under these conditions, and so could not provide evidence supporting or contradicting aryl radical formation.



Scheme 3.47: Arylation using radical trap aryl iodide

For the different excess experiments varying the amount of AgTFA (Figure 3.30), a zero rate dependence was also observed as the increase in product yield between the control and both different excess experiments occurs at the same rate up to the point of the maximum yield. The final yield is markedly dependent on the amount of AgTFA; with just 1 equiv of AgTFA (experiment D2), the yield dropped significantly.

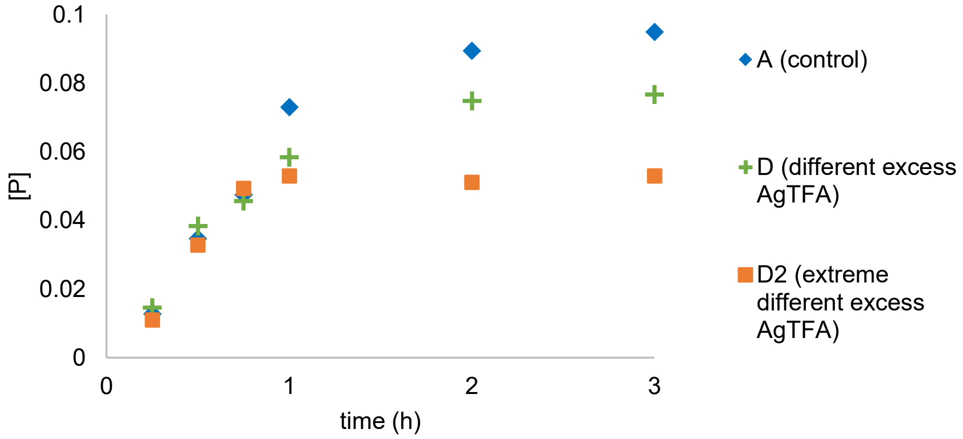


Figure 3.30: Different excess experiment, AgTFA

A "same excess" experiment was very informative. This experiment mimics starting the reaction at a later time point, and can be used to identify the presence of product inhibition or catalyst deactivation.[119,132] In this study, a time point was selected where the reaction had progressed a significant amount, in 1 h, where there is 40% product formed. The reaction was set up as normal, but using only 60% of the usual amine concentration, and less ArI to keep the same excess (assuming only 0.4 of the 3 equivalents had reacted, so 2.6 equivalents). The loadings of catalyst, acetal, water, and silver were kept constant.

To consider product inhibition, a same excess experiment was also conducted with the addition of the product for each discrete experiment at the concentration expected at the 1 h time point. The concentrations of each of the components that change in these experiments are given in Table 3.32.

	Experiment	Concentration SM	Concentration ArI	Concentration P added
A	Control	0.183	0.548	0
B	Same Excess t = 1 h	**0.110**	**0.475**	0
C	Same Excess t = 1 h + product **45a**	**0.110**	**0.475**	**0.073**

Table 3.32: Starting concentrations (M) for same excess experiments.

Figure 3.31a shows the raw data collected for the same excess experiments, with comparison to the control reaction. To compare the data, the graphs had to be normalised. The same excess curves were hence time shifted forward by 1 h (Figure 3.31b). As using product concentration, same excess experiment (B) was also adjusted to account for the expected product concentration under standard conditions (+ 0.073 M added to each point).

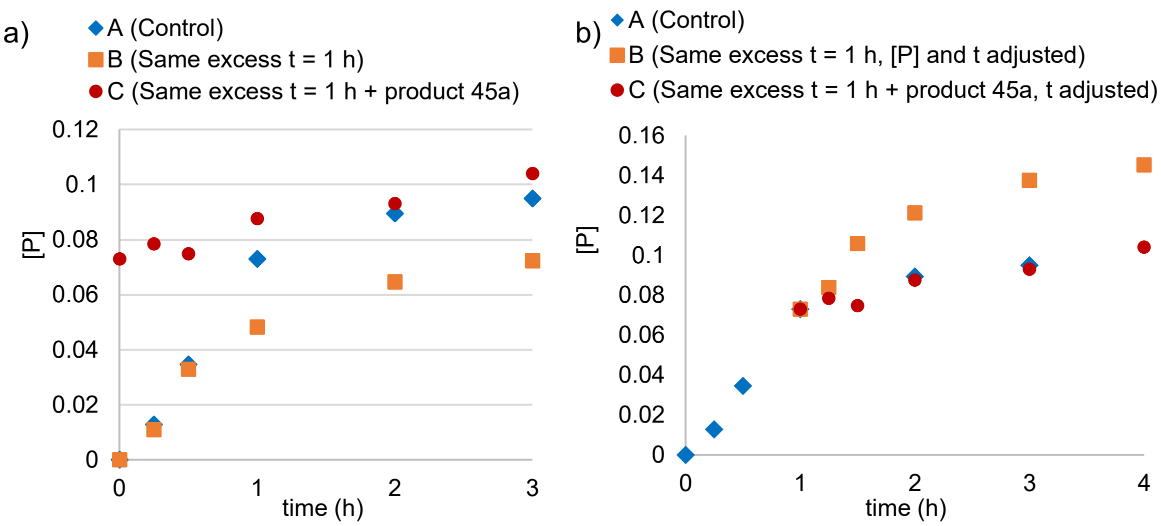


Figure 3.31: a) Plot of observed/raw product concentration for same excess experiments. b) Plot using adjusted time and [P]

The same excess experiment (B, orange) shows that the product is formed at a faster rate to the standard control reaction (A, blue) representing inhibition at the later time points. For the same experiment but in the presence of product (C, red) the points follow the control curve, suggesting that product inhibition is a significant cause of the arrested rate, preventing full conversion. The mechanism of this inhibition is likely due to competitive coordination of the product to the Pd catalyst.

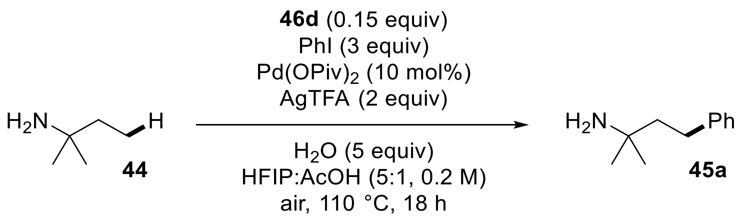
The observed concentration profiles (a linear increase which then tails off and plateaus) can be rationalised from the obtained orders in reagents from the different excess experiments. The amine arylation reaction has a first order rate dependence for catalyst and a zero order in all other reaction components, meaning a simple rate equation can be proposed (Equation 1).

$$rate = k[cat]_t, \qquad where\ [cat]_t = [cat]_0 - y[P]^x$$

Equation 1: Zero order rate law for amine arylation at constant catalyst concentrations. When product catalyst complexation occurs the rate becomes related to product complexation multiplied by and raised to arbitrary constants y and x.

In the early stages of the reaction, at low product concentrations, little to no Pd-product amine complexation occurs, therefore $[cat]_t = [cat]_0$ and the reaction is linear with zero order kinetics. However, at a critical higher product concentration (at approx. 40% conversion), inactive Pd-product complexes begin to be formed, removing active catalyst from the reaction. This causes a gradual reduction in $[cat]_t$ and therefore rate. Eventually, all the catalyst is trapped in these complexes ([cat]$_t$ = 0]), causing the yield to plateau. Addition of more catalyst at t = 1 h did not lead to increased conversion; presumably also due to rapid formation of the inactive complexes at high product concentrations, or as the acetal had degraded.

Reagent spiking experiments, where further catalyst or acetal **46d** was added, were also conducted to investigate possible catalyst/ligand deactivation (Table 3.33).

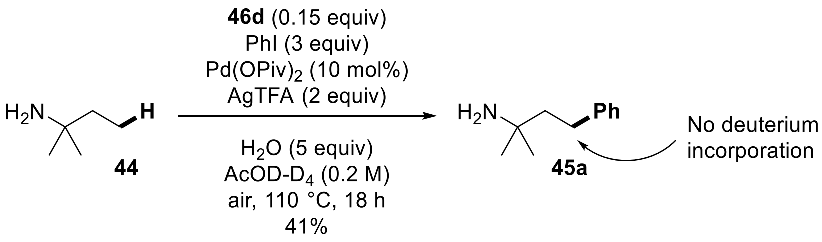


Entry	Description	yield 45a (%)[a]
1	After 3 h, open, seal, heat 2 h	54
2	After 3 h, open, add 0.15 equiv ligand, seal, heat 2 h	54
3	After 3 h, open, add 5 mol% catalyst, seal, heat 2 h	53

Table 3.33: Spiking experiments. [a]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The spiking experiments showed no advantage compared to the control reaction, potentially suggesting that catalyst or ligand deactivation is not what is inhibiting the reaction.

Studies were performed using deuterium labeling to provide insight into the C–H activation step. When running the reaction in deuterated acetic acid, no incorporation of deuterium into the benzylic position of the arylated product could be observed (Scheme 3.48). This is suggestive of an irreversible C–H activation step. This was identified by the relative integrals of the benzylic and second methylene signal of the product, compared to the relative result in non-deuterated acetic acid (Figure 3.32).



Scheme 3.48: C–H Arylation in AcOD-D_4

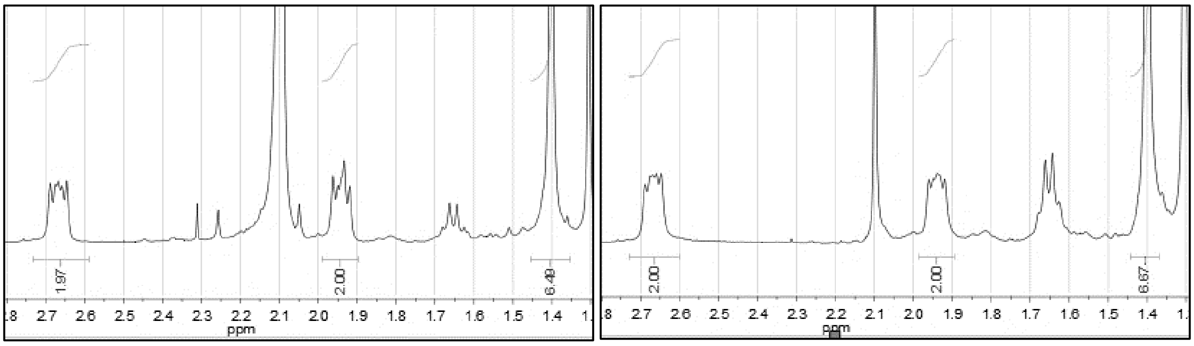
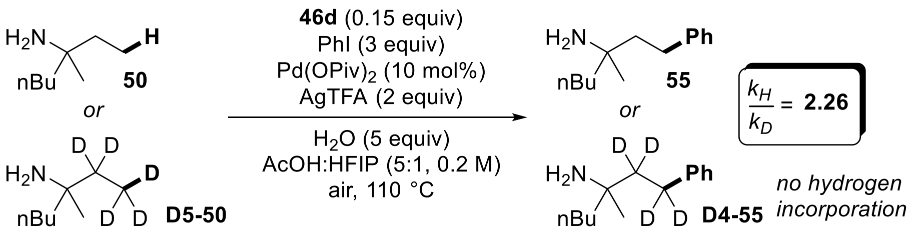


Figure 3.32: ^1H NMR spectra showing product signals for arylation reaction in CH_3CO_2H (left) and CD_3CO_2D (right)

A deuterated equivalent of the *n*-butyl substrate **50** was synthesised, and the rate of arylation compared to the parent proteo species (Scheme 3.49, Figure 3.33).



Scheme 3.49: KIE experiment

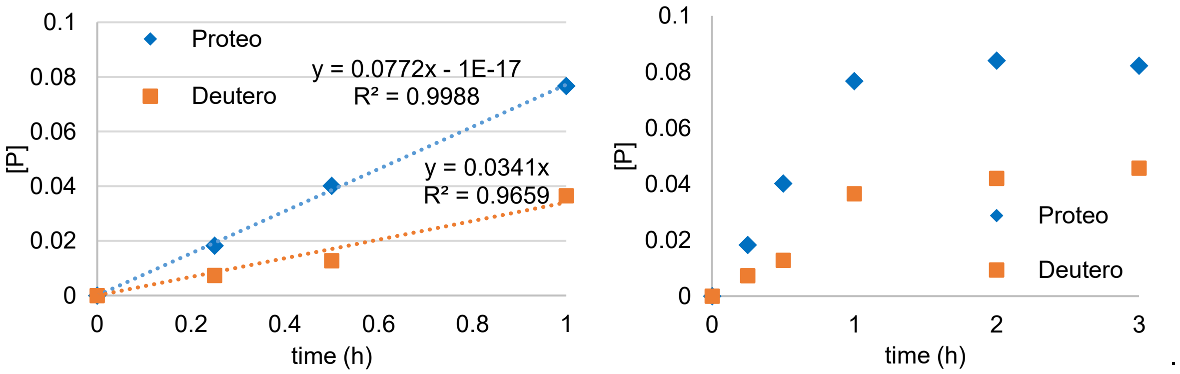
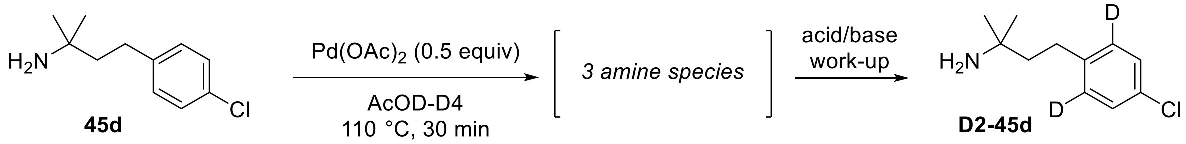


Figure 3.33: Plots of product formation with proteo and deutero amine substrates. Left: initial (zero order) stages of the reaction, with fitted linear trendline, right: full profile

The reaction displayed zero-order kinetics at early time points, and so linear trendlines with good R^2 (coefficient of determination) values for both substrates gave rate values directly from the gradients. A rate of 0.0772 $M \cdot h^{-1}$ for the proteo species and 0.0341 $M \cdot h^{-1}$ for the deutero was observed; giving a KIE of 2.26. This significant value suggests a C–H activation is the TOLS. After this time, the reaction rate reduces as the catalyst concentration decreases due to complexation to the product.

Complexation between the product and catalyst was investigated using ^{1}H NMR. It was expected that the inhibiting coordination might be related to the formation of bis(amine) product palladium complexes, and so 50 mol% $Pd(OAc)_2$ was added to arylated amine **45d** in deuterated acetic acid (Scheme 3.50). This amine was selected as any changes in the aromatic signals would be more discernable than the phenyl used in the kinetic experiments.



Scheme 3.50: Interactions of arylated amine **45d** with $Pd(OAc)_2$

However, what was observed was a mixture of three amine containing species. After heating for 30 min, and working-up the reaction, the **D2-2f** was isolated, fully deuterated at the *ortho*-position, ε-to the amine.

The ^{1}H NMR from this study is given in Figure 3.34.

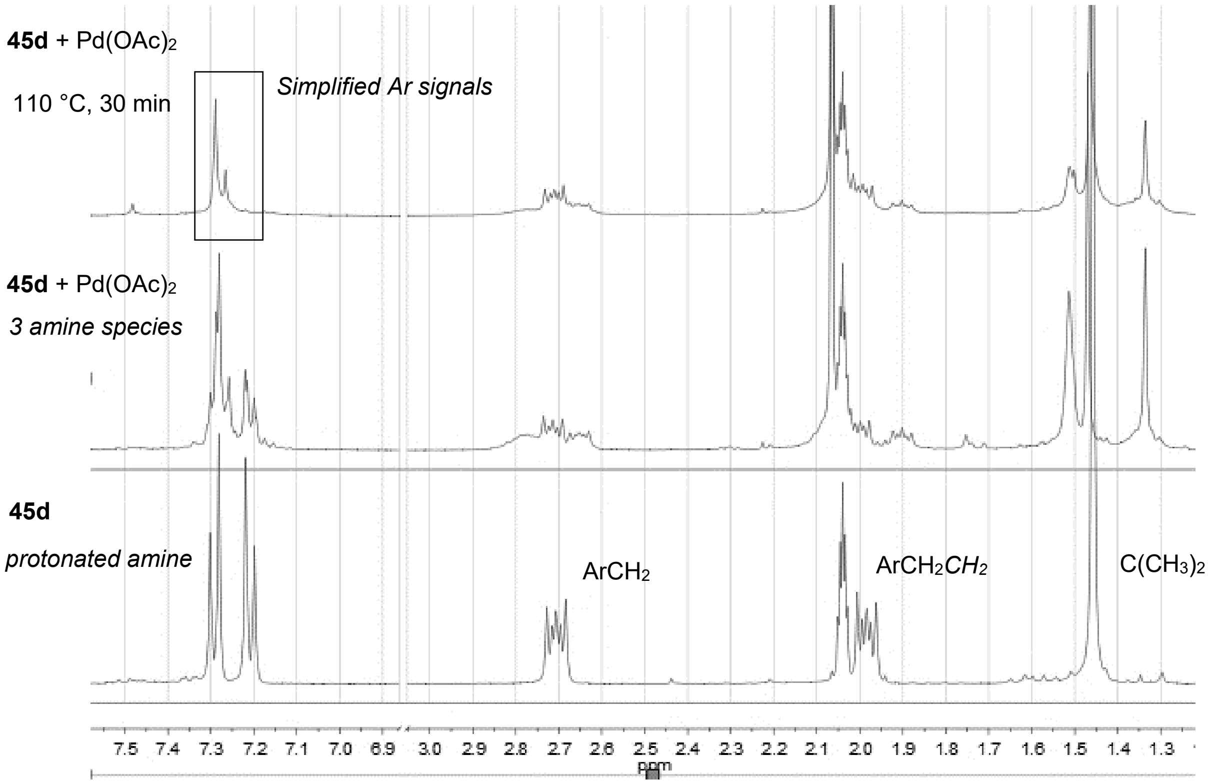
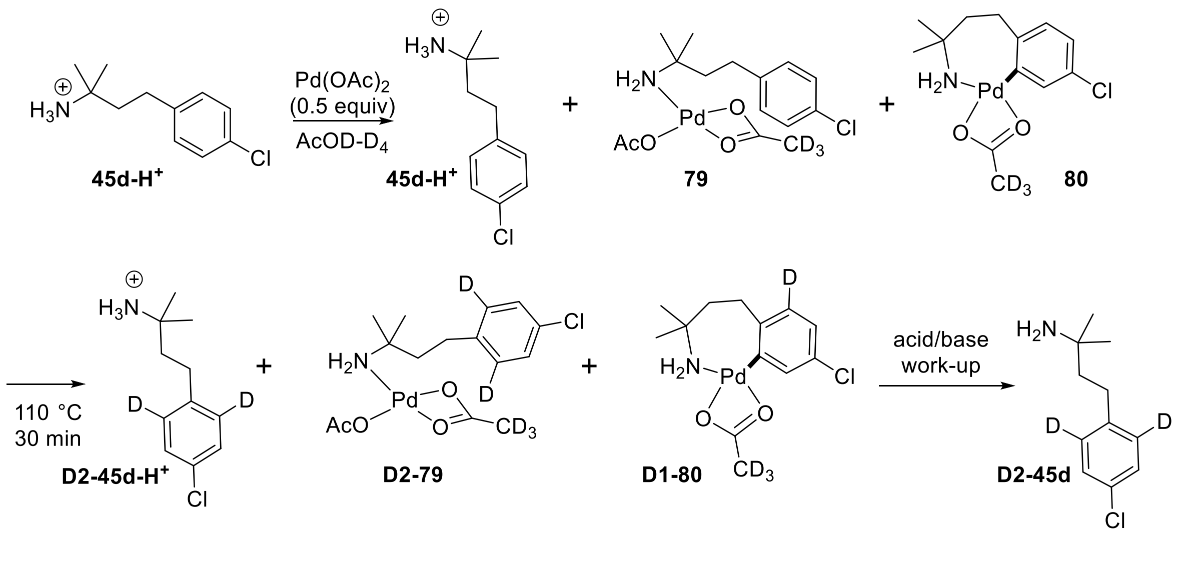


Figure 3.34: ^{1}H NMR experiments demonstrating product-palladium complex formation. Bottom: Amine **45d** in AcOD-D_4; middle: after addition and solubilisation of 0.5 equivalents of $Pd(OAc)_2$; top: after heating to 110 °C for 30 min. Region between 3-7 ppm cut for clarity, no signals were observed in this range

The spectra of the amine **45d** in AcOD-D_4 (bottom) signifies the protonated amine species. Upon adding $Pd(OAc)_2$, the benzylic CH_2 signal (2.7 ppm) shows the formation of 2 additional environments, with corresponding signals for the other CH_2 and *gem*-dimethyl groups (in a 1:0.8 ratio), suggesting 2 new species. In the aromatic region, the typical *p*-substitution pattern becomes more complex and there is a growing singlet at 7.28 ppm. This corresponds to partial deuteration of the Ar signals. Heating this mixture led to further simplification of the aromatic signals. These observations are proposed to arise from reversible C(sp^2)–H activation from cyclometalation of the product, directed by the amine to the *ortho*-position of the aromatic, ε to the amine. In the absence of palladium this deuteration does not occur. In the presence of starting material (in a 1:1 mixture with the Cl arylated product) deuteration still readily occurs, highlighting that this coordination is competitive to complexation of the amine starting material. Using this data, it can be proposed that the product coordinates to the palladium catalyst forming amine complex **79** and cyclometalated complex **80**, with the non-complexed amine resting at its protonated state. A putative assignment of all these species is given in Scheme 3.51.



Scheme 3.51: Full assignment of observed species in the product complexation experiment

The facile amine directed ε-cyclopalladation of the product is likely to be the main cause of product inhibition, outcompeting coordination of the starting material amine or imine. At high concentrations of product, this process is competitive to the turnover limiting C(sp^3)–H activation step, with the catalyst resting as these product complexes. No evidence of functionalisation at the product ε-position indicates that although the C–H activation can occur at room temperature, there are high energy barriers for oxidative addition or reductive elimination of these species, even at the C(sp^3)–H arylation temperature of 110 °C.

Figure 3.35 shows the fully assigned spectra for the mixture of deuterated amine species.

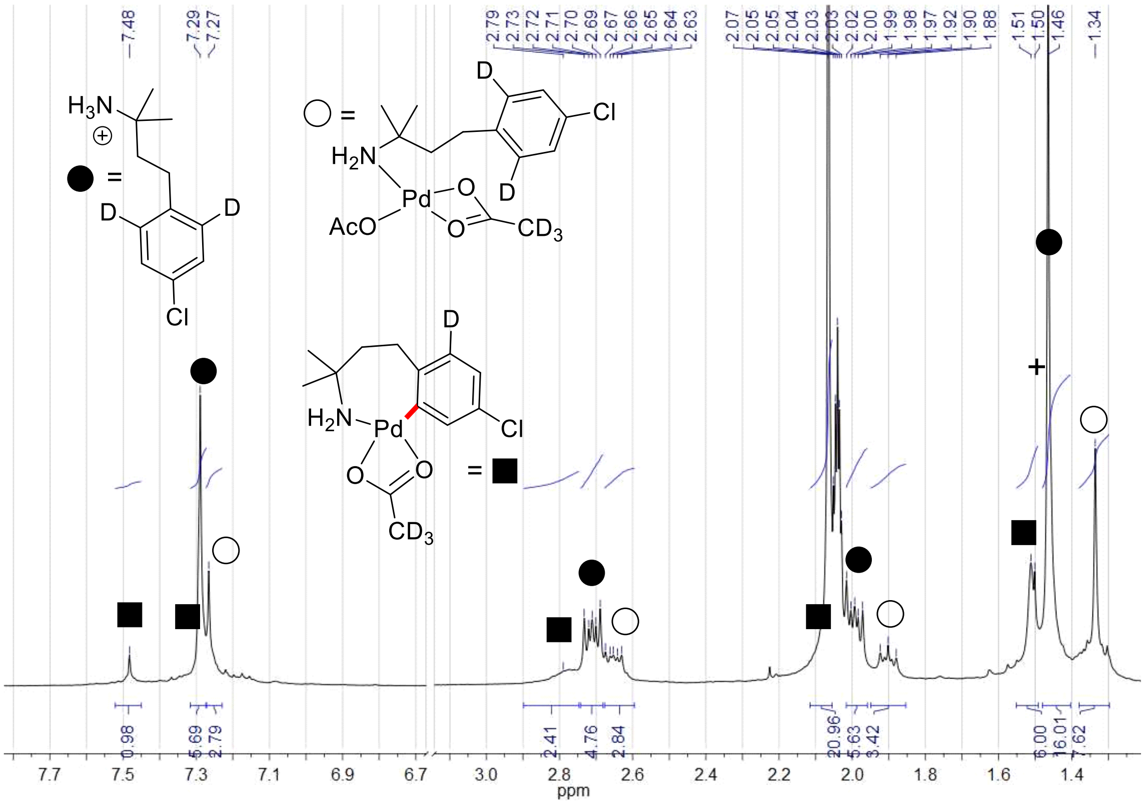


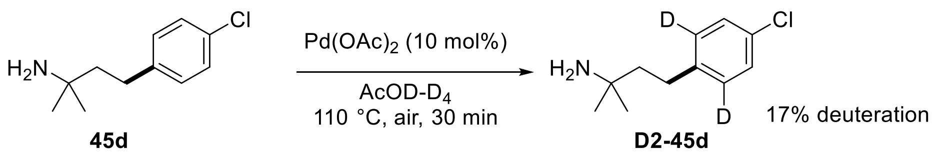
Figure 3.35: ^{1}H NMR of free and complexed amine species after heating at 110 °C for 30 min in AcOD-D_4

Tentative support for these species was also obtained by mass spectrometry studies on the reaction mixture, from a 1:1 **45d**/$Pd(OAc)_2$ mixture in AcOD, with the following observed masses displaying appropriate Pd isotope patterns:

Complex **D2-79**: HRMS (TOF-ES+) m/z Calcd. for $C_{13}H_{14}D_5{}^{35}ClNO_2{}^{106}Pd$ [M-OAc]$^+$: 367.0453; Found: 367.0314.

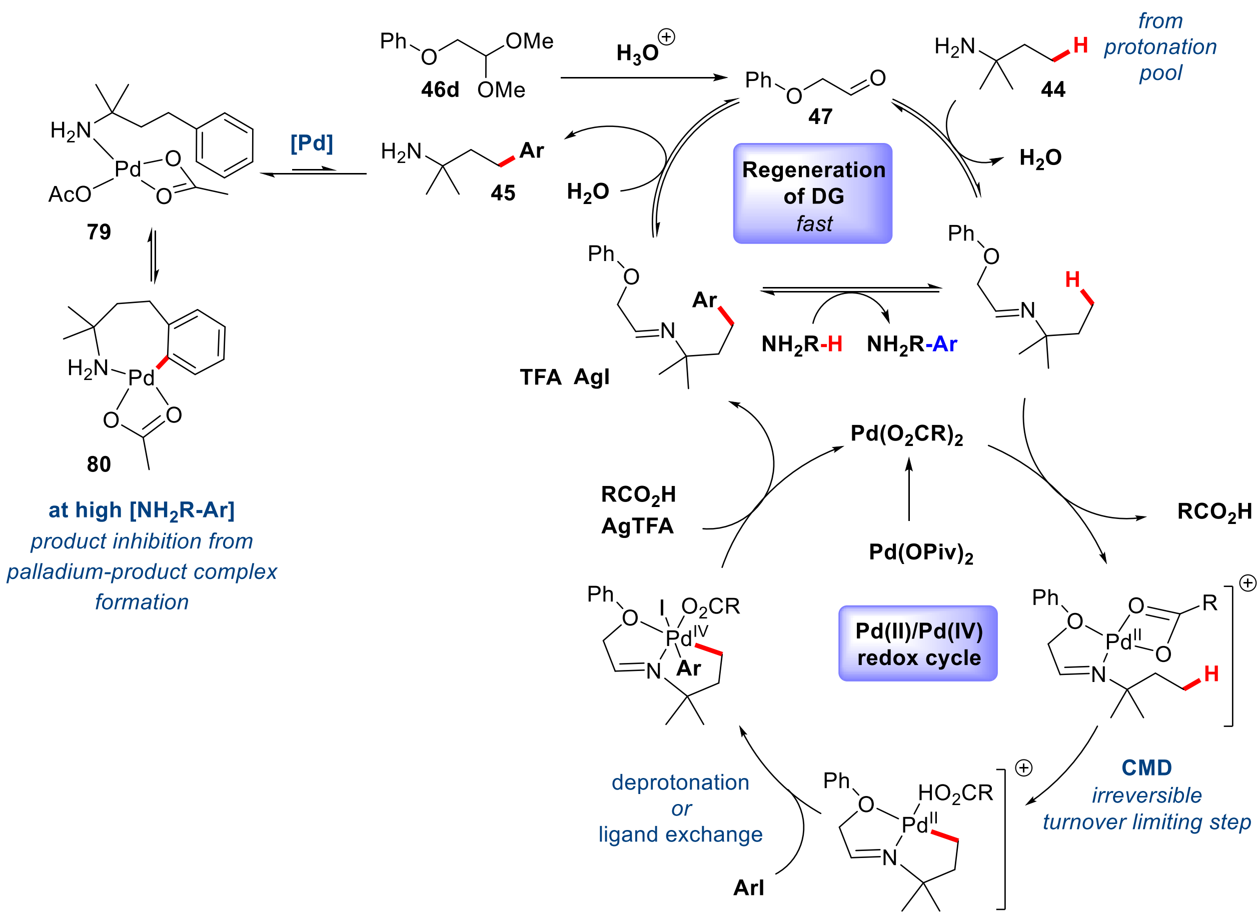
Complex **D1-80**: HRMS (TOF-ES+) m/z Calcd. for $C_{13}H_{14}D_4{}^{35}ClNO_2{}^{106}PdNa$ [M+Na]$^+$: 388.0204; Found: 388.0563.

To test the potential development of this ε-deuteration, the product was reacted with only 10 mol% Pd for 30 minutes, which led to only low (17%) levels of deuteration (Scheme 3.52). An insoluble precipitate, assumed to be Pd-black, was also formed in large amounts.



Scheme 3.52: Catalytic ε-deuteration of arylated product **45d**

Based on the results from kinetic and mechanistic investigations, the following dual catalytic cycle is proposed (Scheme 3.53)



Scheme 3.53: Proposed catalytic cycle for C–H arylation of amines with a transient imine directing group

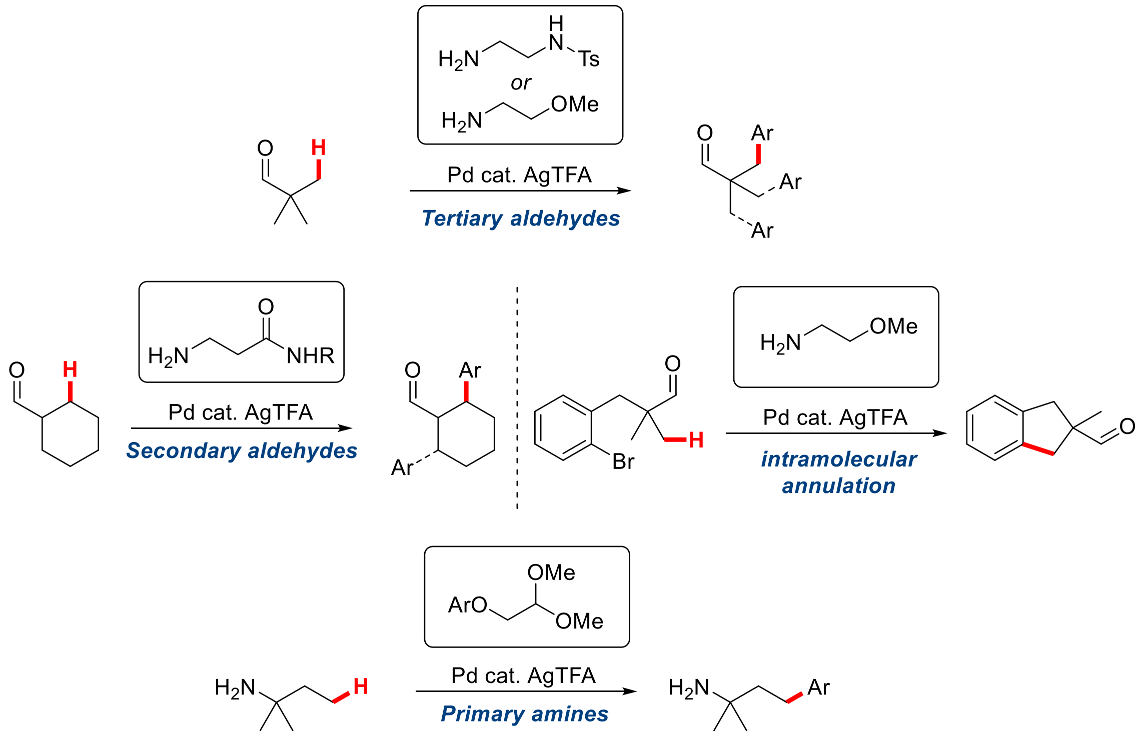
Under the reaction conditions, the acetal is hydrolysed to the corresponding aldehyde **47**, which can be observed in the early stages of the reaction by ^{1}H NMR. The aldehyde condenses with the free amine from a pool of the protonated amine species, forming the active imine. Complexation of the imine to the palladium catalyst with loss of acetic acid (or pivalic acid/trifluoracetic acid) would give a positively charged imine-Pd species to undergo turnover-limiting concerted metalation deprotonation (inner or outer-sphere)[19] to afford the cyclometalated imine intermediate. It is likely that deprotonation or ligand exchange occurs to form a neutral species which then undergoes oxidative addition to a Pd^{IV} intermediate. The oxidative addition step may be assisted by the presence of silver and/or air. C–C bond formation by reductive elimination would afford the product imine and regenerate the Pd^{II} catalyst. The aldehyde is turned over by hydrolysis with water, or direct transamination, generating the product **45**. The product amine inhibits the reaction by competitive coordination to the catalyst and cyclometalation, removing palladium from the productive cycle. A catalytic cycle can also be drawn for the reaction in absence of the imine TDG, where the amine acts as a monodentate directing group; corresponding to the 31% background reaction observed in absence of acetal.[19]

In summary, aliphatic amines branched at the α-and β-positions can be arylated with a large selection of aryl iodides using a transient *exo*-imine directing group formed from simple alkyl acetals. α-Oxidation becomes problematic when using amines bearing α-hydrogens, but this can be circumvented by using slightly milder reaction conditions. RPKA and NMR studies were critical in elucidating additional information about the catalytic cycle and observed concentration profile. Reaction orders in all reagents were obtained and the presence of product inhibition rationalised by an unusual ε-cyclopalladation of the arylated product. For a concise account of this project, see: *Chem. Eur. J.*, **2018**, DOI:10.1002/chem.201804515.[135]

4. Conclusions and Future Work

Transient imine directing groups offer a step-efficient approach to C(sp^3)–H functionalisation by avoiding the need for discrete DG installation and removal steps required for traditional amide bound directing groups.

In this thesis, transient *endo*-imine directing groups have been explored in three applications for the one-pot functionalisation of aliphatic aldehydes. *exo*-Imine transient directing groups with secondary ether coordinating groups have also been exploited for the direct C–H functionalisation of primary aliphatic amines. In each case, the focus has predominantly been on the structure of the transient directing groups and how this affects the reactivity.



Scheme 4.1: Summary of C(sp^3)–H arylations using diverse transient directing groups developed in this thesis

For tertiary aldehydes, following a prerequisite study on arylation of pre-formed imines, *N*-tosyl and O-methyl secondary binding groups were optimal. Aryl iodide and aldehyde scope was explored, and the proposed mechanism of the reaction supported through ^{1}H NMR studies and the isolation and crystal structure of a cyclometalated palladium complex.

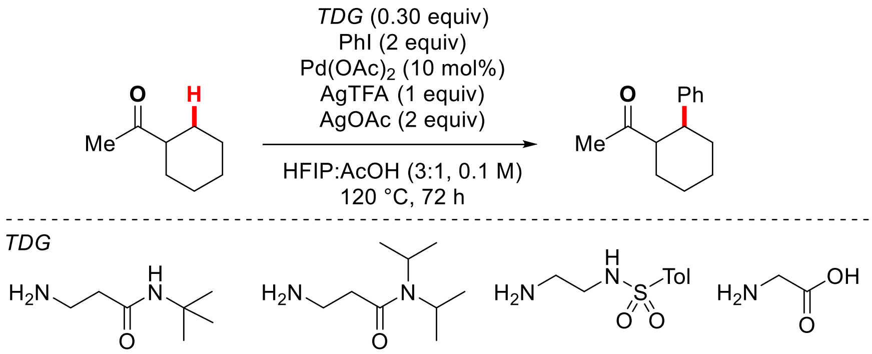
The tertiary aldehyde study led to the development of a secondary aldehyde arylation, where amino-amides, coordinating through the carbonyl oxygen through a 6-membered cycle, could enable activation of methylene C(sp^3)–H bonds. The structure of the amide group was explored to observe changes in the reactivity, which found that highly hindered alkyl amides (secondary and tertiary) were optimal. A palladacyclic species has been isolated. Preliminary optimisation demonstrated the potential for greater selectivity for mono- *or* diarylation. This work is to be further explored, to identify the optimal conditions for substrate scope.

Aryl bromides have been shown to be unreactive in other aldehyde arylation studies in this thesis as well as through the transient imine C(sp^3)–H functionalisation literature. By using an intramolecular approach, where transient amino-ether directing groups are optimal, more challenging C–Br oxidative addition was achieved. The indane-aldehydes formed are highly perfumed with potential use in fragrance applications. This reaction is at a preliminary stage, needing further optimisation prior to reaction scope.

Transient C–H functionalisation of amines is more challenging due to the strong complexation of amines to palladium. γ-C–H arylation of amines was achieved using catalytic amounts of alkyl acetals with aryl ether secondary binding groups to form efficient transient directing groups. A wide range of aryl iodides were successful in this reaction as well as α,β-branched amines with Pd catalysis. Key structural features of the TDG are examined, demonstrating the important role for the masked carbonyl and ether groups. Detailed kinetic (RPKA) and mechanistic investigations determined a zero order in all reagents and first order in palladium, with C–H activation as the turnover limiting step. Product inhibition occurs through an unusual ε-palladation of the arylated products, pulling the catalyst out of the active cycle.

At the outset of these investigations, there were no examples of transient imine directing groups for C(sp^3)–H functionalisation. Over the course of this thesis, since the seminal example by Yu in 2016,[80] over 15 new examples have emerged for the one-pot functionalisation of aldehydes, ketones or amines, and the field is continuing to rapidly progress. This thesis presents important contributions to the field regarding the effect of the structure of the directing group on the product yield and rate of reaction. This included the nature of the secondary binding centre, chelation size and steric and electronic effects. Optimum features of the directing group are not unanimous across substrates, with each example requiring a distinct optimised transient directing group. For example, for methylene C–H functionalisation of secondary aldehydes (Section 3.2), 6-membered chelation of an amide directing group is optimal, however for the indane precursors (Section 3.3), 5-membered chelation through a methoxy ether directing group is preferred. There is a clear synergy between the aldehyde or amine substrate with the ideal transient imine directing group, and so the examples of novel secondary binding sites (sulfonamide, amide, ether) divulged here will be important for the development of future methods. Additionally, we present the only underivatised palladacycle, characterised by X-ray crystallography, as well as the only detailed kinetic study in the field.

There are extensive opportunities for future studies using transient imine directing groups for C−H functionalisation. Preliminary examples of methylene C–H arylation of aliphatic ketones using the developed amino amide and amino sulfonamide directing groups has been demonstrated under conditions developed by Yu, with scope for further elaboration.[89] Additional future prospects will be to develop both enantioselective C(sp^3)–H arylation with transient imine directing groups, as well as to potentially apply base metal catalysis.



26h 21% **26n** 21% **1a** 4% **1v** 41%

Scheme 4.2: Ketone C–H arylation with transient imine directing groups

One-pot methods to form enantioenriched building blocks from simple starting materials by C−H functionalisation would offer huge synthetic value. Enantioselective transient C(sp^3)–H arylation[80] as well as fluorination[83] has been shown by Yu for benzylic positions however there are currently no examples using unactivated C–H bonds. The transient amino sulfonamide or amino amide directing groups developed for the aldehyde arylation studies, modified with chiral groups on the aliphatic backbones, could potentially enable chirality relay onto aldehyde substrates.

Although palladium provides an effective catalyst, its resources are potentially limited, and only low quantities can be included in final compounds if used for medicinal purposes.[136] C–H functionalisation methods using less toxic and more abundant metal catalysts are therefore highly sought, which has not yet been achieved for C(sp^3)–H functionalisation using transient directing groups. Use of earth abundant metals (Ni, Fe, Co etc.) for C(sp^3)–H functionalisation using a step-efficient TDG approach would provide a breakthrough in this field, opening opportunities for the development of many new transformations.

5. Experimental

5.1 General Experimental Considerations

Amine C–H arylation was carried out under air, all other nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, diethyl ether, CH_2Cl_2). Acetic acid, AgOAc and all palladium catalysts were purchased from Sigma Aldrich and used as provided. HFIP and AgTFA were purchased from Fluorochem and used as provided. Commercial aldehydes were used as provided or distilled over CaH_2. The purity of the aldehyde (Section 3.1) had a significant effect on reaction yield. All other commercial reagents were used as supplied or purified by standard techniques where necessary. Reactions were performed in microwave vials sealed with Fisherbrand 20 mm aluminium, plain, centre hole, molded septa butyl, dark grey, 55° shore A, 3.0 mm caps. For the amine arylation (Section 3.4), different batches of AgTFA impacted the yield of the reaction, 98% purity AgTFA from Sigma-Aldrich (T62405) was optimal.

Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid or vanillin stains. Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform δ = 7.27 ppm, acetic acid δ = 7.04 ppm or DMSO δ = 2.50 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet and b = broad), coupling constant in Hz, integration, assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 77.00 ppm, acetic acid δ = 20.00 ppm or DMSO δ = 39.52 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. *J* values are reported in Hz. Assignments of $^1H/^{13}C$ spectra were made by the analysis of δ/J values, and COSY, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected. X-ray data was collected on an Agilent Xcalibur 3 E diffractometer.

5.2 Experimental Details and Characterisation Data

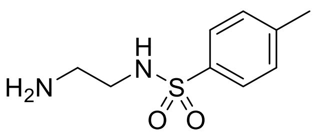
5.2.1 Compounds for Chapter 3.1: Tertiary Aldehyde Arylation

*Preparation of directing groups (**1a-k**)*

General Procedure A: The relevant sulfonyl chloride (1.0 equiv) was added portionwise over a period of 1 h to a stirred solution of ethylenediamine (10 equiv) in CH_2Cl_2 (0.1 M) at 0 °C. The solution was stirred at 0 °C for 0.5 h then warmed to 25 °C and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 and extracted with 1 M aqueous HCl. The combined aqueous extracts were basified to pH 10 with NaOH pellets and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the corresponding sulfonamides.

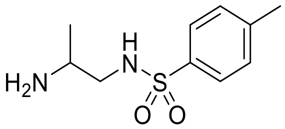
General Procedure B: *tert*-Butyl *N*-(2-aminoethyl)carbamate (1.0 equiv), carboxylic acid (1.0 equiv), EDC·HCl (2.5 equiv), HOBt·H_2O (1.5 equiv) and DIPEA (3.5 equiv) were combined in CH_2Cl_2 (0.3 M) and the reaction was stirred at 25 °C for 20 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, EtOAc:pentane:MeOH) afforded the corresponding Boc intermediate which was stirred in a (1:1) mixture of TFA and CH_2Cl_2 (0.3 M) at 25 °C until the reaction was complete by TLC. The solvents were removed under reduced pressure and the product was dissolved in diethyl ether and evaporated (×3) to remove traces of TFA and afford the corresponding TFA salts.

***N*-(2-Aminoethyl)-4-methylbenzene-1-sulfonamide (1a)**



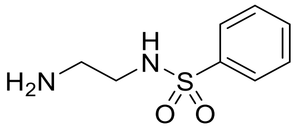
General procedure A was followed using tosyl chloride (2.06 g, 10.0 mmol) to afford sulfonamide **1a** as a white solid (6.35 g, 60%). R_f 0.28 (20% (1% NH_3 in MeOH)/CH_2Cl_2), mp = 123–124 °C (lit = 122−123 °C)[137]. IR (film)/cm^{-1} 3358, 3296, 2591 (br), 1592, 1311, 1298, 1148, 1095, 1054. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.75 (m, 2 H, Ar-H), 7.33–7.30 (m, 2 H, Ar-H), 2.96 (dd, *J* = 6.5, 4.8 Hz, 2 H, NHC*H*$_2$), 2.79 (dd, *J* = 6.5, 4.8 Hz, 2 H, NH_2C*H*$_2$), 2.43 (s, 3 H, CH_3), 1.79 (bs, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (Ar-C_q), 136.9 (Ar-C_q), 129.7 (2 × Ar-C), 127.1 (2 × Ar-C), 45.4 ($NHCH_2$), 40.8 (NH_2CH_2), 21.5 (CH_3). Spectroscopic data for this compound (^{1}H NMR, IR)[138] and ^{13}C NMR[139] is consistent with that shown in the literature.

***N*-(2-Aminopropyl)-4-methylbenzenesulfonamide (1a-Me)**



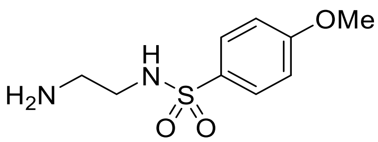
Tosyl chloride (2.06 g, 10.0 mmol) was added portionwise over a period of 1 h to a stirred solution of propane-1,2-diamine (8.5 mL, 100 mmol) in CH_2Cl_2 (0.1 M) at 0 °C. The solution was stirred at 0 °C for 0.5 h then warmed to 25 °C and stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 and extracted with 1 M aqueous HCl. The combined aqueous extracts were basified to pH 10 with NaOH pellets and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the sulfonamide **1a-Me** as a white solid (2.02 g, 92%). R_f 0.34 (20% (1% NH_3 in MeOH)/CH_2Cl_2), mp = 93–96 °C. IR (film)/cm^{-1} 2701, 1739, 1597, 1323, 1278, 1149, 1070, 1089. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.32 (d, *J* = 8.1 Hz, 2 H, Ar-H), 3.00–2.93 (m, 2 H, CH_2), 2.72–2.51 (m, 1 H, C*H*(CH_3)), 2.44 (s, 3 H, Ar-CH_3), 1.43 (bs, 2 H, NH_2), 1.04 (t, *J* = 5.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (Ar-C_q), 136.9 (Ar-C_q), 129.7 (Ar-C), 127.0 (Ar-C), 50.4 (*C*H(CH_3)), 46.2 (CH_2), 21.8 (CH_3), 21.5 (Ar-CH_3). HRMS (ESI) m/z Calcd. for $C_{10}H_{17}NO_2S$ $[M+H]^+$: 229.1011; Found: 229.1022.

***N*-(2-Aminoethyl)benzenesulfonamide (1b)**



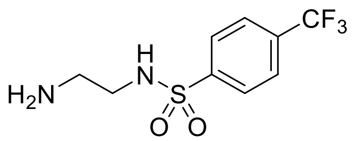
General procedure A was followed using benzenesulfonyl chloride (1.27 mL, 10.0 mmol) to afford sulfonamide **1b** as an off-white solid (634 mg, 32%). R_f 0.23 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 90−91 °C. IR (film)/cm^{-1} 3368 (w, N–H), 3312 (w, N–H), 2931, 2844, 2598, 1596. 1495, 1454, 1436, 1316, 1298, 1261, 1149 (s), 1094, 1028. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.3 Hz, 2 H, Ph-H), 7.60–7.50 (m, 3 H, Ph-H), 2.99–2.96 (m, 2 H, NHC*H_2*), 2.81–2.78 (m, 2 H, NH_2C*H_2*), 2.60 (bs, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9 (Ph-C_q), 132.6 (Ph-C), 129.1 (Ph-C), 127.0 (Ph-C), 45.3 ($NHCH_2$), 40.9 (NH_2CH_2). HRMS (ESI) m/z Calcd. for $C_8H_{13}N_2O_2S$ $[M+H]^+$: 201.0698; Found: 201.0697. Spectroscopic data (^1H NMR, ^{13}C NMR, MS)[140] and (IR)[141] for this compound is consistent with that shown in the literature.

***N*-(2-Aminoethyl)-4-methoxybenzene-1-sulfonamide (1c)**



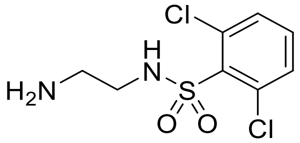
General procedure A was followed using 4-methoxybenzenesulfonyl chloride (2.06 g, 10.0 mmol) to afford sulfonamide **1c** as a white solid (1.63 g, 71%). R_f 0.17 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 98–100 °C (lit = 90–91 °C)[141]. IR (film)/cm^{-1} 3368 (w, N–H), 3312 (w, N–H), 2933, 2844, 2585, 1596, 1579, 1495, 1454, 1435, 1298, 1261, 1148 (s), 1094, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2 H, Ar-H), 7.01–6.96 (m, 2 H, Ar-H), 3.88, (s, 3 H, OCH_3), 2.95 (dd, *J* = 6.5, 4.8 Hz, 2 H, NHC*H*$_2$), 2.79 (dd, *J* = 6.5, 4.8 Hz, 2 H, NH_2C*H*$_2$), 1.53 (bs, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (Ar-C_q), 131.5 (Ar-C_q), 129.2 (2 × Ar-C), 114.2 (2 × Ar-C), 55.6 (OCH_3), 45.4 ($NHCH_2$), 40.8 (NH_2CH_2). HRMS (ESI) m/z Calcd. for $C_9H_{15}N_2O_3S$ $[M+H]^+$: 231.0803; Found: 231.0811. Spectroscopic data (^{1}H NMR, ^{13}C NMR) for this compound is consistent with that shown in the literature.[141]

***N*-(2-Aminoethyl)-4-(trifluoromethyl)benzene-1-sulfonamide (1d)**



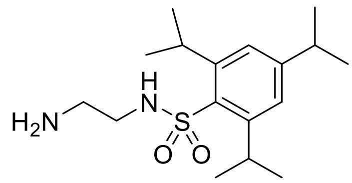
General procedure A was followed using 4-(trifluoromethyl)benzene-1-sulfonyl chloride (2.45 g, 10.0 mmol) to afford sulfonamide **1d** as a white solid (2.11 g, 79%). R_f 0.21 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 112–116 °C (lit = 103–105 °C)[140]. IR (film)/cm^{-1} 3371, 2970, 2637, 1738, 1606, 1402, 1365, 1325, 1217, 1153, 1127, 1100, 1062, 1043, 1016. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.80 (d, *J* = 8.2 Hz, 2 H, Ar-H), 3.01 (t, *J* = 5.6 Hz, 2 H, NHC*H*$_2$), 2.83 (t, *J* = 5.6 Hz, 2 H, NH_2C*H*$_2$), 1.90 (bs, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (Ar-C_q), 134.5 (q, $^2J_{C\text{-}F}$ = 33 Hz, CF_3Ar-C_q), 127.5 (2 × Ar-C), 126.4 (q, $^3J_{C\text{-}F}$ = 4 Hz, 2 × Ar-C), 123.4 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 45.2 ($NHCH_2$), 40.7 (NH_2CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ –63.01 HRMS (ESI) m/z Calcd. for $C_9H_{12}N_2O_2SF_3$ $[M+H]^+$: 269.0572; Found: 269.0584. Spectroscopic data (^{1}H NMR, ^{13}C NMR) for this compound is consistent with that shown in the literature.[140]

***N*-(2-Aminoethyl)-2,6-dichlorobenzene-1-sulfonamide (1e)**



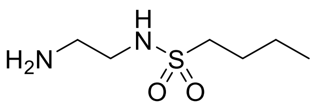
General procedure A was followed using 2,6-dichlorobenzenesulfonyl chloride (980 mg, 4.00 mmol) to afford sulfonamide **1e** as a white solid (921 mg, 86%). R_f 0.34 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 121–123 °C IR (film)/cm^{-1} 3371, 3312, 2936, 1736, 1594, 1560, 1424, 1330, 1292, 1160, 1096, 1047. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.35 (t, *J* = 8.0 Hz, 1 H, Ar-H), 3.07–3.04 (m, 2 H, NHC*H₂*), 2.85–2.83 (m, 2 H, NH_2CH_2), 2.39 (bs, 2 H, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (Ar-C_q), 134.9 (2 × Ar-C_q), 132.4 (Ar-C), 131.4 (Ar-C), 45.5 ($NHCH_2$), 40.8 (NH_2CH_2). HRMS (ESI) m/z Calcd. for $C_8H_{11}N_2O_2SCl_2$ [M+H]$^+$: 268.9918; Found: 268.9928.

***N*-(2-Aminoethyl)-2,4,6-tris(propan-2-yl)benzene-1-sulfonamide (1f)**



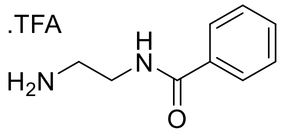
General procedure A was followed using 2,4,6-triisopropylbenzenesulfonyl chloride (7.58 g, 25.0 mmol) to afford sulfonamide **1f** as a white solid (257 mg, 3%). R_f 0.35 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 123–124 °C. IR (film)/cm^{-1} 3369, 2955, 1738, 1594, 1563, 1458, 1422, 1363, 1314, 1295, 1247, 1229, 1153, 1093, 1060. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2 H, Ar-H), 5.02 (bs, 1 H, NH), 4.18 (hept, *J* = 6.6 Hz, 2 H, $CH(CH_3)_2$), 3.01–2.98 (m, 2 H, $NHCH_2$), 2.96–9.87 (m, 1 H, $CH(CH_3)_2$), 2.86–2.84 (m, 2 H, NH_2CH_2), 1.27 (t, *J* = 6.6 Hz, 18 H, 3 × $CH(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (Ar-C_q), 150.2 (2 × Ar-C_q), 132.2 (Ar-C_q), 123.8 (2 × Ar-C), 44.9 ($NHCH_2$), 40.8 (NH_2CH_2), 34.1 ($CH(CH_3)_2$), 29.6 (2 × $CH(CH_3)_2$), 24.9 (2 × $CH(CH_3)_2$), 23.6 ($CH(CH_3)_2$). HRMS (ESI) m/z Calcd. for $C_{17}H_{31}N_2O_2S$ [M+H]$^+$: 327.2106; Found: 327.2100.

***N*-(2-Aminoethyl)butane-1-sulfonamide (1g)**



General procedure A was followed using 1-butanesulfonyl chloride (1.94 mL, 15.0 mmol) to afford sulfonamide **1g** as a pale yellow wax (628 mg, 23%). R_f 0.19 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3295, 2961, 2874, 1596, 1466, 1314, 1276, 1134, 921. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15–3.12 (m, 2 H, SO_2CH_2), 3.05–3.01 (m, 2 H, $NHCH_2$), 2.90–2.87 (m, 2 H, NH_2CH_2), 2.73 (bs, 2 H, NH_2), 1.83–1.75 (m, 2 H, CH_2), 1.50–1.41 (m, 2 H, CH_2), 0.95 (t, *J* = 7.4 Hz, 2 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.3 (SO_2CH_2), 45.4 ($NHCH_2$), 41.6 (NH_2CH_2), 25.6 (CH_2), 21.5 (CH_2), 13.6 (CH_3). HRMS (ESI) m/z Calcd. for $C_6H_{17}N_2O_2S$ [M+H]$^+$: 181.1011; Found: 181.1018.

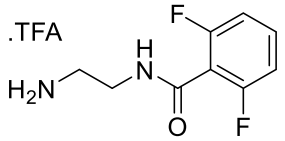
N-(2-Azaniumylethyl)benzamide trifluoroacetate (1h)



General procedure B was followed using benzoic acid (1.46 g, 12.0 mmol) to afford the intermediate *tert*-butyl *N*-[2-(phenylformamido)ethyl]carbamate **1h-Boc** as a white solid (673 mg, 85%). R_f 0.26 (40% EtOAc/pentane). mp = 130–131 °C. IR (film)/cm^{-1} 3354, 3324, 2291, 2970, 2934, 1685, 1637, 1525 (s), 1447, 1387, 1327, 1277, 1234, 1166, 1151. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.4 Hz, 2 H, Ph-H), 7.51–7.47 (m, 1 H, Ph-H), 7.44–7.40 (m, 2 H, Ph-H), 7.21 (bs, 1 H, NH), 5.05 (bs, 1 H, NH) 3.58–3.54 (m, 2 H, BocNHCH_2), 3.41 (dd, *J* = 10.8, 5.7 Hz, 2 H, CONHCH_2), 1.43 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (C=O), 157.5 (C=O), 134.1 (Ph-C_q), 131.4 (Ph-C), 128.5 (Ph-C), 127.0 (Ph-C), 80.0 ($C(CH_3)_3$), 42.0 (BocNHCH_2), 39.9 (CONHCH_2), 28.3 ($C(CH_3)_3$). Spectroscopic data (^1H NMR, ^{13}C NMR, IR) for this compound is consistent with that shown in the literature.[142]

Boc deprotection of *tert*-butyl *N*-[2-(phenylformamido)ethyl]carbamate **1h-Boc** (2.59 g, 9.81 mmol) gave title salt **1h** as an off-white solid (2.77 g, 100%). mp = 130–131 °C. IR (film)/cm^{-1} 3300, 3017, 1779 (w, C=O), 1669 (C=O), 1624, 1595, 1549, 1517, 1425, 1316, 1172 (s), 1158 (s), 1125 (s), 1036. ^1H NMR (400 MHz, DMSO) δ 8.64 (t, *J* = 5.4 Hz, 1 H, CONH), 8.00–7.73 (bm (broad multiplet), 5 H, NH_3 + 2 × Ph-H), 7.57–7.46 (m, 3 H, Ph-H), 3.51 (q, *J* = 6.1 Hz, 2 H, NHCH_2), 3.03–2.96 (m, 2 H, NH_3CH_2). ^{13}C NMR (101 MHz, DMSO) δ 166.9 (C=O), 160.8 (C=O), 134.0 (Ph-C_q), 131.4 (Ph-C), 128.3 (Ph-C), 127.3 (Ph-C), 38.7 (CH_2), 37.1 (CH_2). HRMS (ESI) m/z Calcd. for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1028; Found: 165.1035.

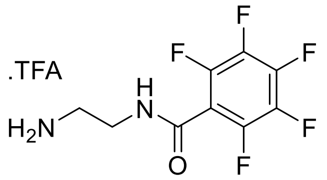
N-(2-Azaniumylethyl)-2,6-difluorobenzamide trifluoroacetate (1i)



General procedure B was followed using 2,6-difluorobenzoic acid (1.90 g, 12.0 mmol) followed by recrystallisation in EtOAc to afford the intermediate *tert*-butyl *N*-{2-[(2,6-difluorophenyl)formamido]ethyl}carbamate **1i-Boc** as a white solid (2.22 g, 62%). R_f 0.26 (40% EtOAc/pentane). mp = 141 °C. IR (film)/cm^{-1} 3306, 2977, 2927, 1696 (C=O), 1652 (C=O), 1626, 1534, 1467, 1367, 1324, 1286, 1235, 1156, 1022, 1004. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (tt, *J* = 8.4, 6.4 Hz, 1 H, Ar-H), 6.97–6.91 (m, 2 H, Ar-H), 6.70 (bs, 1 H, NH), 4.94 (bs, 1 H, NH), 3.59 (dd, *J* = 11.2, 5.5 Hz, 2 H, BocNHC*H₂*), 3.40 (dd, *J* = 11.2, 5.5 Hz, 2 H, CONHC*H₂*), 1.43 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (C=O), 160.0 (dd, $J_{C\text{-}F}$ = 253, 7 Hz, 2 × Ar-C_qF), 131.6 (t, $^3J_{C\text{-}F}$ = 10 Hz, FAr-C), 114.3 (Ar-C_q), 112.0 (dd, J_{CF} = 20, 5 Hz, 2 × FAr-C) 79.9 (*C*(CH_3)$_3$), 41.4 (BocNHCH_2), 39.9 (CONHCH_2), 28.3 (C(CH_3)$_3$) ^{19}F NMR (377 MHz, $CDCl_3$) δ –112.2. HRMS (ESI) m/z Calcd. for $C_{14}H_{19}N_2O_3F_2$ [M+H]$^+$: 301.1364; Found: 301.1368.

Boc deprotection of *tert*-butyl *N*-{2-[(2,6-difluorophenyl)formamido]ethyl}carbamate **1i-Boc** (2.22 g, 7.40 mmol) gave the title salt **1j** as an off-white solid (2.11 g, 94%). mp = 127–128 °C. IR (film)/cm^{-1} 3259, 3083, 2672, 1679 (C=O), 1655, 1644, 1624, 1574, 1560, 1466, 1320, 1234, 1199 (s), 1178 (s), 1150 (s), 1132 (s), 1003. ^{1}H NMR (400 MHz, DMSO) δ 8.90 (t, *J* = 5.4 Hz, 1 H, NH), 7.94 (bs, 3 H, NH_3), 7.54 (m, 1 H, Ar-H), 7.25–7.16 (m, 2 H, Ar-H), 3.48 (dd, *J* = 12.9, 7.0 Hz, 2 H, NHCH_2), 2.95 (bs, 2 H, NH_3CH_2). ^{13}C NMR (101 MHz, DMSO) δ 160.1 (C=O), 158.8 (dd, $J_{C\text{-}F}$ = 249, 7 Hz, 2 × Ar-C_qF), 132.0 (t, $^3J_{C\text{-}F}$ = 9 Hz, FAr-C), 114.8 (Ar-C_q), 112.0 (dd, $J_{C\text{-}F}$ = 20, 5 Hz, 2 × FAr-C), 38.0 (CH_2), 36.9 (CH_2). ^{19}F NMR (377 MHz, DMSO) δ –73.7, –113.7. HRMS (ESI) m/z Calcd. for $C_9H_{11}N_2OF_2$ [M+H]$^+$: 201.0839; Found: 201.0838.

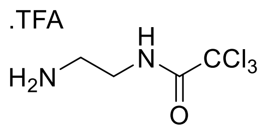
N-(2-Azaniumylethyl)-2,3,4,5,6-pentafluorobenzamide trifluoroacetate (1j)



General procedure B was followed using pentafluorobenzoic acid (1.90 g, 8.90 mmol) followed by recrystallisation in EtOAc to afford the intermediate *tert*-butyl *N*-{2-[(2,3,4,5,6-pentafluorophenyl)formamido]ethyl}carbamate **1j-Boc** as a white solid (1.12 g, 35%). R_f 0.33 (40% EtOAc/pentane). mp = 141 °C. IR (film)/cm^{-1} 3351, 3304, 2950, 1688 (C=O), 1663 (C=O), 1520, 1483, 1448, 1335, 1283, 1237, 1173, 1120. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (bs, 1 H, NH), 4.95 (bs, 1 H, NH), 3.60–3.56 (m, 2 H, BocNHC*H₂*), 3.40 (dd, *J* = 11.2, 5.9 Hz, 2 H, CONHC*H₂*), 1.43 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (C=O), 157.5 (C=O), 80.4 ($\mathit{C}(CH_3)_3$), 42.5 (BocNH$\mathit{C}H_2$), 39.6 (CONH$\mathit{C}H_2$), 28.2 ($C(\mathit{C}H_3)_3$). Ar-C signals not observed due to complex coupling. ^{19}F NMR (377 MHz, $CDCl_3$) δ –140.42 to –140.56 (m, 2 F), –151.08 (t, *J* = 20.5 Hz), –160.31 (td, *J* = 21.2, 6.2 Hz, 2 F). HRMS (ESI) m/z Calcd. for $C_{14}H_{16}N_2O_3F_5$ $[M+H]^+$: 355.1081; Found: 355.1082.

Boc deprotection of *tert*-butyl *N*-{2-[(2,3,4,5,6-pentafluorophenyl)formamido]ethyl}carbamate **1j-Boc** (1.12 g, 3.16 mmol) gave the title salt **1j** as an off-white solid (1.09 g, 87%). mp = 162–165 °C. IR (film)/cm^{-1} 3320, 2966, 2906, 2861, 2819, 1670, 1644, 1579, 1546, 1457, 1357, 1303, 1204, 1179, 1115. ^{1}H NMR (400 MHz, DMSO) δ 9.20 (t, *J* = 5.3 Hz, 1 H, NH), 7.96 (bs, 3 H, NH_3), 3.51 (dd, *J* = 12.8, 6.7 Hz, 2 H, NH$\mathit{C}H_2$), 2.97 (t, *J* = 6.9 Hz, 2 H, $NH_3\mathit{C}H_2$). ^{13}C NMR (101 MHz, DMSO-D_6) δ 157.2 (C=O), 37.9 (CH_2), 37.1 (CH_2). Ar-C signals not observed due to complex coupling. ^{19}F NMR (377 MHz, DMSO) δ –73.9, –141.5 (dd, *J* = 23.1, 5.9 Hz, 2 F), –152.65 (t, *J* = 22.0 Hz), −161.26 to –161.72 (m, 2 F). HRMS (ESI) m/z Calcd. for $C_9H_8N_2OF_5$ $[M+H]^+$: 255.0557; Found: 255.0550.

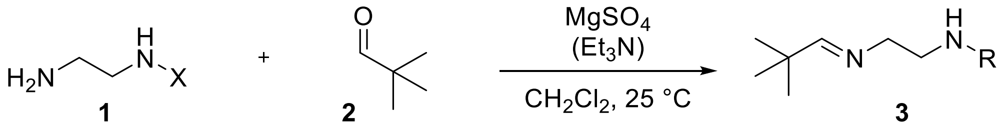
N-(2-Azaniumylethyl)-2,2,2-trichloroacetamide trifluoroacetate (1k)



Trichloroacetyl chloride was added dropwise to a stirred solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (316 µL, 2.00 mmol) and pyridine (163 µL, 2.20 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C. The reaction was allowed to warm to 25 °C and was stirred for 1 h. The reaction mixture was concentrated under reduced pressure and the resulting residue purified by column chromatography (silica, 30% EtOAc/pentane) to afford amide **1k-Boc** as a white solid (526 mg, 86%). Rf 0.40 (30% EtOAc/pentane). mp = 145–146 °C. IR (film)/cm^{-1} 3319, 2966, 2876, 1682 (C=O), 1579, 1516, 1434, 1367, 1310, 1275, 1233, 1159. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (bs, 1 H, NH), 4.91 (bs, 1 H, NH), 3.49–3.45 (m, 2 H, CH_2, BocNHCH_2), 3.43–3.40 (m, 2 H, CH_2, CONHCH_2), 1.45 (s, 9 H, (C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (C=O), 157.6 (C=O), 92.4 (CCl_3), 80.5 (*C*(CH_3)$_3$), 43.9 (BocNH*C*H_2), 39.1 (CONH*C*H_2), 28.3 (C(*C*H_3)$_3$). HRMS (ESI) m/z Calcd. for $C_9H_{14}N_2O_3Cl_3$ $[M+H]^+$: 303.0070; Found: 303.0063.

tert-Butyl *N*-[2-(2,2,2-trichloroacetamido)ethyl]carbamate **1k-Boc** (475 mg, 1.56 mmol) was stirred in a mixture of TFA (2.5 mL) and CH_2Cl_2 (2.5 mL) at 25 °C for 18 h. The solvents were removed under reduced pressure and the resulting gum dissolved in diethyl ether and evaporated (× 3) to afford the title salt **1k** as an off-white solid (425 mg, 85%). mp = 124–126 °C. IR (film)/cm^{-1} 3047 (br), 1698 (C=O), 1675 (C=O), 1536, 1444, 1230, 1202, 1179 (s), 1140 (s), 1092, 1029. ^{1}H NMR (400 MHz, DMSO) δ 9.14 (t, *J* = 5.2 Hz, 1 H, NH), 7.91 (bs, 3 H, NH_3), 3.44 (dd, *J* = 12.5, 6.7 Hz, 2 H, NHCH_2), 2.96 (t, *J* = 6.7 Hz, 2 H, NH_3CH_2). ^{13}C NMR (101 MHz, DMSO) δ 162.1 (C=O), 92.4 (CCl_3), 38.6 (CH_2), 37.6 (CH_2). HRMS (ESI) m/z Calcd. for $C_4H_8N_2OCl_3$ $[M+H]^+$: 204.9702; Found: 204.9697.

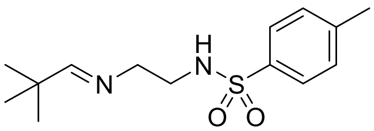
*Preparation of imines (**3a-n**)*



General Procedure C: Pivaldehyde **2** (1 equiv) was added to a stirred suspension of amine **1** (1 equiv) and magnesium sulfate (2 equiv) in CH_2Cl_2 (0.3 M) and the reaction was stirred at 25 °C overnight. The reaction mixture was filtered through a bed of Celite (eluting with CH_2Cl_2), concentrated under reduced pressure and dissolved in either diethyl ether or toluene and evaporated to afford the corresponding imines **3**.

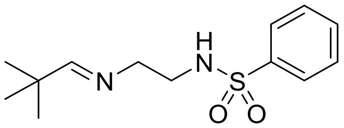
General Procedure D: Pivaldehyde **2** (1 equiv) was added to a stirred suspension of amine **1** salt (1 equiv), triethylamine (1.5 equiv) and magnesium sulfate (2 equiv) in CH_2Cl_2 (0.3 M) and the reaction was stirred at 25 °C overnight. The reaction mixture was filtered through a bed of Celite (eluting with CH_2Cl_2). An equal volume of a 1:1 mixture of saturated aqueous $NaHCO_3$ and distilled water was added and the product extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the corresponding imines **3**.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}-4-methylbenzene-1-sulfonamide (3a)**



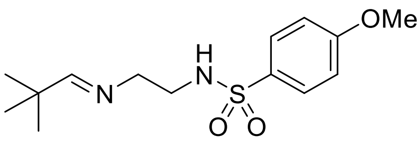
General procedure C was followed using *N*-(2-aminoethyl)-4-methylbenzene-1-sulfonamide **1a** (535 mg, 2.50 mmol) to afford imine **3a** as a white solid (712 mg, 100%) as a mixture of major and minor stereoisomers (3.5:1). NMR data quoted for the major isomer only. mp = 66–67 °C. IR (film)/cm^{-1} 3286, 2959, 2867, 1665, 1598, 1454, 1400, 1326, 1305, 1156 (s), 1091. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.74 (m, 2 H, Ar-H), 7.49 (s, 1 H, N=CH), 7.34–7.30 (m, 2 H, Ar-H), 4.75 (t, *J* = 5.6 Hz, 1 H, NH), 3.40 (t, *J* = 5.6 Hz, 2 H, CH=NCH_2), 3.20–3.13 (m, 2 H, NHCH_2), 2.44 (s, 3 H, Ar-CH_3), 1.03 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (CH=N), 143.4 (Ar-C_q), 137.1 (Ar-C_q), 129.7 (2 × Ar-C), 127.1 (2 × Ar-C), 59.2 (CH=NCH_2), 43.8 (NHCH$_2$), 36.3 (C_q(CH_3)$_3$) 26.8 (C(CH_3)$_3$), 21.5 (Ar-CH_3). HRMS (ESI) m/z Calcd. for $C_{14}H_{23}N_2O_2S$ [M+H]$^+$: 283.1480; Found: 283.1474.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}benzenesulfonamide (3b)**



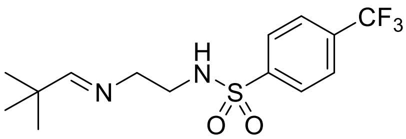
General procedure C was followed using *N*-(2-aminoethyl)-benzenesulfonamide **1b** (300 mg, 1.50 mmol) to afford imine **3b** as a yellow oil (312 mg, 78%) as a mixture of major and minor stereoisomers (7.3:1). NMR data quoted for the major isomer only. IR (film)/cm^{-1} 3301, 2958, 2867, 1738, 1665, 1477, 1446, 1364, 1324, 1217, 1156, 1091. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H, Ph-H), 7.64–7.50 (m, 3 H, Ph-H), 7.48 (t, *J* = 1.2 Hz, 1 H, N=CH), 4.88 (bs, 1 H, NH), 3.40 (td, *J* = 5.7, 1.1 Hz, 2 H, CH=NCH_2), 3.20–3.17 (m, 2 H, NHCH_2), 1.02 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (CH=N), 140.0 (Ph-C_q), 132.6 (Ph-C), 129.1 (Ph-C), 127.0 (Ph-C), 59.1 (CH=N*C*H_2), 43.8 ($NHCH_2$), 36.3 ($C_q(CH_3)_3$), 26.8 ($C(CH_3)_3$). HRMS (ESI) m/z Calcd. for $C_{13}H_{20}N_2O_2S$ $[M+H]^+$: 269.1318; Found: 269.1309.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}-4-methoxybenzene-1-sulfonamide (3c)**



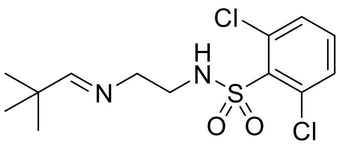
General procedure C was followed using *N*-(2-aminoethyl)-4-methoxybenzene-1-sulfonamide **1c** (345 mg, 1.50 mmol) to afford imine **3c** as an off-white solid (349 mg, 78%) as a mixture of major and minor stereoisomers (6.1:1). NMR data quoted for the major isomer only. mp = 76–79 °C. IR (film)/cm^{-1} 3370, 3312, 2956, 2868, 1737, 1665, 1596, 1579, 1498, 1461, 1413, 1327, 1302, 1257, 1151 (s), 1092, 1024. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2 H, Ar-H), 7.49 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.00–6.96 (m, 2 H, Ar-H), 4.79 (bs, 1 H, NH), 3.87 (s, 3 H, OCH_3), 3.41–3.38 (m, 2 H, CH=NCH_2), 3.18–3.11 (m, 2 H, NHCH_2), 1.02 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (CH=N), 162.8 (Ar-C_q), 129.7 (Ar-C_q), 129.2 (2 × Ar-C), 114.2 (2 × Ar-C), 59.2 (CH=N*C*H_2), 55.6 (OCH_3), 43.7 ($NHCH_2$), 36.3 ($C_q(CH_3)_3$), 26.8 ($C(CH_3)_3$). HRMS (ESI) m/z Calcd. for $C_{14}H_{22}N_2O_2S$ $[M+H]^+$: 299.1424; Found: 299.1422.

N-{2-[(E)-(2,2-Dimethylpropylidene)amino]ethyl}-4-(trifluoromethyl)benzene-1-sulfonamide (3d)



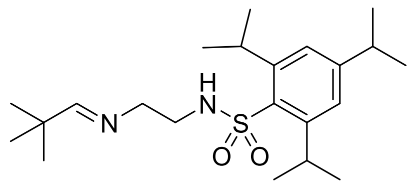
General procedure C was followed using *N*-(2-aminoethyl)-4-(trifluoromethyl)benzene-1-sulfonamide **1d** (500 mg, 1.87 mmol) to afford imine **3d** as a white solid (612 mg, 98%) as a mixture of major and minor stereoisomers (10.1:1). NMR data quoted for the major isomer only. mp = 87–89 °C. IR (film)/cm^{-1} 3075, 2969, 2867, 1738, 1666, 1474, 1457, 1404, 1358, 1333, 1319, 1294, 1229, 1217, 1169, 1138, 1092, 1061, 1018. NMR data quoted for the major isomer only. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.80 (t, *J* = 8.2 Hz, 2 H, Ar-H), 7.51 (t, *J* = 1.2 Hz, 1 H, N=CH), 4.98 (s, 1 H, NH), 3.42 (td, *J* = 5.6, 1.2 Hz, 2 H, CH=NCH_2), 3.24–3.17 (m, 2 H, NHCH_2), 1.02 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0 (CH=N), 143.7 (Ar-C_q), 134.5 (q, $^2J_{C-F}$ = 33 Hz, Ar-C_q), 127.6 (2 × Ar-C), 126.3 (q, $^3J_{C-F}$ = 4 Hz, 2 × Ar-C), 123.4 (q, $^1J_{C-F}$ = 273 Hz, CF_3), 59.0 (CH=NCH_2), 43.9 ($NHCH_2$), 36.4 ($C_q(CH_3)_3$), 26.7 ($C(CH_3)_3$). ^{19}F NMR (377 MHz, CDCl3) δ –63.1. HRMS (ESI) m/z Calcd. for $C_{14}H_{18}N_2O_2F_3S$ [M+H]$^+$: 335.1034; Found: 335.1041.

2,6-Dichloro-N-{2-[(E)-(2,2-dimethylpropylidene)amino]ethyl}benzene-1-sulfonamide (3e)



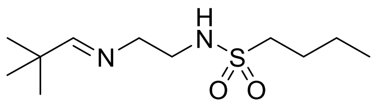
General procedure C was followed using *N*-(2-aminoethyl)-2,6-dichlorobenzene-1-sulfonamide **1e** (404 mg, 1.50 mmol), to afford imine **3e** as an off-white solid (405 mg, 80%) as a mixture of major and minor stereoisomers (8.1:1). NMR data quoted for the major isomer only. mp = 70–71 °C. IR (film)/cm^{-1} 3295, 2955, 2862, 1738, 1669, 1569, 1558, 1471, 1424, 1397, 1359, 1334, 1216, 1938, 1172, 1082, 1042, 1038. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.49–7.47 (m, 2 H, Ar-H), 7.37–7.33 (m, 1 H, Ar-H), 5.79, (bs, 1 H, NH), 3.45 (td, *J* = 5.6, 1.1 Hz, 2 H, CH=NCH_2), 3.26–3.23 (m, 2 H, NHCH_2), 1.05 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (CH=N), 135.3 (Ar-C_q), 134.9 (2 × Ar-C_q) 132.3 (Ar-C), 131.4 (Ar-C), 58.8 (CH=NCH_2), 44.0 ($NHCH_2$), 36.4 ($C_q(CH_3)_3$), 26.8 ($C(CH_3)_3$). HRMS (ESI) m/z Calcd. for $C_{13}H_{16}N_2O_2SCl_2$ [M+H]$^+$: 337.0544; Found: 337.0550.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}-2,4,6-tris(propan-2-yl)benzene-1-sulfonamide (3f)**



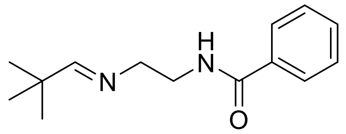
General procedure C was followed using *N*-(2-aminoethyl)-2,4,6-tris(propan-2-yl)benzene-1-sulfonamide **1f** (230 mg, 0.71 mmol) to afford imine **3f** as a white solid (270 mg, 97%) as a single stereoisomer. mp = 88–91 °C. IR (film)/cm^{-1} 3316, 2959, 2868, 1738, 1665, 1601, 1462, 1425, 1405, 1380, 1361, 1318, 1255, 1229, 1216, 1153, 1097, 1058, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.17 (s, 2 H, Ar-H), 4.77 (t, *J* = 6.2 Hz, 1 H, NH), 4.21–4.11 (m, 2 H, $CH(CH_3)_2$), 3.48 (td, *J* = 5.6, 1.1 Hz, 2 H, $CH{=}NCH_2$), 3.19–3.15 (m, 2 H, $NHCH_2$), 2.96–2.85 (m, 1 H, $CH(CH_3)_2$), 1.27 (t, *J* = 6.9 Hz, 18 H, 3 × $CH(CH_3)_2$), 1.04 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (CH=N), 152.6 (Ar-C_q), 150.2 (3 × Ar-C_q), 123.8 (2 × Ar–C), 59.5 ($CH{=}NCH_2$), 43.4 ($NHCH_2$), 36.4 ($C_q(CH_3)_3$), 34.1 ($CH(CH_3)_2$), 29.6 (2 × $CH(CH_3)_2$), 26.8 ($C(CH_3)_3$), 24.9 (2 × $CH(CH_3)_2$), 23.6 ($CH(CH_3)_2$). HRMS (ESI) m/z Calcd. for $C_{22}H_{37}N_2O_2S$ $[M+H]^+$: 393.2576; Found: 393.2570.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}butane-1-sulfonamide (3g)**



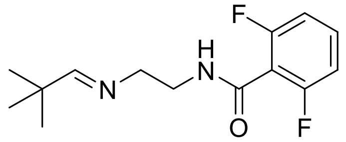
General procedure C was followed using *N*-(2-aminoethyl)butane-1-sulfonamide **1g** (400 mg, 2.22 mmol) to afford imine **3g** as a yellow oil (457 mg, 83%) as a mixture of major and minor stereoisomers (19:1). NMR data quoted for the major isomer only. IR (film)/cm^{-1} 3294, 2960, 2873, 1666, 1458, 1363, 1321, 1140 (s), 1096. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 1.2 Hz, 1 H, N=CH), 4.59 (bs, 1 H, NH), 3.51 (td, *J* = 5.7, 1.2 Hz, 2 H, $CH{=}NCH_2$), 3.33–2.29 (m, 2 H, $NHCH_2$), 3.05–3.01 (m, 2 H, SO_2CH_2), 1.83–1.75 (m, 2 H, CH_2), 1.50–1.41 (m, 2 H, CH_2), 1.06 (s, 9 H, $C(CH_3)_3$), 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (CH=N), 60.0 ($CH{=}NCH_2$), 52.3 (SO_2CH_2), 43.9 ($NHCH_2$), 36.4 ($C_q(CH_3)_3$), 26.8 ($C(CH_3)_3$), 25.6 (CH_2), 21.5 (CH_2), 13.6 (CH_3). HRMS (ESI) m/z Calcd. for $C_{11}H_{24}N_2O_2S$ $[M+H]^+$: 249.1631; Found: 249.1629.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}benzamide (3h)**



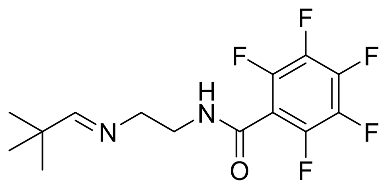
General procedure D was followed using *N*-(2-azaniumylethyl)benzamide trifluoroacetate **1h** (566 mg, 2.00 mmol) to afford imine **3h** as an off-white solid (404 mg, 87%) as a mixture of major and minor stereoisomers (7.3:1). NMR data quoted for the major isomer only. mp = 82–84 °C IR (film)/cm^{-1} 3319, 2966, 2907, 2861, 2819, 1671, 1644, 1602, 1579, 1547, 1457, 1358, 1303, 1260, 1205, 1115, 1020. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.75 (m, 2 H, Ph-H), 7.60 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.52–7.48 (m, 1 H, Ph-H), 7.45–7.41 (m, 2 H, Ph-H), 6.53 (bs, 1 H, NH), 3.71–3.66 (m, 2 H, NHCH_2), 3.59 (t, *J* = 5.8 Hz, 2 H, CH=NCH_2), 1.07 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (CH=N), 167.3 (C=O), 134.7 (Ph-C_q), 131.4 (Ph-C), 128.5 (Ph-C), 126.8 (Ph-C), 59.7 (CH=NCH_2), 40.6 ($NHCH_2$), 36.3 ($C_q(CH_3)_3$), 26.9 ($C(CH_3)_3$). HRMS (ESI) m/z Calcd. for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1654; Found: 233.1648.

***N*-{2-[(*E*)-(2,2-Dimethylpropylidene)amino]ethyl}-2,6-difluorobenzamide (2i)**



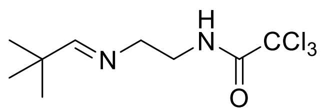
General procedure D was followed using *N*-(2-azaniumylethyl)-2,6-difluorobenzamide trifluoroacetate **1i** (453 mg, 1.50 mmol) to afford imine **2i** as a pale yellow solid (157 mg, 40%) as a mixture of major and minor stereoisomers (4.3:1). NMR data quoted for the major isomer only. mp = 65–70 °C. IR (film)/cm^{-1} 3267, 3097, 2959, 2867, 1650 (s, C=O), 1625 (s), 1592, 1564, 1465 (s), 1437, 1360, 1312, 1272, 1234, 1114, 1004 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1 H, N=CH), 7.36 (tt, *J* = 8.5, 6.3 Hz, 1 H, Ar-H), 6.97–6.91 (m, 2 H, Ar-H), 6.27 (bs, 1 H, NH), 3.73–7.68 (m, 2 H, NHCH_2), 3.60–3.57 (m, 2 H, CH=NCH_2), 1.06 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (CH=N), 160.3 (dd, J_{CF} = 253, 7 Hz, (2 × Ar-C_qF), 160.3 (C=O), 131.6 (t, J_{CF} = 10 Hz, FAr-C), 112.0 (m, 2 × FAr-C), 59.6 (CH=NCH_2), 40.6 ($NHCH_2$), 36.3 ($C_q(CH_3)_3$), 26.8 ($C(CH_3)_3$). ^{19}F NMR (377 MHz, $CDCl_3$) δ –112.2. HRMS (ESI) m/z Calcd. for $C_{14}H_{19}N_2OF_2$ $[M+H]^+$: 269.1465; Found: 269.1470.

N-{2-[(E)-(2,2-Dimethylpropylidene)amino]ethyl}-2,3,4,5,6-pentafluorobenzamide (3j)



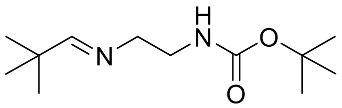
General procedure D was followed using *N*-(2-azaniumylethyl)-2,3,4,5,6-pentafluorobenzamide trifluoroacetate **1j** (552 mg, 1.50 mmol) to afford imine **3j** as a pale yellow solid (291 mg, 60%) as a mixture of major and minor stereoisomers (7.3:1). NMR data quoted for the major isomer only. mp = 74–75 °C. IR (film)/cm^{-1} 3289, 2964, 1738 (w), 1653 (s, C=O), 1555, 1520, 1359, 1331, 1269, 1114, 1066, 1047. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 1.1 Hz, 1 H, N=CH), 6.39 (bs, 1 H, NH), 3.71–3.67 (m, 2 H, NHC*H₂*), 3.59–3.56 (m, 2 H, CH=NC*H₂*), 1.07 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (CH=N), 157.3 (C=O), 59.1 (CH=N*C*H_2), 41.1 ($NHCH_2$), 36.3 ($C_q(CH_3)_3$), 26.8 (C(*C*H_3)$_3$), Ar-C signals not observed due to complex coupling. ^{19}F NMR (377 MHz, $CDCl_3$) δ –140.4 to –140.6 (m), –150.7 to –150.8 (m), –156.0 to –160.1 (m). HRMS (ESI) m/z Calcd. for $C_{14}H_{16}N_2OF_5$ [M+H]$^+$: 323.1183; Found: 323.1182.

2,2,2-Trichloro-N-{2-[(E)-(2,2-dimethylpropylidene)amino]ethyl}acetamide (3k)



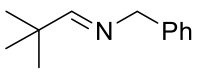
General procedure D was followed using *N*-(2-azaniumylethyl)-2,2,2-trichloroacetamide trifluoroacetate **1k** (383 mg, 1.20 mmol) to afford imine **3k** as an orange gum (328 mg, 100%) as a mixture of major and minor stereoisomers (7.3:1). NMR data quoted for the major isomer only. IR (film)/cm^{-1} 3311, 2961, 2862, 1693 (C=O), 1661, 1521, 1474, 1439, 1359, 1264, 1203, 1120. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.12 (bs, 1 H, NH), 3.64–3.59 (m, 2 H, NHC*H₂*), 3.57–3.54 (m, 2 H, CH=NC*H₂*), 1.08 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (CH=N), 161.8 (C=O), 58.5 (CH=N*C*H_2), 41.7 ($NHCH_2$), 36.4 ($C_q(CH_3)_3$), 26.8 (C(*C*H_3)$_3$). HRMS (ESI) m/z Calcd. for $C_9H_{16}N_2OCl_3$ [M+H]$^+$: 273.0328; Found: 273.0323.

tert-Butyl N-{2-[(E)-(2,2-dimethylpropylidene)amino]ethyl}carbamate (2l)



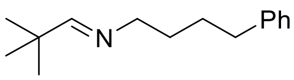
General procedure C was followed using *N*-Boc-ethylenediamine **1l** (636 mg, 4.00 mmol) to afford imine **2l** as a yellow oil (913 mg, 100%) as a mixture of major and minor stereoisomers (10.1:1). NMR data quoted for the major isomer only. IR (film)/cm^{-1} 3344, 2964, 1694 (C=O), 1667, 1512, 1477, 1453, 1364, 1268, 1249, 1167, 1117. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, *J* = 1.1 Hz, 1 H, N=CH), 4.74 (bs, 1 H, NH), 3.45 (t, *J* = 5.7 Hz, 2 H, CH=NCH_2), 3.34–3.30 (m, 2 H, NHCH_2), 1.43 (s, 9 H, $C(CH_3)_3$ (Boc)), 1.06 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (CH=N), 155.8 (C=O), 79.1 ($C_q(CH_3)_3$ (Boc)), 60.3 (CH=NCH_2), 41.2 ($NHCH_2$), 36.2 ($C_q(CH_3)_3$), 28.6 (C(CH_3)$_3$), 26.8 (C(CH_3)$_3$). HRMS (ESI) m/z Calcd. for $C_{12}H_{25}N_2O_2$ $[M+H]^+$: 229.1916; Found: 229.1922.

(*E*)-*N*-Benzyl-2,2-dimethylpropan-1-imine (2m)



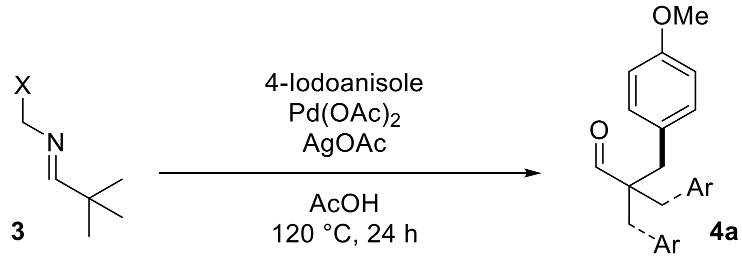
General procedure C was followed using benzylamine **1m** (327 μL mg, 3.00 mmol) to afford imine **2m** as a colourless amorphous solid (578 mg, 100%) as a single stereoisomer. IR (film)/cm^{-1} 2959, 2866, 2815, 1665, 1453, 1363. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 1.3 Hz, 1 H, N=CH), 7.35–7.31 (m, 2 H, Ph-H), 7.26–7.23 (m, 3 H, Ph-H), 4.59 (s, 2 H, CH_2), 1.13 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (CH=N), 139.7 (Ph-C_q), 128.3 (Ph-C), 127.6 (Ph-C), 126.7 (Ph-C), 64.5 (CH_2), 36.3 ($C_q(CH_3)_3$) 26.9 (C(CH_3)$_3$). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR) is consistent with that shown in the literature.[143]

(*E*)-2,2-Dimethyl-N-(4-phenylbutyl)propan-1-imine (2n)



General procedure C was followed using 4-phenylbutan-1-amine **1m** (474 μL, 3.00 mmol) to afford imine **2n** as a yellow oil (699 mg, 100%) as a single stereoisomer. IR (film)/cm^{-1} 3027, 2932, 2861, 2863, 1667, 1496, 1453, 1363. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 1.2 Hz, 1 H, N=CH), 7.30–7.26 (m, 2 H, Ph-H), 7.20–7.16 (m, 3 H, Ph-H), 3.38 (td, *J* = 6.9, 1.1 Hz, 2 H, CH=NCH_2), 2.63 (t, *J* = 6.9 Hz, 2 H, PhCH_2), 1.65–1.60 (m, 4 H, 2 × CH_2), 1.07 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (CH=N), 142.6 (Ph-C_q), 128.4 (Ph-C), 128.2 (Ph-C), 125.6 (Ph-C), 61.1 (CH=NCH_2), 35.9 (PhCH_2), 35.6 ($C_q(CH_3)_3$), 30.4 (CH_2), 28.9 (CH_2), 26.9 (C(CH_3)$_3$). HRMS (pNSI) m/z Calcd. for $C_{15}H_{24}N$ $[M+H]^+$: 218.1903; Found: 218.1904.

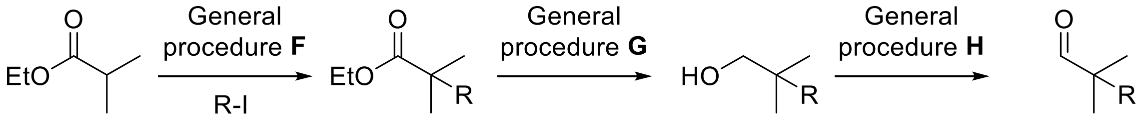
C(sp³)–H Arylation of Imines



General Procedure E: Imine **3** (0.40 mmol), 4-iodoanisole (243 mg, 1.04 mmol), palladium acetate (9 mg, 10 mol%), silver acetate (133 mg, 0.80 mmol) and acetic acid (1.3 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 120 °C for 24 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Yields of the arylated aldehyde products were calculated by ^{1}H NMR using *gem*-dimethyl (mono: 1.05 ppm), methyl (di: 0.97 ppm) and methylene (tri: 2.85 ppm) signals of **4a** in comparison to a known amount of 1,3,5-trimethoxybenzene as an internal standard.

*Preparation of aldehydes (**6-13**)*

Aldehydes with alternate chain lengths (**6-8**) were synthesised in 3 steps:



R = *n*Hex **6-CO_2Et**
R = *n*Oct **7-CO_2Et**
R = *n*Dec **8-CO_2Et**

R = *n*Hex **6-OH**
R = *n*Oct **7-OH**
R = *n*Dec **8-OH**

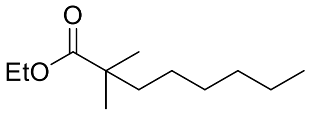
R = *n*Hex **6**
R = *n*Oct **7**
R = *n*Dec **8**

General Procedure F: Based on conditions developed by Shi.[144] *n*-Butyllithium (2.76 mL, 2.28 M in hexanes) was added dropwise to a stirred solution of freshly distilled diisopropylamine (883 µL, 6.30 mmol) in THF (6 mL) at -78 °C. The reaction was warmed to 0 °C and stirred for 30 min. The prepared LDA was then cooled to -78 °C and ethyl isobutyrate (806 µL, 6.00 mmol) was added dropwise and the reaction stirred at -78 °C for 1 h. The iodoalkane (6.18 mmol, 1.03 equiv) was added dropwise and the reaction stirred at room temperature overnight. The reaction was poured into ice water and extracted with diethyl ether (3 × 15 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, diethyl ether/pentane) afforded the corresponding alkylated ester.

General Procedure G: DIBAL (5.25 mL, 1 M in hexane) was added dropwise to a stirred solution of ester (2.50 mmol) in CH_2Cl_2 (2.8 mL). The reaction was warmed to 0 °C and stirred overnight. The reaction was quenched by addition of MeOH (1.25 mL), diluted with brine and filtered through Celite, the aqueous phase was extracted with diethyl ether (3 × 15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, diethyl ether/pentane) afforded the corresponding alcohol.

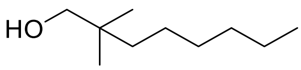
General Procedure H: Dess-Martin periodinane (DMP) (1.2 equiv) was added to a stirred solution of alcohol (1 equiv) in CH_2Cl_2 (0.2 M) at 25 °C and the reaction was stirred for 1 h. The reaction was quenched by addition of aqueous sodium thiosulfate (10% w/v) and the crude product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, Diethyl ether/pentane) afforded the corresponding aldehyde.

Ethyl 2,2-dimethyloctanoate (6-CO_2Et)



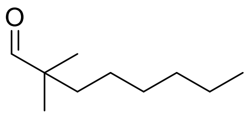
General procedure F was followed using 1-iodohexane (912 µL, 6.18 mmol) to afford alkylated ester **6-CO_2Et** as a colourless oil (1.07 g, 89%). R_f 0.63 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2930, 2859, 1728 (s, C=O), 1472, 1176, 1144, 1029. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2), 1.52–1.48 (m, 2 H, CH_2), 1.32–1.18 (m, 11 H, 4 × CH_2 + CH_3), 1.16 (s, 6 H, $C(CH_3)_2$), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2 (C=O), 60.1 (OCH_2), 42.2 ($C_q(CH_3)_2$), 40.8 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 25.1 ($C(CH_3)_2$), 24.8 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3). HRMS (pNSI) m/z Calcd. For $C_{12}H_{25}O_2$ $[M+H]^+$: 201.1849; Found: 201.1849. Spectroscopic data for this compound (^{1}H NMR) is consistent with that shown in the literature.[145]

2,2-Dimethyloctan-1-ol (6-OH)



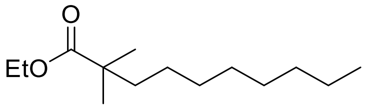
General procedure G was followed using ethyl 2,2-dimethyloctanoate **6-CO_2Et** (501 mg, 2.50 mmol) to afford alcohol **6-OH** as a colourless oil (233 mg, 59%). R_f 0.15 (20% diethyl ether/pentane). IR (film)/cm^{-1} 3323 (br, OH), 2858, 2927, 2858, 1468, 1363, 1041. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 2 H, CH_2), 1.34–1.20 (m, 11 H, 5 × CH_2 + OH), 0.91–0.87 (m, 9 H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.1 (OCH_2), 38.7 (CH_2), 35.0 ($C_q(CH_3)_2$), 31.9 (CH_2), 30.3 (CH_2), 23.83 ($C(CH_3)_2$), 23.81 (CH_2), 22.7 (CH_2), 14.1 (CH_3). Spectroscopic data for this compound (^{1}H NMR) is consistent with that shown in the literature.[145]

2,2-Dimethyloctanal (6)



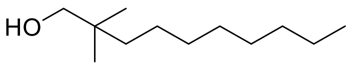
General procedure H was followed using ethyl 2,2-dimethyloctanol **6-OH** (223 mg, 1.41 mmol) to afford aldehyde **6** as a colourless oil (177 mg, 79%). R_f 0.50 (5% diethyl ether/pentane). IR (film)/cm^{-1} 2959, 2929, 2858, 2690, 1726 (s, C=O), 1468. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H, CHO), 1.48–1.44 (m, 2 H, CH_2), 1.33–1.15 (m, 8 H, 4 × CH_2), 1.05 (s, 6 H, $C(CH_3)_2$), 0.92–0.84 (t, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (C=O), 45.8 ($C_q(CH_3)_2$), 37.3 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 21.3 ($C(CH_3)_2$), 14.0 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{10}H_{21}O$ $[M+H]^+$: 157.1592; Found: 157.1587. Spectroscopic data for this compound (^{1}H NMR) is consistent with that shown in the literature.[145]

Ethyl 2,2-dimethyldecanoate (7-CO_2Et)



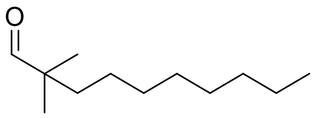
General procedure F was followed using 1-iodooctane (1.12 mL, 6.18 mmol) to afford alkylated ester **7-CO_2Et** as a colourless oil (846 mg, 62%). R_f 0.63 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2925, 2855, 1729 (s, C=O), 1469, 1174, 1143, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2), 1.52–1.48 (m, 2 H, CH_2), 1.34–1.17 (m, 15 H, 6 × CH_2 + CH_3), 1.16 (s, 6 H, $C(CH_3)_2$), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2 (C=O), 60.1 (OCH_2), 42.2 ($C_q(CH_3)_2$), 40.8 (CH_2), 31.9 (CH_2), 30.1 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.1 ($C(CH_3)_2$), 24.9 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3). HRMS (ESI) m/z Calcd. For $C_{14}H_{29}O_2$ $[M+H]^+$: 229.2168; Found: 229.2177.

2,2-Dimethyldecan-1-ol (7-OH)



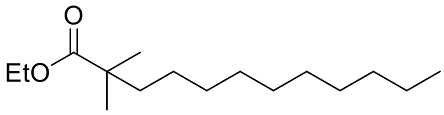
General procedure G was followed using ethyl 2,2-dimethyldecanoate **7-CO_2Et** (580 mg, 2.50 mmol) to afford alcohol **7-OH** as a colourless oil (361 mg, 78%). R_f 0.22 (20% diethyl ether/pentane). IR (film)/cm^{-1} 3358 (br, OH), 1738, 1467, 1363, 1038. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 2 H, OCH_2), 1.42 (bs, 1 H, OH), 1.33–1.20 (m, 14 H, 7 × CH_2), 0.91– 0.87 (m, 9 H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.1 (OCH_2), 38.7 (CH_2), 35.0 ($C_q(CH_3)_2$), 31.9 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 23.9 (CH_2), 23.8 ($C(CH_3)_2$), 22.7 (CH_2), 14.1 (CH_3). HRMS (ASAP(DCM)) m/z Calcd. For $C_{12}H_{25}O$ $[M-H]^-$: 185.1905; Found: 185.1901.

2,2-Dimethyldecanal (7)



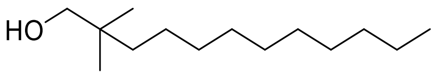
General procedure H was followed using ethyl 2,2-dimethyldecanol **7-OH** (254 mg, 1.41 mmol) to afford aldehyde **7** as a colourless oil (209 mg, 81%). R_f 0.41 (5% diethyl ether/pentane). IR (film)/cm^{-1} 2958, 2926, 2855, 1727, 1467. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H, CHO), 1.47–1.43 (m, 2 H, CH_2), 1.30–1.20 (m, 12 H, 6 × CH_2), 1.04 (s, 6 H, $C(CH_3)_2$), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (C=O), 45.8 ($C_q(CH_3)_2$), 37.4 (CH_2), 31.8 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 21.3 ($C(CH_3)_2$), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{12}H_{25}O$ $[M+H]^+$: 185.1905; Found: 185.1903. Spectroscopic data for this compound (^{1}H NMR) is consistent with that shown in the literature.[146]

Ethyl 2,2-dimethyldodecanoate (8-CO_2Et)



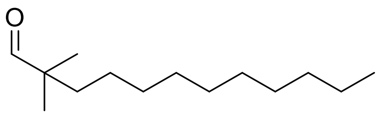
General procedure F was followed using 1-iododecane (1.32 mL, 6.18 mmol) to afford alkylated ester **8-CO_2Et** as a colourless oil (945 mg, 61%). R_f 0.15 (pentane). IR (film)/cm^{-1} 2924, 2854, 1729 (s, C=O), 1467, 1173, 1142, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 1.52–1.48 (m, 2 H, CH_2), 1.30–1.20 (m, 19 H, 8 × CH_2 + CH_3), 1.16 (s, 6 H $C(CH_3)_2$), 0.89 (t, J = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2 (C=O), 60.1 (OCH_2), 42.2 ($C_q(CH_3)_2$), 40.8 (CH_2), 31.9 (CH_2), 30.1 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.1 ($C(CH_3)_2$), 24.9 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3). HRMS (pNSI) m/z Calcd. for $C_{16}H_{33}O_2$ $[M+H]^+$: 257.2475; Found: 257.2478.

2,2-Dimethyldodecan-1-ol (8-OH)



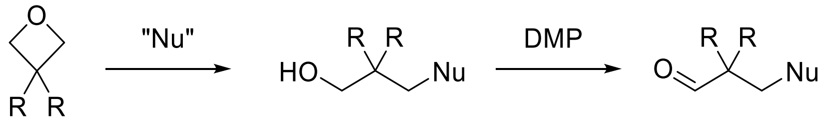
General procedure G was followed using ethyl 2,2-dimethyldodecanoate **8-CO_2Et** (641 mg, 2.50 mmol) to afford alcohol **8-OH** as a colourless oil (447 mg, 83%). R_f 0.31 (20% diethyl ether/pentane). IR (film)/cm^{-1} 3358 (br, OH), 2955, 2923 (s), 2853, 1738, 1467, 1364, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 2 H, CH_2), 1.32–1.20 (m, 19 H, 9 × CH_3 + OH), 0.90–0.87 (m, 9 H, 3 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.1 (OCH_2), 38.7 (CH_2), 35.0 ($C_q(CH_3)_2$), 31.9 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 29.6 (2 × CH_2), 29.3 (CH_2), 23.9 (CH_2), 23.8 ($C(CH_3)_2$), 22.7 (CH_2), 14.1 (CH_3). HRMS (ASAP(DCM)) m/z Calcd. For $C_{14}H_{29}O$ $[M-H]^-$: 213.2218; Found: 213.2214.

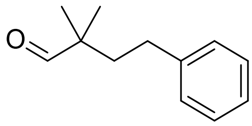
2,2-Dimethyldodecanal (8)



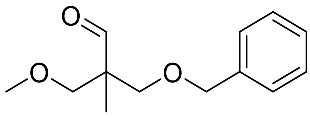
General procedure H was followed using ethyl 2,2-dimethyldodecanol **8-OH** (302 mg, 1.41 mmol) to afford aldehyde **8** as a colourless oil (193 mg, 64%). R_f 0.47 (5% diethyl ether/pentane). IR (film)/cm^{-1} 2924, 2854, 1728 (s, C=O), 1467, 1365, 1217. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H, CHO), 1.47–1.43 (m, 2 H, CH_2), 1.30–1.20 (m, 18 H, 9 × CH_2), 1.04 (s, 6 H, $C(CH_3)_2$), 0.89 (t, J = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (C=O), 45.8 ($C_q(CH_3)_2$), 37.4 (CH_2), 31.9 (CH_2), 30.2 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 24.3 (CH_2), 22.7 (CH_2), 21.3 ($C(CH_3)_2$), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{14}H_{29}O$ $[M+H]^+$: 213.2218; Found: 213.2218.

Aside from commercially available **12**, all other aldehydes were synthesised by either ring opening of 3,3-disubstituted oxetanes, or mono-benzylation of 2,2-dimethylpropane-1,3-diol:

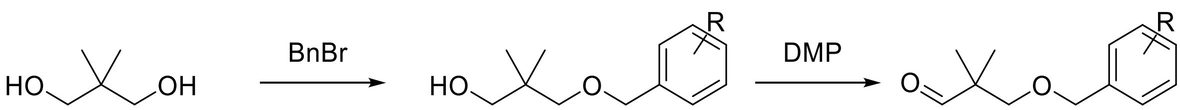


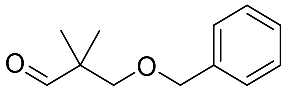


9

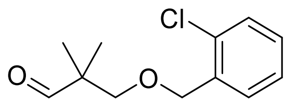


13



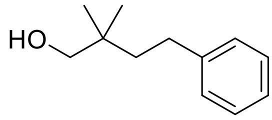


10



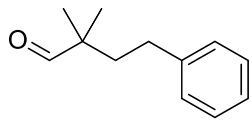
11

2,2-Dimethyl-4-phenylbutan-1-ol (9-OH)



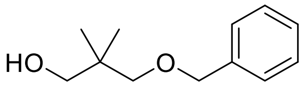
Conditions developed by Madsen.[147] Benzyl magnesium bromide (2.5 mL, 0.94 M in THP, formed from magnesium turnings and benzyl bromide in THP using standard techniques) and 3,3-dimethyloxetane (0.5 mL, 4.85 mmol) were combined in a 2–5 mL microwave vial. The vial was purged with Ar, sealed, and heated to 180 °C in a microwave reactor for 4 h. The reaction was allowed to cool to room temperature, diluted with diethyl ether, quenched with water and the aqueous phase extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride solution, water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, 20% EtOAc/pentane) afforded alcohol **9-OH** as a pale yellow oil (252 mg, 60%). R_f 0.38 (10% diethyl ether/pentane). IR (film)/cm^{-1} 3355 (br, OH), 2953, 2868, 1496, 1472, 1454, 1364, 1047, 1030. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.21–7.17 (m, 3 H, Ph-H), 3.39 (s, 2 H, OCH_2), 2.62–2.57 (m, 2 H, CH_2), 1.60–1.56 (m, 2 H, CH_2), 1.39 (bs, 1 H, OH), 0.97 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (Ph-C_q), 128.34 (Ph-C), 128.27 (Ph-C), 125.6 (Ph-C), 71.8 (OCH_2), 40.9 (CH_2), 35.3 ($C_q(CH_3)_2$), 30.5 ($PhCH_2$), 23.8 ($C(CH_3)_2$). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR, IR) is consistent with that shown in the literature.[148]

2,2-Dimethyl-4-phenylbutanal (9)



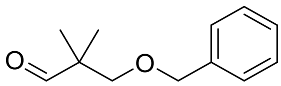
General procedure H was followed using 2,2-dimethyl-4-phenylbutan-1-ol **9** (178 mg, 1.00 mmol) to afford aldehyde **9** as a colourless oil (151 mg, 86%). R_f 0.32 (5% diethyl ether/pentane). IR (film)/cm^{-1} 1965, 2868, 1696, 1723 (s, C=O), 1497, 1469, 1454, 1366. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H, CHO), 7.31–7.28 (m, 2 H, Ph-H), 7.22–7.17 (m, 3 H, Ph-H), 2.56–2.52 (m, 2 H, $PhCH_2$), 1.82–1.78 (m, 2 H, CH_2), 1.14 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9 (CHO), 141.9 (Ph-C_q), 128.5 (Ph-C), 128.2 (Ph-C), 126.0 (Ph-C), 45.9 ($C_q(CH_3)_2$), 39.3 ($PhCH_2$), 30.8 (CH_2), 21.4 ($C(CH_3)_2$). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR, IR) is consistent with that shown in the literature.[149]

3-(Benzyloxy)-2,2-dimethylpropan-1-ol (10-OH)



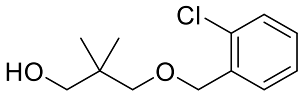
Sodium hydride (400 mg, 10.0 mmol, as a 60% dispersion in mineral oil) was slowly added to a solution of 2,2-dimethylpropane-1,3-diol (1.04 g, 10.0 mmol) in THF (35 mL) at 0 °C. After 10 minutes at 0 °C, benzyl bromide (950 µL, 8.00 mmol) was added dropwise and the reaction was stirred at 25 °C over the weekend. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (25% EtOAc/pentane) afforded benzylated alcohol **10-OH** as a pale-yellow oil (1.07 g, 69%). R_f 0.42 (25% EtOAc/pentane). IR (film)/cm^{-1} 3399 (br, OH), 2955, 2869, 1453, 1360, 1094, 1044. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H, Ph-H), 4.53 (s, 2 H, OC*H*$_2$Ph), 3.47 (d, *J* = 5.8 Hz, 2 H, C*H*$_2$OH), 3.34 (s, 2 H, OCH_2), 2.69 (t, *J* = 5.8 Hz, 1 H, OH), 0.95 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (Ph-C_q), 128.4 (Ph-C), 127.6 (Ph-C), 127.4 (Ph-C), 79.3 (O*C*H$_2$Ph), 73.5 (CH_2), 71.6 (CH_2OH), 36.2 ($C_q(CH_3)_2$), 21.8 (C(*C*H$_3$)$_2$). Spectroscopic data for this compound (^{1}H NMR),[150] (^{13}C NMR)[151] and (IR)[152] is consistent with that shown in the literature.

3-(Benzyloxy)-2,2-dimethylpropanal (10)



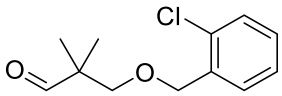
General procedure H was followed using 3-(benzyloxy)-2,2-dimethylpropan-1-ol **10-OH** (365 mg, 1.88 mmol) to afford aldehyde **10** as a colourless oil (292 mg, 81%). R_f 0.46 (10% EtOAc/pentane). IR (film)/cm^{-1} 2971, 2931, 1726 (m, C=O), 1454, 1245, 1095, 1012. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1 H, CHO), 7.38–7.28 (m, 5 H, Ph-H), 4.52 (s, 2 H, OCH_2), 3.46 (s, 2 H, OCH_2), 1.10 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 138.1 (Ph-C_q), 128.4 (Ph-C), 127.6 (Ph-C), 127.4 (Ph-C), 75.1 (OCH_2), 73.4 (OCH_2), 47.1 ($C_q(CH_3)_2$), 19.0 (C(*C*H$_3$)$_2$). Spectroscopic data for this compound (^{1}H NMR),[151] (^{13}C NMR)[153] and (IR)[152] is consistent with that shown in the literature.

3-((2-Chlorobenzyl)oxy)-2,2-dimethylpropan-1-ol (11-OH)



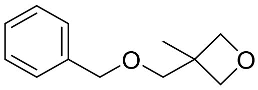
Sodium hydride (400 mg, 10.0 mmol, as a 60% dispersion in mineral oil) was slowly added to a solution of 2,2-dimethylpropane-1,3-diol (1.04 g, 10.0 mmol) in THF (35 mL) at 0 °C. After 10 minutes at 0 °C, 2-chlorobenzyl bromide (1.04 mL, 8.00 mmol) was added dropwise and the reaction was stirred at 25 °C overnight. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, 25% EtOAc/pentane) afforded benzylated alcohol **11-OH** as a pale yellow oil (819 mg, 40%). R_f 0.18 (20% EtOAc/pentane). IR (film)/cm^{-1} 3390 (br, OH), 2956, 2870, 1473, 1443, 1355, 1098, 1049. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 1 H, Ar-H), 7.38–7.35 (m, 1 H, Ar-H), 7.30–7.22 (m, 2 H, Ar-H), 4.61 (s, 2 H, OCH_2Ar), 3.49 (s, 2 H, CH_2OH), 3.41 (s, 2 H, OCH_2), 2.46 (bs, 1 H, OH), 0.97 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (Ar-C_q), 133.0 (Ar-C_q), 129.3 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 126.8 (Ar-C), 79.7 (OCH$_2$Ph), 71.6 (CH_2OH), 70.7 (OCH_2), 36.4 ($C_q(CH_3)_2$), 21.9 (C(CH$_3$)$_2$). HRMS (ESI) m/z Calcd. For $C_{12}H_{18}O_2Cl$ $[M+H]^+$: 229.0995; Found: 229.0993.

3-((2-Chlorobenzyl)oxy)-2,2-dimethylpropanal (11)



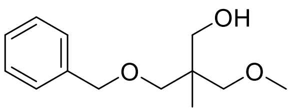
General procedure H was followed using 3-((2-chlorobenzyl)oxy)-2,2-dimethylpropan-1-ol **11-OH** (345 mg, 1.50 mmol) to afford aldehyde **11** as a colourless oil (200 mg, 59%). R_f 0.40 (10% EtOAc/pentane). IR (film)/cm^{-1} 2969, 2872 1730 (s, C=O), 1443, 1472, 1098, 1051. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H, CHO), 7.43–7.41 (m, 1 H, Ar-H), 7.35–7.33 (m, 1 H, Ar-H), 7.28–7.19 (m, 2 H, Ar-H), 4.60 (s, 2 H, OCH_2), 3.56 (s, 2 H, OCH_2), 1.13 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.1 (CHO), 135.7 (Ar-C_q), 132.6 (Ar-C_q), 129.1 (Ar-C), 128.62 (Ar-C), 128.56 (Ar-C), 126.7 (Ar-C), 75.6 (OCH_2), 70.3 (OCH_2), 47.1 ($C_q(CH_3)_2$), 19.0 (C(CH$_3$)$_2$). HRMS (ESI) m/z Calcd. For $C_{12}H_{16}O_2Cl$ $[M+H]^+$: 227.0833; Found: 227.0835.

3-((Benzyloxy)methyl)-3-methyloxetane (13-Oxetane)



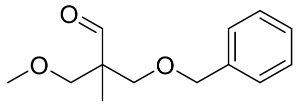
Sodium hydride (440 mg, 11.0 mmol, as a 60% dispersion in mineral oil) was slowly added to a solution of (3-methyloxetan-3-yl)methanol (998 µL, 10.0 mmol) in THF (35 mL) at 0 °C. After 10 minutes at 0 °C, benzyl bromide (1.31 mL, 11.0 mmol) was added dropwise and the reaction was stirred at 25 °C overnight. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/pentane) afforded benzylated alcohol **13-Oxetane** as a colourless oil (1.49 g, 77%). R_f 0.55 (20% EtOAc/pentane). IR (film)/cm^{-1} 2957, 2931, 2864 (m), 1453, 1361, 1093 (s), 976 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5 H, Ph-H), 4.59 (s, 2 H, OC*H*$_2$Ph), 4.54 (d, *J* = 5.7 Hz, 2 H, 2 × OC(*H*)H), 4.38 (d, *J* = 5.7 Hz, 2 H, 2 × OC(H)*H*), 3.54 (s, 2 H, CH_2), 1.35 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (Ph-C_q), 128.4 (Ph-C), 127.63 (Ph-C), 127.55 (Ph-C), 80.2 (2 × CH_2), 75.4 (OCH_2), 73.3 (OCH_2), 39.9 (C_q(CH_3)), 21.4 (CH_3). Spectroscopic data for this compound (^{1}H NMR),[154] (^{13}C NMR)[155] and (IR)[154] is consistent with that shown in the literature.

3-(Benzyloxy)-2-(methoxymethyl)-2-methylpropan-1-ol (13-OH)



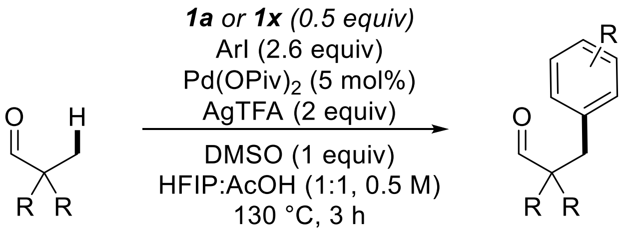
5 drops of H_2SO_4 (98%) was added to a solution of 3-((benzyloxy)methyl)-3-methyloxetane **13-Oxetane** (481 mg, 2.5 mmol) in MeOH (2.5 mL) at 25 °C. The reaction was heated to 65 °C in a sealed vial and stirred for 1 h. The reaction mixture was neutralised by slow addition of saturated aqueous sodium bicarbonate solution (5 mL) and the aqueous layer extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/pentane) afforded alcohol **13-OH** as a pale yellow oil (377 mg, 67%). R_f 0.48 (20% diethyl ether/pentane). IR (film)/cm^{-1} 3448 (br, OH), 2875, 1453, 1363, 1197, 1094. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H, Ph-H), 4.53 (s, 2 H, OC*H*$_2$Ph), 3.59 (d, *J* = 5.8 Hz, 2 H, OCH_2), 3.50–3.36 (m, 4 H, 2 × OCH_2), 3.34 (s, 3 H, OCH_3), 2.86 (t, *J* = 6.0 Hz, 1 H, OH), 0.89 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (Ph-C_q), 128.4 (Ph-C), 127.6 (Ph-C), 127.4 (Ph-C), 77.5 (OCH_2), 74.7 (OCH_2), 73.5 (OCH_2), 69.3 (OCH_2), 59.4 (OCH_3), 40.5 (C_q(CH_3)), 17.5 (CH_3). HRMS (ESI) m/z Calcd. for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1491; Found: 225.1491.

3-(Benzyloxy)-2-(methoxymethyl)-2-methylpropanal (13)



General procedure H was followed using 3-(benzyloxy)-2-(methoxymethyl)-2-methylpropan-1-ol **12-OH** (224 mg, 1.00 mmol) to afford aldehyde **12** as a colourless oil (127 mg, 57%). R_f 0.23 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2861, 1728 (s, C=O), 1453, 1365, 1203, 1098 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 7.37–7.29 (m, 5 H, Ph-H), 4.52 (s, 2 H, OC*H*$_2$Ph), 3.65–3.48 (m, 4 H, 2 × OCH_2), 3.33 (s, 3 H, OCH_3), 1.11 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (CHO), 138.1 (Ph-C_q), 128.3 (Ph-C), 127.6 (Ph-C), 127.4 (Ph-C), 74.0 (OCH_2), 73.4 (OCH_2), 71.3 (OCH_2), 59.4 (OCH_3), 51.7 (C_q(CH_3)), 14.9 (CH_3). HRMS (pNSI) m/z Calcd. for $C_{13}H_{19}O_3$ [M+H]$^+$: 223.1329; Found: 223.1328.

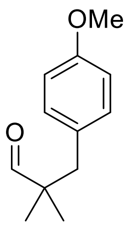
*C(sp^3)–H arylation of aldehydes with a transient directing group (compounds **4a-j** and **14-21**)*



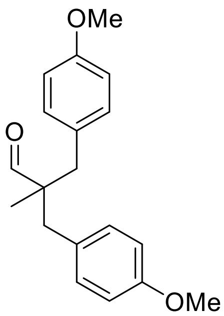
General Procedure J: Aldehyde (0.40 mmol), *N*-tosylethylenediamine **1a** (43 mg, 0.20 mmol) or 2-methoxyethan-1-amine **1x** (17 µL, 0.20 mmol), aryl iodide (2.6 equiv), palladium pivalate (6.2 mg, 5 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), DMSO (28.4 µL, 0.40 mmol), acetic acid (0.4 mL) and HFIP (0.4 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 3 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica (eluting with CH_2Cl_2) and concentrated under reduced pressure. Purification by flash chromatography (silica) afforded the arylated aldehydes.

3-(4-Methoxyphenyl)-2,2-dimethylpropanal (4a-mono), 2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-2-methylpropanal (4a-di) and 2,2-Bis(4-methoxybenzyl)-3-(4-methoxyphenyl)propanal (4a-tri)

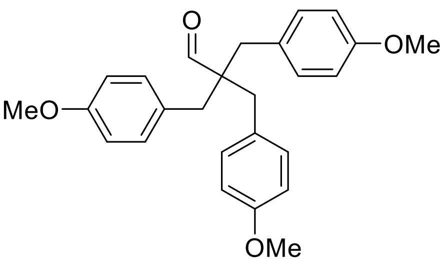
Prepared according to general procedure J using pivaldehyde (44 µL, 0.40 mmol) and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (7.5% diethyl ether/pentane) afforded monoarylated aldehyde **4a-mono** as a colourless oil (19 mg, 25%) followed by diarylated aldehyde **4a-di** as a pale yellow wax (19 mg, 16%) followed by triarylated aldehyde **4a-tri** as a pale orange oil (19 mg, 12%).



4a-mono: R_f 0.29 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2963, 2932, 2836, 1722 (s, C=O), 1611, 1511 (s), 1465, 1244 (s), 1178, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1 H, CHO), 7.04–7.00 (m, 2 H, Ar-H), 6.84–6.80 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.73 (s, 2 H, CH_2), 1.05 (s, 6 H, C(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2 (C=O), 158.3 (Ar-C_q), 131.2 (2 × Ar-C), 128.9 (Ar-C_q), 113.6 (2 × Ar-C), 55.2 (OCH_3), 47.0 (C_q(CH_3)$_2$), 42.4 (CH_2), 21.3 (C(CH_3)$_2$). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR, IR) is consistent with that shown in the literature.[156]



4a-di: R_f 0.08 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2915, 2836, 1760, 1720 (C=O), 1610, 1509, 1462, 1369, 1244, 1215, 1192, 1177, 1031. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1 H, CHO), 7.02–7.00 (m, 4 H, Ar-H), 6.82–6.80 (m, 4 H, Ar-H), 3.79 (s, 6 H, OCH_3), 2.97 (d, J = 13.8 Hz, 2 H, *CH*(H)), 2.64 (d, J = 13.8 Hz, 2 H, CH(*H*)), 0.97 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (C=O), 158.3 (2 × Ar-C_q), 131.3 (4 × Ar-C), 128.6 (2 × Ar-C_q), 113.6 (4 × Ar-C), 55.3 (2 × OCH_3), 51.4 (C_q(CH_3)), 41.9 (2 × CH_2), 18.0 (CH_3). HRMS (ESI) m/z Calcd. for $C_{19}H_{26}O_3N$ [M+NH$_4$]$^+$: 316.1907; Found: 316.1910.

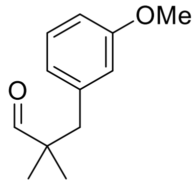


4a-tri: R_f 0.05 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2934, 1720 (C=O), 1610, 1582, 1509, 1463, 1440, 1300, 1242 (s), 1176, 1114, 1031. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H, CHO), 7.05–7.02 (m, 6 H, Ar-H), 6.84–6.80 (m, 6 H, Ar-H), 3.80 (s, 9 H, OCH_3), 2.85 (s, 6 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4 (C=O), 158.2 (3 × Ar-C_q), 131.5 (6 × Ar-C), 128.6 (3 × Ar-C_q), 113.6 (6 × Ar-C), 55.2 (3 × OCH_3), 53.8 (C_q(CHO)), 39.2 (3 × CH_2). HRMS (ESI) m/z Calcd. for $C_{26}H_{29}O_4$ [M+H]$^+$: 405.2060; Found: 405.2046.

Resubjection of aldehydes 4a-mono and 4a-di to the reaction conditions

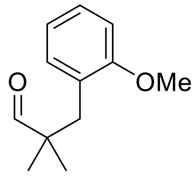
According to general procedure J, 3-(4-methoxyphenyl)-2,2-dimethylpropanal **4a-mono** (19 mg, 0.10 mmol) or 2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-2-methylpropanal **4a-di** (19 mg, 0.06 mmol) with 4-iodoanisole (2.6 equiv) were subjected to the arylation conditions. Yields of the arylated aldehyde products were calculated by ^{1}H NMR using *gem*-dimethyl (mono: 1.05 ppm), methyl (di: 0.97 ppm) and methylene (tri: 2.85 ppm) signals in comparison to a known amount of 1,3,5-trimethoxybenzene as an internal standard.

3-(3-Methoxyphenyl)-2,2-dimethylpropanal (4b-mono)



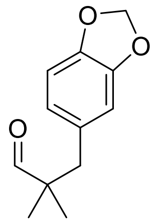
Prepared according to general procedure *J* using pivaldehyde (44 μL, 0.40 mmol) and 1-iodo-3-methoxybenzene (244 mg, 1.04 mmol). Purification by flash column chromatography (5% diethyl ether/pentane) afforded monoarylated aldehyde **4b-mono** as a colourless oil (15 mg, 20%). R_f 0.31 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2958, 2835, 2710, 1723 (s, C=O), 1600, 1583, 1488, 1465, 1436, 1261 (s), 1154, 1049. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1 H, CHO), 7.20 (t, *J* = 8.0 Hz, 1 H, Ar-H), 6.79–6.76 (m, 1 H, Ar-H), 6.69 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.66–6.65 (m, 1 H, Ar-H), 3.80 (s, 3 H, OCH_3), 2.77 (s, 2 H, CH_2), 1.07 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9 (C=O), 159.3 (Ar-C_q), 138.5 (Ar-C_q), 129.1 (Ar-C), 122.7 (Ar-C), 116.2 (Ar-C), 111.6 (Ar-C), 55.1 (OCH_3), 46.9 ($C_q(CH_3)_2$), 43.2 (CH_2), 21.5 ($C(CH_3)_2$). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{12}H_{17}O_2$ $[M+H]^+$: 193.1229; Found: 193.1225.

3-(2-Methoxyphenyl)-2,2-dimethylpropanal (4c-mono)



Prepared according to general procedure *J* using pivaldehyde (44 μL, 0.40 mmol) and 1-iodo-2-methoxybenzene (244 mg, 1.04 mmol). Purification by flash column chromatography (5% diethyl ether/pentane) afforded monoarylated aldehyde **4c-mono** as a colourless oil (7 mg, 9%). R_f 0.21 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2962, 1722 (C=O), 1493, 1463, 1243, 1178, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1 H, CHO), 7.21 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1 H, Ar-H), 7.06 (dd, *J* = 7.5, 1.7 Hz, 1 H, Ar-H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 6.83 (dd, *J* = 8.1, 1.0 Hz, 1 H, Ar-H), 3.77 (s, 3 H, OCH_3), 2.82 (s, 2 H, CH_2), 1.04 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (C=O), 157.4 (Ar-C_q), 132.1 (Ar-C), 128.0 (Ar-C), 125.7 (Ar-C_q), 120.2 (Ar-C), 110.4 (Ar-C), 54.9 (OCH_3), 46.9 ($C_q(CH_3)_2$), 38.0 (CH_2), 21.6 ($C(CH_3)_2$). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{12}H_{17}O_2$ $[M+H]^+$: 193.1229; Found: 193.1226.

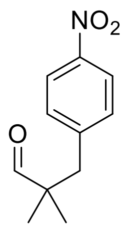
3-(Benzo[d][1,3]dioxol-5-yl)-2,2-dimethylpropanal (4d-mono)



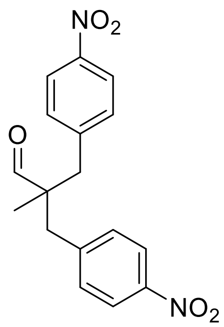
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 5-iodobenzo[d][1,3]dioxole (153 µL, 1.04 mmol). Purification by flash column chromatography (7.5% diethyl ether/pentane) afforded monoarylated aldehyde **4d-mono** as a pale yellow oil (9 mg, 11%). R_f 0.29 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2965, 2704, 1721 (C=O), 1489, 1440, 1360, 1240, 1190, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H, CHO), 6.72 (d, *J* = 7.9 Hz, 1 H, Ar-H), 6.59 (d, *J* = 1.7 Hz, 1 H, Ar-H), 6.55 (dd, *J* = 7.9, 1.7 Hz, 1 H, Ar-H), 5.93 (s, 2 H, OCH_2O), 2.71 (s, 2 H, CH_2), 1.05 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (C=O), 147.4 (Ar-C_q), 146.2 (Ar-C_q), 130.6 (Ar-C_q), 123.2 (Ar-C), 110.5 (Ar-C), 108.0 (Ar-C), 100.9 (OCH_2O), 47.0 ($C_q(CH_3)_2$), 42.9 (CH_2), 21.4 ($C(CH_3)_2$). HRMS (ASAP(DCM)) m/z Calcd. for $C_{12}H_{13}O_3$ [M-H]$^+$: 205.0865; Found: 205.0859.

2,2-Dimethyl-3-(4-nitrophenyl)propanal (4e-mono) and 2-methyl-2-(4-nitrobenzyl)-3-(4-nitrophenyl)propanal (4e-di)

Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 1-iodo-4-nitrobenzene (259 mg, 1.04 mmol). Purification by flash column chromatography (10%–50% diethyl ether/pentane) afforded monoarylated aldehyde **4e-mono** as an orange oil (24 mg, 29%) followed by diarylated aldehyde **4e-mono** as a pale yellow amorphous solid (21 mg, 16%).



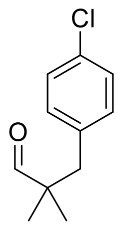
4e-mono: R_f 0.16 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2967, 1722 (C=O), 1597, 1514, 1341, 1109. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1 H, CHO), 8.17–8.14 (m, 2 H, Ar-H), 7.32–7.28 (m, 2 H, Ar-H), 2.92 (s, 2 H, CH_2), 1.10 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7 (C=O), 146.8 (Ar-C_q), 145.0 (Ar-C_q), 131.1 (2 × Ar-C), 123.3 (2 × Ar-C), 46.9 ($C_q(CH_3)_2$), 42.4 (CH_2), 21.5 ($C(CH_3)_2$). HRMS (ASAP(DCM)) m/z Calcd. for $C_{11}H_{14}NO_3$ [M+H]$^+$: 208.0974; Found: 208.0973.



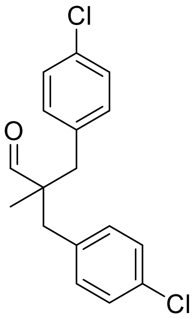
4e-di: R_f 0.08 (30% diethyl ether/pentane). IR (film)/cm^{-1}2970, 1723 (C=O), 1598, 1515, 1339, 1107, 1089. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 8.19–8.15 (m, 4 H, Ar-H), 7.31–7.27 (m, 4 H, Ar-H), 3.16 (d, *J* = 13.5 Hz, 2 H, 2 × C(H)*H*), 2.84 (d, *J* = 13.5 Hz, 2 H, 2 × C(*H*)H), 1.08 (s, 3 H, CH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C=O), 147.0 (2 × Ar-C_q), 143.7 (2 × Ar-C_q), 131.2 (4 × Ar-C), 123.5 (4 × Ar-C), 51.1 ($C_q(CH_3)$), 42.2 (2 × CH_2), 18.5 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{17}H_{17}N_2O_5$ [M+H]$^+$: 329.1137; Found: 329.1138.

3-(4-Chlorophenyl)-2,2-dimethylpropanal (4f-mono), 2-(4-chlorobenzyl)-3-(4-chlorophenyl)-2-methylpropanal (4f-di) and 2,2-bis(4-chlorobenzyl)-3-(4-chlorophenyl)propanal (4f-tri)

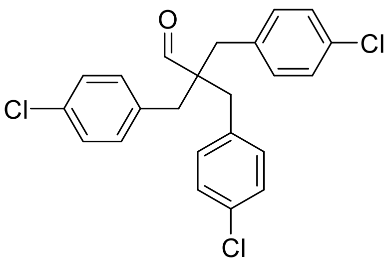
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 1-chloro-4-iodobenzene (248 mg, 1.04 mmol). Purification by flash column chromatography (2.5% diethyl ether/pentane) afforded monoarylated aldehyde **4f-mono** as a colourless oil (24 mg, 31%) followed by a 5.2:1 mixture of diarylated aldehyde **4f-di** (29 mg, 24%) and triarylated aldehyde **4f-tri** (7 mg, 4%) as an off-white solid.



4f-mono: R_f 0.32 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2966, 2929, 2704, 1723 (s, C=O), 1491, 1467, 1198, 1090, 1015. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H, CHO), 7.27–7.23 (m, 2 H, Ar-H), 7.05–7.01 (m, 2 H, Ar-H), 2.76 (s, 2 H, CH_2), 1.05 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (CHO), 135.4 (Ar-C_q), 132.5 (Ar-C_q), 131.5 (2 × Ar-C), 128.3 (2 × Ar-C), 46.8 ($C_q(CH_3)_2$), 42.3 (CH_2), 21.4 ($C(CH_3)_2$). HRMS (ASAP(DCM)) m/z Calcd. for $C_{11}H_{13}O_1Cl_1$ $[M+CH_3]^+$: 196.0655; Found: 196.0651.



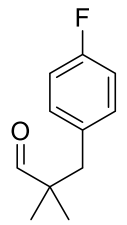
4f-di: R_f 0.20 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2921, 1724 (s, C=O) 1491 (s), 1409, 1093, 1015. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1 H, CHO), 7.27–7.23 (m, 4 H, Ar-H), 7.02–7.00 (m, 4 H, Ar-H), 2.98 (d, *J* = 13.7 Hz, 2 H, 2 × C(*H*)H), 2.66 (d, *J* = 13.7 Hz, 2 H, 2 × C(H)*H*), 0.98 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (CHO), 134.8 (2 × Ar-C_q), 132.7 (2 × Ar-C_q), 131.6 (4 × Ar-C), 128.4 (4 × Ar-C), 51.0 ($C_q(CH_3)$), 41.9 (2 × CH_2), 18.2 (CH_3). HRMS (ASAP(DCM)) m/z Calcd. for $C_{17}H_{17}OCl_2$ $[M+H]^+$: 307.0656; Found: 307.0651.



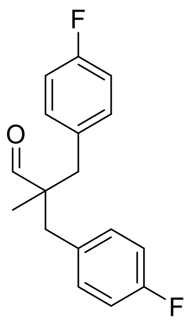
4f-tri: R_f 0.20 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2921, 1724 (s, C=O) 1491 (s), 1409, 1093, 1015. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1 H, CHO), 7.27–7.23 (m, 6 H, Ar-H), 7.02–7.00 (m, 6 H, Ar-H), 2.86 (s, 6 H, 3 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (CHO), 134.5 (3 × Ar-C_q), 132.8 (3 × Ar-C_q), 131.8 (6 × Ar-C), 128.5 (6 × Ar-C), 53.5 (C_q(CHO)), 39.6 (3 × CH_2). HRMS (ASAP(DCM)) m/z Calcd. for $C_{23}H_{20}OCl_3$ $[M+H]^+$: 417.0580; Found: 417.0577.

3-(4-Fluorophenyl)-2,2-dimethylpropanal 4g-mono), 2-(4-fluorobenzyl)-3-(4-fluorophenyl)-2-methylpropanal (4g-di) and 2,2-bis(4-fluorobenzyl)-3-(4-fluorophenyl)propanal (4g-tri)

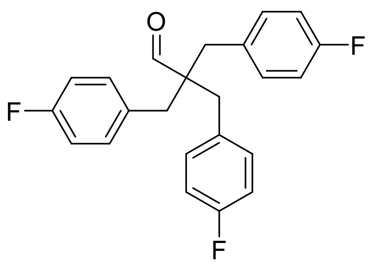
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 1-fluoro-4-iodobenzene (124 µL, 1.04 mmol). Purification by flash column chromatography (2.5% diethyl ether/pentane) afforded monoarylated aldehyde **4g-mono** as a colourless oil (19 mg, 26%) followed by a 4.5:1 mixture of diarylated aldehyde **4g-di** (26 mg, 24%) and triarylated aldehyde **4g-tri** (8 mg, 5%) as a pale-yellow oil.



4g-mono: R_f 0.32 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2970, 2701, 1723 (C=O), 1605, 1508 (s), 1468, 1221, 1159. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1 H, CHO), 7.08–7.04 (m, 2 H, Ar-H), 6.99–6.94 (m, 2 H, Ar-H), 2.76 (s, 2 H, CH_2), 1.05 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (C=O), 161.7 (d, $^1J_{C\text{-}F}$ = 244.8 Hz, Ar-C_q), 132.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C_q), 131.6 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2 × Ar-C), 115.0 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, 2 × Ar-C), 46.9 ($C_q(CH_3)_2$), 42.2 (CH_2), 21.3 ($C(CH_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.6.



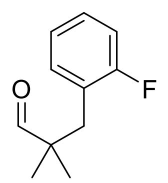
4g-di: R_f 0.20 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2922, 1722 (C=O), 1603, 1507, 1219, 1158. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 7.08–7.03 (m, 4 H, Ar-H), 7.00–6.95 (m, 4 H, Ar-H), 2.99 (d, *J* = 13.8 Hz, 2 H, 2 × C(H)*H*), 2.67 (d, *J* = 13.8 Hz, 2 H, 2 × C(H)*H*), 0.98 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8 (C=O), 161.8 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, 2 × Ar-C_q), 132.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, 2 × Ar-C_q), 131.7 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 4 × Ar-C), 115.1 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, 4 × Ar-C), 51.1 ($C_q(CH_3)$), 41.8 (2 × CH_2), 18.1 (CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.2. HRMS (ASAP(SOLID)) m/z Calcd. for $C_{17}H_{17}OF_2$ $[M+H]^+$: 275.1247; Found: 275.1246.



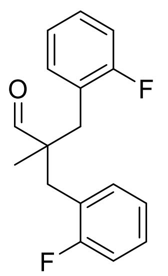
4g-tri: R_f 0.20 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2922, 1722 (C=O), 1603, 1507, 1219, 1158. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1 H, CHO), 7.08–7.03 (m, 6 H, Ar-H), 7.00–6.95 (m, 6 H, Ar-H), 2.87 (s, 6 H, 3 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9 (C=O), 161.8 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, 3 × Ar-C_q), 132.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, × Ar-C_q), 131.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, 6 × Ar-C), 115.2 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, 6 × Ar-C), 53.5 (C_q(CHO)), 39.4 (3 × CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.0. HRMS (ASAP(SOLID)) m/z Calcd. for $C_{23}H_{20}OF_3$ $[M+H]^+$: 369.1466; Found: 369.1464.

3-(2-Fluorophenyl)-2,2-dimethylpropanal (4h-mono), 2-(2-fluorobenzyl)-3-(2-fluorophenyl)-2-methylpropanal (4h-di) and 2,2-bis(2-fluorobenzyl)-3-(2-fluorophenyl)propanal (4h-tri)

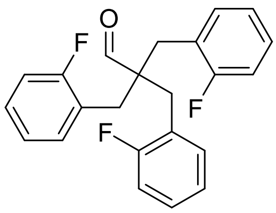
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 1-fluoro-2-iodobenzene (121 µL, 1.04 mmol). Purification by flash column chromatography (2.5% diethyl ether/pentane) afforded monoarylated aldehyde **4h-mono** as a colourless oil (10 mg, 12%) followed by a 8.2:1 mixture of diarylated aldehyde **4h-di** (6 mg, 5%) and triarylated aldehyde **4h-tri** (1 mg, 1%) as an off-white solid.



4h-mono: R_f 0.35 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2970, 1725 (C=O), 1492, 1453, 1229, 1183. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, J_{H-F} = 1.7 Hz, 1 H, CHO), 7.25–7.19 (m, 1 H, Ar-H), 7.13–7.00 (m, 3 H, Ar-H), 2.84 (d, J_{H-F} = 1.6 Hz, 2 H, CH_2), 1.08 (d, J_{H-F} = 0.6 Hz, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (C=O), 161.3 (d, $^1J_{C-F}$ = 244.8 Hz, Ar-C_q), 132.6 (d, $^3J_{C-F}$ = 4.4 Hz, Ar-C), 128.5 (d, $^3J_{C-F}$ = 8.3 Hz, Ar-C), 124.0 (d, $^2J_{C-F}$ = 15.6 Hz, Ar-C_q), 123.8 (d, $^4J_{C-F}$ = 3.4 Hz, Ar-C), 115.4 (d, $^2J_{C-F}$ = 23.1 Hz, Ar-C), 47.1 ($C_q(CH_3)_2$), 35.7 (CH_2), 21.2 ($C(CH_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ –115.3. HRMS (EI) m/z Calcd. for $C_{11}H_{13}OF$ $[M+H]^+$: 180.0950; Found: 180.0957.



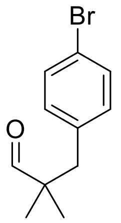
4h-di: R_f 0.27 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2927, 1724 (C=O), 1584, 1491, 1455, 1228, 1182. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, J_{H-F} = 2.1 Hz, 1 H, CHO), 7.25–7.20 (m, 2 H, Ar-H), 7.13–7.01 (m, 6 H, Ar-H), 3.08 (dd, *J* = 13.8, $1.2_{(H-F)}$ Hz, 2 H, 2 × C(H)*H*), 2.84 (dd, *J* = 13.8, $1.5_{(H-F)}$ Hz, 2H, 2 × C(*H*)H), 0.99 (t, J_{H-F} = 1.1 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9 (C=O), 161.2 (d, $^1J_{C-F}$ = 245.0 Hz, 2 × Ar-C_q), 132.6 (d, $^3J_{C-F}$ = 4.2 Hz, 2 × Ar-C), 128.7 (d, $^3J_{C-F}$ = 8.3 Hz, 2 × Ar-C), 123.9 (d, $^4J_{C-F}$ = 3.3 Hz, 2 × Ar-C), 123.6 (d, $^2J_{C-F}$ = 15.9 Hz, 2 × Ar-C_q), 115.5 (d, $^2J_{C-F}$ = 22.7 Hz, 2 × Ar-C), 51.6 ($C_q(CH_3)$), 35.4 (2 × CH_2), 17.3 (CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ –114.9. HRMS (ASAP(SOLID)) m/z Calcd. for $C_{17}H_{17}OF_2$ $[M+H]^+$: 275.1247; Found: 275.1251.



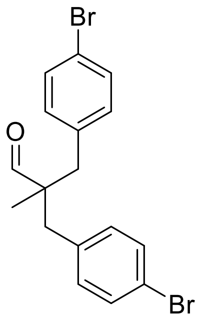
4h-tri: R_f 0.27 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2927, 1724 (C=O), 1584, 1491, 1455, 1228, 1182. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H, CHO), 7.25–7.20 (m, 3 H, Ar-H), 7.13–7.01 (m, 9 H, Ar-H), 2.99 (s, 6H, 3 × CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ –114.1. HRMS (ASAP(SOLID)) m/z Calcd. for $C_{23}H_{20}OF_3$ $[M+H]^+$: 369.1466; Found: 369.1463.

3-(4-Bromophenyl)-2,2-dimethylpropanal (4i-mono), 2-(4-bromobenzyl)-3-(4-bromophenyl)-2-methylpropanal (4i-di) and 2,2-bis(4-bromobenzyl)-3-(4-bromophenyl)propanal (4i-tri)

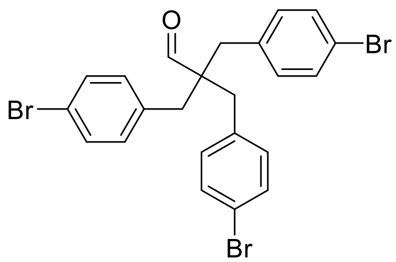
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 1-bromo-4-iodobenzene (294 mg, 1.04 mmol). Purification by flash column chromatography (2.5% diethyl ether/pentane) afforded monoarylated aldehyde **4i-mono** as a colourless oil (29 mg, 30%) followed by a 5:1 mixture of diarylated aldehyde **4i-di** (36 mg, 23%) and triarylated aldehyde **4i-tri** (10 mg, 5%) as a colourless oil.



4i-mono: R_f 0.31 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2967, 2702, 1722 (s, C=O), 1487, 1467, 1404, 1197. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H, CHO), 7.42–7.38 (m, 2 H, Ar-H), 7.00–6.96 (m, 2 H, Ar-H), 2.74 (s, 2 H, CH_2), 1.05 (s, *J* = 5.0 Hz, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (C=O), 135.9 (Ar-C_q), 131.9 (2 × Ar-C), 131.2 (2 × Ar-C), 120.5 (Ar-C_q), 46.8 ($C_q(CH_3)_2$), 42.4 (CH_2), 21.4 ($C(CH_3)_2$). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR, IR) is consistent with that shown in the literature.[37]

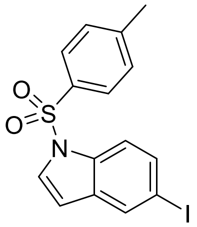


4i-di: R_f 0.19 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2971, 2919, 1722 (C=O), 1487, 1405, 1072, 1010. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.41–7.39 (m, 4 H, Ar-H), 6.97–6.95 (m, 4 H, Ar-H), 2.96 (d, *J* = 13.7 Hz, 2 H, 2 × C(H)*H*), 2.65 (d, *J* = 13.7 Hz, 2 H, 2 × C(*H*)H), 0.98 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (C=O), 135.3 (2 × Ar-C_q), 132.0 (4 × Ar-C), 131.4 (4 × Ar-C), 120.8 (2 × Ar-C_q), 50.9 ($C_q(CH_3)$), 41.9 (2 × CH_2), 18.2 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{18}H_{19}OBr_2$ $[M+CH_3]^+$: 408.9803; Found: 408.9805.



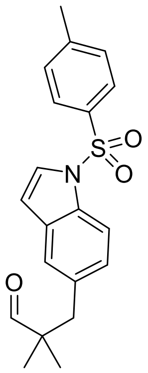
4i-tri: R_f 0.19 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2971, 2919, 1722 (C=O), 1487, 1405, 1072, 1010. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1 H, CHO), 7.42–7.39 (m, 6 H, Ar-H), 6.97–6.95 (m, 6 H, Ar-H), 2.84 (s, 6 H, 3 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (C=O), 135.0 (3 × Ar-C_q), 132.12 (6 × Ar-C), 131.5 (6 × Ar-C), 120.9 (3 × Ar-C_q), 53.3 (C_q(CHO)), 39.6 (3 × CH_2). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{23}H_{20}OBr_3$ $[M+H]^+$: 548.9064; Found: 548.9066.

5-Iodo-1-tosyl-1H-indole (4j-ArI)



Tosyl chloride (836 mg, 4.4 mmol) in DMF (2.2 mL) was added dropwise to a stirred suspension of 5-iodo-1-tosyl-1H-indole (936 mg, 4.0 mmol) and sodium hydride (192 mg, 4.8 mmol, 60% dispersion in mineral oil) in DMF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 minutes then allowed to warm to rt and stirred for 2 h. The reaction was quenched by addition of water and the product extracted with EtOAc. The combined organic extracts were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 0-20% diethyl ether/hexane) afforded tosyl indole **4j-ArI** (1.38 g, 87%) as a white solid. R_f 0.17 (10% diethyl ether/hexane). mp = 132–137 °C (lit = 136–138 °C)[157]. IR (film)/cm^{-1} 1595, 1437, 1361, 1252, 1193, 1168, 1130, 1092. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1 H, Ar-H), 7.77–7.73 (m, 3 H Ar-H), 7.58 (d, *J* = 8.7 Hz, 1 H, Ar-H), 7.53 (d, *J* = 3.6 Hz, 1 H, Ar-H), 7.24 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.58 (d, *J* = 3.6 Hz, 1 H, Ar-H), 2.36 (s, 3 H, Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (Ar-C_q), 135.0 (Ar-C_q) 134.1 (Ar-C_q), 133.0 (Ar-C), 133.0 (Ar-C_q) 130.2 (Ar-C), 130.0 (2 × Ar-C), 127.2 (Ar-C), 126.8 (2 × Ar-C), 115.3 (Ar-C), 108.0 (Ar-C), 87.4 (Ar-C_q), 21.6 (Ar-CH_3). Spectroscopic data for this compound (^{1}H NMR, ^{13}C NMR, IR) is consistent with that shown in the literature.[158]

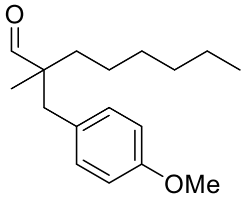
2,2-Dimethyl-3-(1-tosyl-1H-indol-5-yl)propanal (4j-mono)



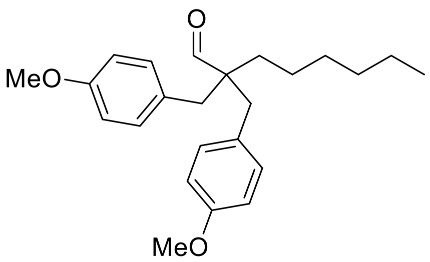
Prepared according to general procedure *J* using pivaldehyde (44 µL, 0.40 mmol) and 5-iodo-1-tosyl-1H-indole **S23** (294 mg, 1.04 mmol). Purification by flash column chromatography (15% diethyl ether/hexane) afforded monoarylated aldehyde **12a** as an amorphous off white solid (26 mg, 18%). R_f 0.41 (40% diethyl ether/hexane). IR (film)/cm^{-1} 2966, 1722 (C=O), 1459, 1370, 1173, 1129, 1092. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1 H, CHO), 7.87 (d, *J* = 8.6 Hz, 1 H, Ar-H), 7.77 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.54 (d, *J* = 3.6 Hz, 1 H, Ar-H), 7.24 (d, *J* = 8.3 Hz, 3 H, Ar-H), 7.04 (dd, *J* = 8.6, 1.6 Hz, 1 H, Ar-H), 6.59 (dt, *J* = 5.3, 2.7 Hz, 1 H, Ar-H), 2.84 (s, 2 H, CH_2), 2.35 (s, 3 H, Ar-CH_3), 1.05 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1 (CHO), 144.9 (Ar-C_q), 135.3 (Ar-C_q), 133.6 (Ar-C_q), 131.9 (Ar-C_q), 130.8 (Ar-C_q), 129.9 (2 × Ar-C), 126.9 (Ar-C), 126.8 (2 × Ar-C), 126.5 (Ar-C), 122.7 (Ar-C), 113.0 (Ar-C), 108.7 (Ar-C), 47.1 ($C_q(CH_3)_2$), 43.0 (CH_2), 21.6 (Ar-CH_3), 21.4 ($C(CH_3)_2$). HRMS (ESI) m/z Calcd. for $C_{20}H_{20}NO_3S$ $[M-H]^-$: 354.1164; Found: 354.1171.

2-(4-Methoxybenzyl)-2-methyloctanal (14-mono) and 2,2-bis(4-methoxybenzyl)octanal (14-di)

Prepared according to general procedure *J* using 2,2-dimethyloctanal **6** (63 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (2.5–5% diethyl ether/pentane) afforded monoarylated aldehyde **14-mono** as a colourless oil (33 mg, 31%) followed by diarylated aldehyde **14-di** as a pale yellow oil (33 mg, 22%).



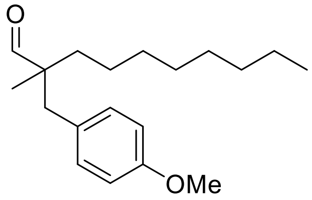
14-mono: R_f 0.34 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2929, 2856, 1725 (C=O), 1611, 1511, 1463, 1372, 1246, 1178. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H, CHO), 7.02–6.98 (m, 2 H, Ar-H), 6.83–6.79 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.82 (d, *J* = 13.8 Hz, 1 H, C(H)*H*), 2.66 (d, *J* = 13.8 Hz, 1 H, C(*H*)H), 1.61–1.54 (m, 1 H, CH_2C(H)*H*), 1.44–1.38 (m, 1 H, CH_2C(*H*)H), 1.32–1.17 (m, 8 H, 4 × CH_2), 0.99 (s, 3 H, CH_3), 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7 (C=O), 158.2 (Ar-C_q), 131.1 (2 × Ar-C), 128.9 (Ar-C_q), 113.5 (2 × Ar-C), 55.2 (OCH_3), 50.4 (C_q(CH_3)), 41.1 (CH_2), 35.6 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 18.2 (CH_3), 14.0 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{17}H_{27}O_2$ $[M+H]^+$: 263.2011; Found: 263.2005.



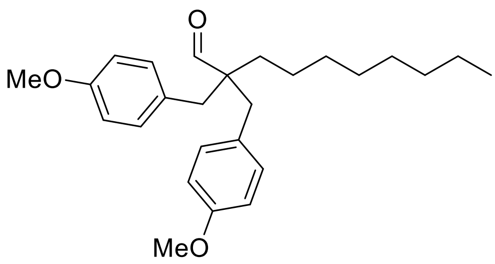
14-di: R_f 0.14 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2930, 2855, 1722 (C=O), 1611, 1510, 1463, 1245, 1177, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.03–6.99 (m, 4 H, Ar-H), 6.83–6.80 (m, 4 H, Ar-H), 3.80 (s, 6 H, 2 × OCH_3), 2.89 (d, *J* = 14.2 Hz, 2 H, 2 × C(H)*H*), 2.75 (d, *J* = 14.2 Hz, 2 H, 2 × C(*H*)H), 1.47–1.35 (m, 4 H, 2 × CH_2), 1.33–1.24 (m, 6 H, 3 × CH_2), 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (C=O), 158.2 (2 × Ar-C_q), 131.2 (4 × Ar-C), 128.7 (2 × Ar-C_q), 113.6 (4 × Ar-C), 55.2 (2 × OCH_3), 54.0 (C_q(CHO)), 38.8 (2 × CH_2), 31.7 (CH_2), 31.0 (CH_2), 29.8 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{24}H_{33}O_3$ $[M+H]^+$: 369.2430; Found: 369.2422.

2-(4-Methoxybenzyl)-2-methyldecanal (15-mono) and 2,2-bis(4-methoxybenzyl)decanal (15-di)

Prepared according to general procedure *J* using 2,2-dimethyldecanal **7** (74 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (2.5–5% diethyl ether/pentane) afforded monoarylated aldehyde **15-mono** as a colourless oil (35 mg, 30%) followed by diarylated aldehyde **15-di** as a pale yellow oil (38 mg, 24%).



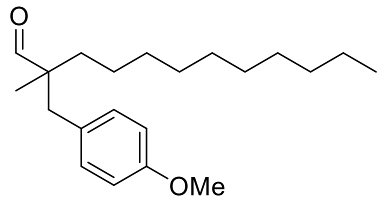
15-mono: R_f 0.38 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2925, 2853, 1723 (C=O), 1611, 1512, 1463, 1246, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H, CHO), 7.02–6.98 (m, 2 H, Ar-H), 6.83–6.79 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.82 (d, *J* = 13.8 Hz, 1 H, C(H)*H*), 2.66 (d, *J* = 13.8 Hz, 1 H, C(*H*)H), 1.56–1.53 (m, 1 H, CH_2C(H)*H*), 1.44–1.37 (m, 1 H CH_2C(*H*)H) 1.32–1.19 (m, 12 H, 6 × CH_2), 0.99 (s, 3 H, CH_3), 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7 (C=O), 158.2 (Ar-C_q), 131.1 (2 × Ar-C), 128.9 (Ar-C_q), 113.5 (2 × Ar-C), 55.2 (OCH_3), 50.4 (C_q(CH_3)), 41.1 (CH_2), 35.6 (CH_2), 31.8 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 18.2 (CH_3), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{19}H_{31}O_2$ [M+H]$^+$: 291.2324; Found: 291.2317.



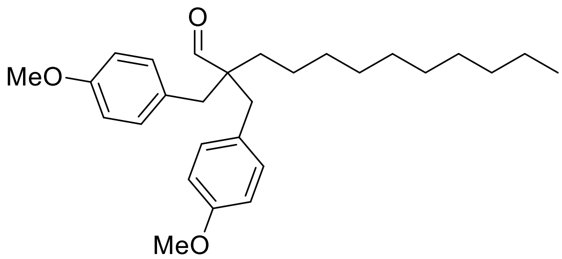
15-di: R_f 0.19 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2926, 2853, 1721 (C=O), 1611, 1510, 1246, 1177, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.02–7.00 (m, 4 H, Ar-H), 6.82–6.80 (m, 4 H, Ar-H), 3.80 (s, 6 H, 2 × OCH_3), 2.89 (d, *J* = 14.2 Hz, 2 H, 2 × C(H)*H*), 2.74 (d, *J* = 14.2 Hz, 2 H, 2 × C(*H*)H), 1.46–1.37 (m, 4 H, 2 × CH_2) 1.33–1.27 (m, 10 H, 5 × CH_2), 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (C=O), 158.2 (2 × Ar-C_q), 131.2 (4 × Ar-C), 128.7 (2 × Ar-C_q), 113.6 (4 × Ar-C), 55.2 (2 × OCH_3), 54.0 (C_q(CHO)), 38.8 (2 × CH_2), 31.8 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{26}H_{37}O_3$ [M+H]$^+$: 397.2743; Found: 397.2735.

2-(4-Methoxybenzyl)-2-methyldodecanal (16-mono) and 2,2-bis(4-methoxybenzyl)dodecanal (16-di)

Prepared according to general procedure *J* using 2,2-dimethyldodecanal **8** (85 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (2.5–5% diethyl ether/pentane) afforded monoarylated aldehyde **16-mono** as a colourless oil (43 mg, 34%) followed by diarylated aldehyde **16-di** as a pale yellow oil (35 mg, 21%).



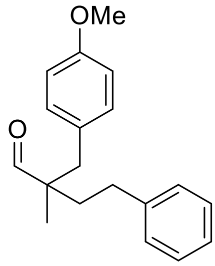
16-mono: R_f 0.35 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2924, 2853, 1725 (C=O), 1611, 1512, 1463, 1246, 1178, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H, CHO), 7.01–6.98 (m, 2 H, Ar-H), 6.83–6.79 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.82 (d, *J* = 13.8 Hz, 1 H, C(H)*H*), 2.66 (d, *J* = 13.8 Hz, 1 H, C(*H*)H), 1.60–1.53 (m, 1 H, CH_2C(H)*H*), 1.44–1.37 (m, 1 H, CH_2C(*H*)H), 1.33–1.19 (m, 16 H, 8 × CH_2), 0.99 (s, 3 H, CH_3), 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8 (C=O), 158.2 (Ar-C_q), 131.2 (2 × Ar-C), 128.9 (Ar-C_q), 113.6 (2 × Ar-C), 55.2 (OCH_3), 50.4 (C_q(CH_3)), 41.1 (CH_2), 35.6 (CH_2), 31.9 (CH_2), 30.2 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 18.2 (CH_3), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{21}H_{35}O_2$ $[M+H]^+$: 319.2637; Found: 319.2635.



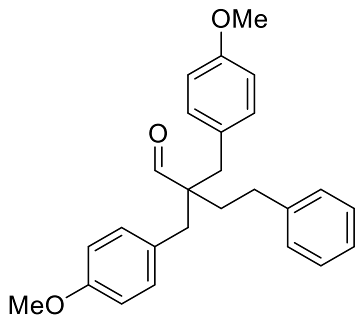
16-di: R_f 0.21 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2926, 2853, 1723 (C=O), 1611, 1512, 1248, 1178, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.02–6.99 (m, 4 H, Ar-H), 6.83–6.80 (m, 4 H, Ar-H), 3.79 (s, 6 H, 2 × OCH_3), 2.89 (d, *J* = 14.2 Hz, 2 H, 2 × C(H)*H*), 2.74 (d, *J* = 14.2 Hz, 2 H, 2 × C(*H*)H), 1.46–1.37 (m, 4 H, 2 × CH_2), 1.33–1.26 (m, 14 H, 7 × CH_2), 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (CHO), 158.2 (2 × Ar-C_q), 131.2 (4 × Ar-C), 128.7 (2 × Ar-C_q), 113.6 (4 × Ar-C), 55.2 (2 × OCH_3), 54.0 (C_q(CHO)), 38.8 (2 × CH_2), 31.9 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. For $C_{26}H_{41}O_3$ $[M+H]^+$: 425.3056; Found: 425.3053.

2-(4-Methoxybenzyl)-2-methyl-4-phenylbutanal (17-mono) and 2,2-bis(4-methoxybenzyl)-4-phenylbutanal (17-di)

Prepared according to general procedure *J* using 2,2-dimethyl-4-phenylbutanal **9** (70 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (5% diethyl ether/pentane) afforded monoarylated aldehyde **17-mono** as an amorphous white solid (21 mg, 19%) followed by diarylated aldehyde **17-di** as a yellow oil (20 mg, 13%).



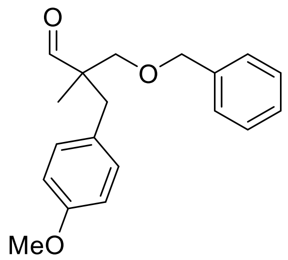
17-mono: R_f 0.11 (5% diethyl ether/pentane). IR (film)/cm^{-1} 2931, 1725 (C=O), 1609, 1510, 1457, 1298, 1246, 1176, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.31–7.28 (m, 2 H, Ph-H), 7.22–7.16 (m, 3 H, Ph-H), 7.05–7.02 (m, 2 H, Ar-H), 6.84–6.80 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.88 (d, *J* = 13.9 Hz, 1 H, C(*H*)H), 2.75 (d, *J* = 13.9 Hz, 1 H, C(H)*H*), 2.63–2.49 (m, 2 H, CH_2), 1.91 (ddd, *J* = 13.9, 12.2, 5.2 Hz, 1 H, C(*H*)H), 1.73 (ddd, *J* = 13.9, 12.2, 5.6 Hz, 1 H, C(H)*H*), 1.11 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2 (CHO), 158.3 (Ar-C_q), 141.8 (Ar-C_q), 131.2 (2 × Ar-C), 128.5 (Ph-C), 128.2 (Ph-C + Ph-C_q), 126.0 (Ph-C), 113.6 (2 × Ar-C), 55.2 (OCH_3), 50.4 (C_q(CH_3)), 41.2 (CH_2), 37.4 (CH_2), 30.7 (CH_2), 18.3 (CH_3). HRMS (ASAP(SOLID)) m/z Calcd. for $C_{19}H_{23}O_2$ $[M+H]^+$: 283.1698; Found: 283.1693.



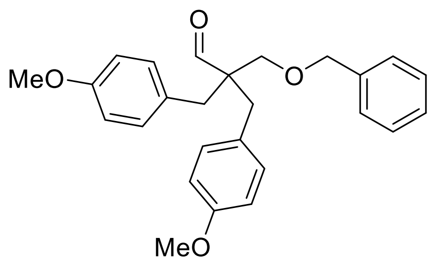
17-di: R_f 0.07 (5% diethyl ether/pentane). IR (film)/cm^{-1} 2934, 1720 (C=O), 1611, 1510, 1454, 1301, 1246, 1178, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1 H, CHO), 7.31–7.27 (m, 2 H, Ph-H), 7.22–7.19 (m, 1 H, Ph-H), 7.14–7.08 (m, 6 H, 4 × Ar-H + 2 × Ph-H), 6.87–6.84 (m, 4 H, Ar-H), 3.82 (s, 6 H, 2 × OCH_3), 3.04 (d, *J* = 14.3 Hz, 2 H, 2 × C(*H*)H), 2.87 (d, *J* = 14.3 Hz, 2 H, 2 × C(H)*H*), 2.74–2.70 (m, 2 H, CH_2), 1.82–1.78 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1 (CHO), 158.4 (2 × Ar-C_q), 141.8 (2 × Ar-C_q), 131.2 (4 × Ar-C), 128.44 (Ph-C), 128.36 (Ph-C_q), 128.2 (Ph-C), 126.0 (Ph-C), 113.8 (4 × Ar-C), 55.2 (2 × OCH_3), 54.0 (C_q(CHO)), 39.0 (2 × CH_2), 32.9 (CH_2), 30.1 (CH_2). HRMS (pNSI) m/z Calcd. for $C_{26}H_{32}O_3N_1$ $[M+NH_4]^+$: 406.2377; Found: 406.2375.

3-(Benzyloxy)-2-(4-methoxybenzyl)-2-methylpropanal (18-mono) and 3-(benzyloxy)-2,2-bis(4-methoxybenzyl)propanal (18-di)

Prepared according to general procedure *J* using 3-(benzyloxy)-2,2-dimethylpropanal (77 mg, 0.40 mmol) **10** and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (2.5–10% diethyl ether/pentane) afforded monoarylated aldehyde **18-mono** as a colourless oil (39 mg, 33%) followed by diarylated aldehyde **18-di** as a pale yellow oil (33 mg, 21%).



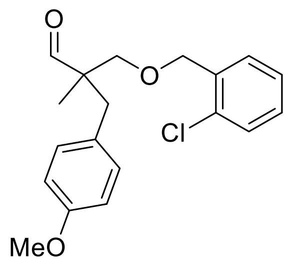
18-mono: R_f 0.15 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2903, 2858, 2721, 1722 (s, C=O), 1610, 1510, 1492, 1251, 1072 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1 H, CHO), 7.39–7.31 (m, 5 H, Ph-H), 7.03–6.99 (m, 2 H, Ar-H), 6.81–6.77 (m, 2 H, Ar-H), 4.51 (s, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.41 (s, 2 H, CH_2), 2.92 (d, *J* = 13.7 Hz, 1 H, C(*H*)H), 2.78 (d, *J* = 13.7 Hz, 1 H, C(H)*H*), 1.00 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (CHO), 158.3 (Ar-C_q), 138.0 (Ph-C_q), 131.3 (2 × Ar-C), 128.4 (Ph-C), 128.3 (Ar-C_q), 127.7 (Ph-C), 127.6 (Ph-C), 113.6 (2 × Ar-C), 73.3 (CH_2), 72.5 (CH_2), 55.2 (OCH_3), 51.2 (C_q(CH_3)), 37.3 (CH_2), 16.7 (CH_3). HRMS (pNSI) m/z Calcd. for $C_{19}H_{26}O_3N$ $[M+NH_4]^+$: 316.1907; Found: 316.1910.



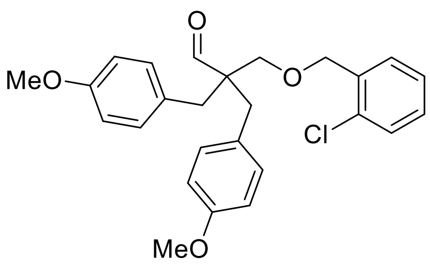
18-di: R_f 0.09 (10% diethyl ether/pentane). IR (film)/cm^{-1} 3003, 2939, 2858, 2721, 1733 (s, C=O), 1610, 1510, 1251, 1444, 1072 (s), 1035. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1 H, CHO), 7.42–7.33 (m, 5 H, Ph-H), 7.03–6.99 (m, 4 H, Ar-H), 6.80–6.76 (m, 4 H, Ar-H), 4.48 (s, 2 H, OCH_2), 3.79 (s, 6 H, 2 × OCH_3), 3.35 (s, 2 H, OCH_2), 3.01 (d, *J* = 13.9 Hz, 2 H, 2 × C(*H*)H), 2.88 (d, *J* = 13.9 Hz, 2 H, 2 × C(H)*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (CHO), 158.3 (2 × Ar-C_q), 138.0 (Ph-C_q), 131.2 (4 × Ar-C), 128.4 (Ph-C), 128.3 (2 × Ar-C_q), 127.8 (Ph-C), 127.7 (Ph-C), 113.7 (4 × Ar-C), 73.3 (OCH_2), 68.3 (OCH_2), 55.8 (C_q(CHO)), 55.2 (2 × OCH_3), 37.7 (2 × CH_2). HRMS (pNSI) m/z Calcd. for $C_{26}H_{32}O_4N$ $[M+NH_4]^+$: 422.2326; Found: 422.2322.

3-((2-Chlorobenzyl)oxy)-2-(4-methoxybenzyl)-2-methylpropanal (19-mono) and 2-(4-methoxybenzyl)-3-(4-methoxyphenyl)acrylaldehyde (19-di)

Prepared according to general procedure *J* using 3-((2-chlorobenzyl)oxy)-2,2-dimethylpropanal (92 mg, 0.40 mmol) **11** and 4-iodoanisole (244 mg, 1.04 mmol). Purification by flash column chromatography (20% diethyl ether/pentane) afforded monoarylated aldehyde **19-mono** as a colourless oil (40 mg, 30%) followed by diarylated aldehyde **19-di** as an off-white solid (43 mg, 24%).

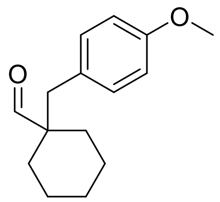


19-mono: R_f 0.32 (7.5% EtOAc/pentane). IR (film)/cm^{-1} 2932, 2836, 2704, 1725 (m, C=O), 1611, 1511, 1441, 1245, 1178, 1101, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H, CHO), 7.47 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar-H), 7.37 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar-H), 7.32–7.23 (m, 2 H, Ar-H), 7.06–7.02 (m, 2 H, Ar-H), 6.83–6.79 (m, 2 H, Ar-H), 4.60 (s, 2 H, OCH_2), 3.79 (s, 3 H, OCH_3), 3.53–3.48 (m, 2 H, OCH_2), 2.95 (d, *J* = 13.7 Hz, 1 H, C(*H*)H), 2.80 (d, *J* = 13.7 Hz, 1 H C(H)*H*), 1.04 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (CHO), 158.3 (Ar-C_q), 135.7 (Ar-C_q), 132.7 (Ar-C_q), 131.3 (2 × Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.2 (Ar-C_q), 126.8 (Ar-C), 113.6 (2 × Ar-C), 73.0 (OCH_2), 70.3 (OCH_2), 55.2 (OCH_3), 51.3 ($C_q(CH_3)$), 37.3 (CH_2), 16.7 (CH_3). HRMS (pNSI) m/z Calcd. for $C_{19}H_{25}O_3N_1Cl_1$ $[M+NH_4]^+$: 350.1517; Found: 350.1521.



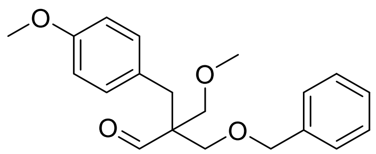
19-di: R_f 0.20 (7.5% EtOAc/pentane). mp = 69–73 °C. IR (film)/cm^{-1} 2836, 2900, 2836, 1714 (m, C=O), 1611, 1510, 1441, 1243 (s), 1177, 1094, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H, CHO), 7.53 (dd, *J* = 7.2, 1.8 Hz, 1 H, Ar-H), 7.41 (dd, *J* = 7.2, 1.8 Hz, 1 H, Ar-H), 7.34–7.26 (m, 2 H, Ar-H), 7.04–7.01 (m, 4 H, Ar-H), 6.80–6.77 (m, 4 H, Ar-H), 4.56 (s, 2 H, OCH_2), 3.78 (s, 6 H, 2 × OCH_3), 3.42 (s, 2 H, OCH_2), 3.03 (d, *J* = 13.9 Hz, 2 H, 2 × C(*H*)H), 2.90 (d, *J* = 13.9 Hz, 2 H, 2 × C(H)*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (CHO), 158.3 (2 × Ar-C_q), 135.8 (Ar-C_q), 132.9 (Ar-C_q), 131.2 (4 × Ar-C), 129.3 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.1 (Ar-C), 126.8 (2 × Ar-C_q), 113.7 (4 × Ar-C), 70.2 (OCH_2), 68.7 (OCH_2), 55.8 (C_q(CHO)), 55.2 (2 × OCH_3), 37.7 (2 × CH_2). HRMS (pNSI) m/z Calcd. for $C_{26}H_{31}O_4N_1Cl_1$ $[M+NH_4]^+$: 456.1936; Found: 456.1923.

1-(4-Methoxybenzyl)cyclohexane-1-carbaldehyde (20)



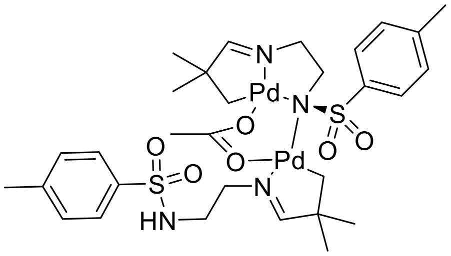
Prepared according to general procedure *J* using 1-methylcyclohexane-1-carbaldehyde (50.5 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.20 mmol). Purification by flash column chromatography (10% diethyl ether/pentane) afforded monoarylated aldehyde **20** as a colourless oil (35 mg, 38%). R_f 0.26 (10% diethyl ether/pentane). IR (film)/cm^{-1} 2929, 2854, 1718 (C=O), 1610, 1510 (s), 1451, 1300, 1243 (s), 1176, 1109, 1033. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1 H, CHO), 7.00–6.96 (m, 2 H, Ar-H), 6.82–6.78 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.67 (s, 2 H, CH_2), 1.92–1.86 (m, 2 H), 1.65–1.54 (m, 3 H), 1.34–1.24 (m, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (CHO), 158.3 (Ar-C_q), 131.1 (2 × Ar-C), 128.2 (Ar-C_q), 113.5 (2 × Ar-C), 55.2 (OCH_3), 50.8 (C_q(CHO)), 42.7 (CH_2), 31.1 (2 × CH_2), 25.6 (CH_2), 22.7 (2 × CH_2). HRMS (ESI) m/z Calcd. for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1536; Found: 233.1534.

3-(Benzyloxy)-2-(4-methoxybenzyl)-2-(methoxymethyl)propanal (21)



Prepared according to general procedure *J* using 3-(benzyloxy)-2-(methoxymethyl)-2-methylpropanal (89 mg, 0.40 mmol) and 4-iodoanisole (244 mg, 1.20 mmol). Purification by flash column chromatography (15% diethyl ether/pentane) afforded arylated aldehyde **21** as a colourless oil (34 mg, 40%). R_f 0.30 (15% diethyl ether/pentane). IR (film)/cm^{-1} 2836, 1727 (s, C=O), 1611, 1511, 1454, 1364, 1246, 1178, 1099, 1031. ^{1}H NMR (400 MHz, CDCl3) δ 9.71 (s, 1 H, CHO), 7.39–7.30 (m, 5 H, Ph-H), 7.05–7.01 (m, 2 H, Ar-H), 6.82–6.78 (m, 2 H, Ar-H), 4.51 (s, 2 H, OCH_2), 3.79 (s, 3 H, $ArOCH_3$), 3.53 (d, *J* = 2.7 Hz, 2 H, OCH_2), 3.44 (s, 2 H, OCH_2), 3.33 (s, 3 H, OCH_3), 2.92 (s, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (CHO), 158.3 (Ar-C_q), 138.0 (Ph-C_q), 131.2 (2 × Ar-C), 128.4 (Ph-C), 127.8 (Ar-C_q), 127.7 (Ph-C), 127.6 (Ph-C), 113.6 (2 × Ar-C), 73.4 (OCH_2), 71.2 (OCH_2), 68.7 (OCH_2), 59.1 (OCH_3), 55.9 (C_q(CHO)), 55.1 ($ArOCH_3$), 33.2 (CH_2). HRMS (pNSI) m/z Calcd. for $C_{20}H_{28}O_4N_1$ $[M+NH_4]^+$: 346.2013; Found: 346.2014.

Synthesis of palladacycle dimer (3a-Pd-dimer)



Palladium acetate (673 mg, 3.00 mmol) was added to a stirred solution of *N*-{2-[(*E*)-(2,2-dimethylpropylidene)amino]ethyl}-4-methylbenzene-1-sulfonamide **2a** (846 mg, 3.00 mmol) in CH_3CN (6 mL) and the reaction was stirred at 60 °C for 3 h. Toluene (25 mL) was added and the reaction was filtered through Celite and concentrated to afford the crude palladacycle **2a-Pd-dimer** (1.39 g, 56%). A sample was purified by recrystallisation in CH_2Cl_2/pentane at -20 °C to obtain analytical data. mp = decomposition occurs at 136 °C. IR (film)/cm^{-1} 3155, 2956, 2925, 1557, 1401, 1322, 1299, 1157, 1143, 1088. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.97 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.53 (s, 1 H, N=CH), 7.47 (s, 1 H, N=CH), 7.36 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.30 (d, *J* = 8.1 Hz, 2 H, Ar-H), 6.69 (t, *J* = 4.7 Hz, 1 H, NH), 3.95 (t, *J* = 11.8 Hz, 1 H, C(H)*H*), 3.65–3.56 (m, 2 H, CH_2), 3.50–3.46 (m, 1 H, C(*H*)H), 3.19–3.12 (m, 2 H, C(*H*)H + C(H)*H*), 2.70 (dd, *J* = 12.0, 3.8 Hz, 1 H, C(*H*)H), 2.44–2.41 (m, 7 H, C(*H*)H + 2 × Ar-CH_3), 2.36 (d, *J* = 8.8 Hz, 1 H, PdC(H)*H*), 2.26 (d, *J* = 8.5 Hz, 1 H, PdC(H)*H*), 2.09–2.07 (m, 4 H, PdC(*H*)H + CO_2CH_3), 1.65 (d, *J* = 8.5 Hz, 1 H, PdC(*H*)H), 1.16–1.07 (m, 12 H, 2 × $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0 (C=N), 183.7 (C=N), 181.2 (C=O), 143.1 (Ar-C_q), 142.1 (Ar-C_q), 137.2 (2 × Ar-C_q), 129.7 (2 × Ar-H), 129.4 (2 × Ar-H), 128.7 (2 × Ar-H), 127.4 (2 × Ar-H), 58.6 (CH_2), 57.3 (CH_2), 54.0 ($C_q(CH_3)_2$), 50.8 (CH_2), 50.1 ($C_q(CH_3)_2$), 44.4 (CH_2), 34.4 ($PdCH_2$), 33.8 ($PdCH_2$), 28.4 (CH_3), 26.3 (CH_3), 26.2 (CH_3), 24.5 (CH_3), 24.0 (CO_2CH_3), 21.5 (2 × Ar-CH_3). Data for crystal structure can be found in Appendix 2. CCDC: 1534094.

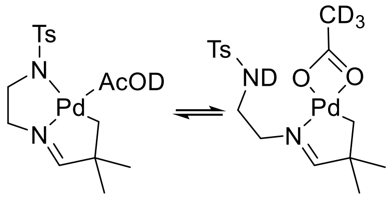
Arylation of palladacycle dimer (3a-Pd-dimer)

Palladacycle dimer **3a-Pd-dimer** (33.3 mg, 0.04 mmol), AgTFA (35.2 mg, 0.16 mmol), 4-iodoanisole (55.7 mg, 0.24 mmol) and AcOH (0.13 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 120 °C for 24 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Yields of the arylated aldehyde products were calculated by ^{1}H NMR using gem dimethyl (mono: 1.05 ppm), methyl (di: 0.97 ppm) and methylene (tri: 2.85 ppm) signals following in comparison to a known amount of 1,3,5-trimethoxybenzene as an internal standard.

Arylation of pivaldehyde using palladacycle dimer (3a-Pd-dimer) as the catalyst

Pivaldehyde (22 μL, 0.20 mmol), *N*-tosylethenediamine **1a** (21.4 mg, 0.10 mmol), 4-iodoanisole (122 mg, 0.52 mmol), **3a-Pd-dimer** (4.2 mg, 2.5 mol%), silver trifluoroacetate (88 mg, 0.40 mmol), DMSO (14.2 μL, 0.20 mmol), acetic acid (0.2 mL) and HFIP (0.2 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 3 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Yields of the arylated aldehyde products were calculated by ^{1}H NMR using *gem*-dimethyl (mono: 1.05 ppm), methyl (di: 0.97 ppm) and methylene (tri: 2.85 ppm) signals in comparison to a known amount of 1,3,5-trimethoxybenzene as an internal standard.

Formation of palladacycle monomer as a solution in AcOD-*d₄* (3a-Pd-monomer)



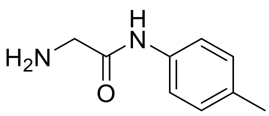
Prepared from dissolving dimer **3a-Pd-dimer** in AcOD-d_4. IR (film)/cm^{-1} 2962, 1563, 1402, 1267, 1157, 1090. ^{1}H NMR (400 MHz, AcOD-d_4) δ 7.80 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.66 (s, 1 H, N=CH), 7.38 (d, *J* = 8.1 Hz, 2 H, Ar-H), 3.38 (bs, 2 H, CH_2), 3.20 (bs, 1 H, CH_2), 2.43 (s, 3 H, Ar-CH_3), 2.33 (bs, 2 H, PdCH_2), 2.07 (s, 3 H, CO_2CH_3), 1.22 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, AcOD-d_4) δ 191.5 (C=N), 178.4 (Ar-C_q), 144.8 (Ar-C_q), 138.2 (2 × Ar-C), 130.8 (2 × Ar-C), 128.1 (CH_2), 60.6 ($C_q(CH_3)_2$), 51.3 (CH_2), 43.0 (PdCH_2), 26.2 ($C(CH_3)_2$), 21.6 (Ar-CH_3).

5.2.2 Compounds for Chapter 3.2: Secondary Aldehyde Arylation

*Synthesis of directing groups (**24–28**)*

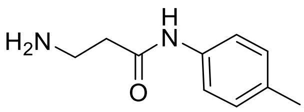
General Procedure K: Acid (1 equiv), amine (2 equiv), EDC·HCl (1.5 equiv), HOBt·H_2O (1.5 equiv and Et_3N (3 equiv) were combined in DMF (0.15 M) and the reaction was stirred at 25 °C overnight. The reaction mixture was diluted with CH_2Cl_2, washed with 1 M aqueous HCl, saturated aqueous sodium bicarbonate solution and brine. The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, Et_2O) afforded the Boc intermediate. HCl (10 equiv, 4 M solution in dioxane) was added and the reaction stirred until complete by TLC. 1 M aqueous NaOH was added and the free amine extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and solvent removed under reduced pressure to afford the title amines.

2-Amino-*N*-(*p*-tolyl)acetamide (24)



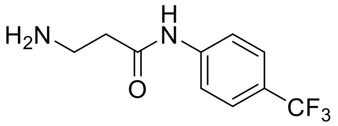
General procedure K was followed using (*tert*-Butoxycarbonyl)glycine (701 mg, 4.00 mmol) and *p*-toluidine (429 mg, 4.00 mmol) to afford amide **24** as an off white solid (470 mg, 72%). R_f 0.39 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 102–103 °C (lit = 105–107).[159] IR (film)/cm^{-1} 2918 (br), 1682, 1649 (C=O), 1611, 1593, 1544, 1510, 1309, 1257, 1196. ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (bs, 1 H, NH), 7.49 (d, J = 8.3 Hz, 2 H, Ar-H), 7.14 (d, J = 8.3 Hz, 2 H, Ar-H), 3.47 (s, 2 H, CH_2), 2.32 (s, 3 H, Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C=O), 135.1 (Ar-C_q), 133.7 (Ar-C_q), 129.5 (2 × Ar-C), 119.4 (2 × Ar-C), 45.1 (CH_2), 20.9 (Ar-CH_3). HRMS (ESI) m/z Calcd. for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1028; Found: 165.1032.

3-Amino-N-phenylpropanamide (26a)



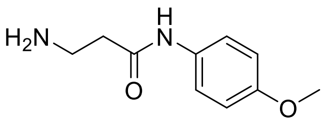
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (946 mg, 5 mmol) and p-toluidine (541 mg, 5 mmol), to afford amide **26a** as an off white amorphous solid (490 mg, 55%). R_f 0.06 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3345, 3290, 2922, 2882, 1660 (C=O), 159, 1539, 1507, 1401, 1298, 1255, 1046. ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1 H, NH), 7.43 (d, J = 8.3 Hz, 2H, Ar-H), 7.11 (d, J = 8.3 Hz, 2 H, Ar-H), 3.13–3.10 (m, 2 H, $NH_2C\mathit{H_2}$), 2.48–2.45 (m, 2 H, O=CC$\mathit{H_2}$), 2.31 (s, 3 H, Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O), 135.9 (Ar-C_q), 133.3 (Ar-C_q), 129.4 (2 × Ar-C), 119.8 (Ar-C), 119.7 (Ar-C), 38.8 (CH_2), 37.9 (CH_2), 20.8 (Ar-CH_3). HRMS (pNSI) m/z Calcd. for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1179; Found: 179.1178.

3-Amino-*N*-(4-(trifluoromethyl)phenyl)propanamide (26b)



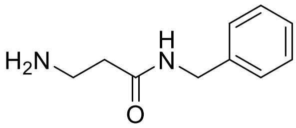
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (378 mg, 2.00 mmol) and 4-(trifluoromethyl)aniline (251 μL, 2.00 mmol) to afford amide **26b** as an off white solid (281 mg, 61%) which was further purified by recrystallisation in EtOAc (121 mg, 26%). R_f 0.12 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 118–120 °C. IR (film)/cm^{-1} 2879, 1666 (C=O), 1607, 1561, 1410, 1321, 1307, 1156. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1 H, NH), 7.68 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.56 (d, *J* = 8.6 Hz, 2 H, Ar-H), 3.16–3.13 (m, 2 H, NH_2CH_2), 2.51–2.48 (m, 2 H, O=CCH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C=O), 141.6 (Ar-C_q), 126.1 (q, $^3J_{C\text{-}F}$ = 4 Hz, 2 × Ar-C), 125.31 (q, $^2J_{C\text{-}F}$ = 33 Hz, Ar-C_q), 124.20 (q, $^1J_{C\text{-}F}$ = 271 Hz, CF_3), 119.3 (2 × Ar-C), 38.4 (CH_2), 37.7 (CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.99. HRMS (ESI) m/z Calcd. for $C_{10}H_{12}N_2OF_3$ $[M+H]^+$: 233.0902; Found: 233.0904.

3-Amino-*N*-(4-methoxyphenyl)propanamide (26c)



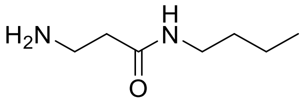
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (378 mg, 2.00 mmol) and 4-methoxyaniline (246 mg, 2.00 mmol) to afford amide **26c** as a pale purple solid (176 mg, 45%). R_f 0.09 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 141–152 °C. IR (film)/cm^{-1} 3300, 2835, 1656 (C=O), 1586, 1530, 1510, 1440, 1401, 1364, 1242, 1171, 1027. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H, NH), 7.48–7.44 (m, 2 H, Ar-H), 6.88–6.84 (m, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 3.13–3.10 (m, 2 H, NH_2CH_2), 2.48–2.45 (m, 2 H, O=CCH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C=O), 156.0 (Ar-C_q), 131.7 (Ar-C_q), 121.5 (2 × Ar-C), 114.1 (2 × Ar-C), 55.5 (OCH_3), 38.7 (CH_2), 38.0 (CH_2). HRMS (ESI) m/z Calcd. for $C_{10}H_{15}N_2O_2$ $[M+H]^+$: 195.1134; Found: 195.1139.

3-Amino-*N*-benzylpropanamide (26d)



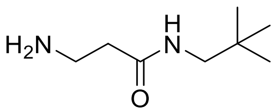
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (946 mg, 5.00 mmol) and benzylamine (546 µL, 5.00 mmol) to afford amide **26d** as an off white solid (403 mg, 45%). R_f 0.09 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 133–139 °C. IR (film)/cm^{-1} 3348, 3302, 2918, 1648 (C=O), 1560, 1439, 1360, 1240, 1040, 1019. ^{1}H NMR (400 MHz, DMSO) δ 8.42 (s, 1 H, NH), 7.33–7.29 (m, 2 H, Ph-H), 7.25–7.21 (m, 3 H, Ph-H), 4.26 (d, *J* = 5.9 Hz, 2 H, NHC*H*$_2$Ph), 2.78 (t, *J* = 6.6 Hz, 2 H, CH_2), 2.24 (t, *J* = 6.6 Hz, 2 H, CH_2). ^{13}C NMR (101 MHz, DMSO) δ 171.3 (C=O), 139.7 (Ph-C_q), 128.3 (Ph-C), 127.2 (Ph-C), 126.7 (Ph-C), 41.9 (NH*C*H$_2$Ph), 38.8 (CH_2), 38.2 (CH_2). HRMS (ESI) m/z Calcd. for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1184; Found: 179.1185.

3-Amino-*N*-butylpropanamide (26e)



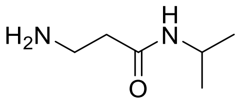
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (460 mg, 2.50 mmol) and butan-1-amine (247 µL, 2.50 mmol) to afford amide **26e** as an off white solid (125 mg, 35%). R_f 0.08 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 133–138 °C. IR (film)/cm^{-1} 3341, 3296, 2927, 1872, 2860, 1644 (C=O), 1541, 1440, 1397, 1365, 1145. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (bs, 1 H, NH), 3.26 (td, *J* = 7.1, 4.5 Hz, 2 H, CH_2), 3.00 (t, *J* = 5.8 Hz, 2 H, CH_2), 2.30 (t, *J* = 5.8 Hz, 2 H, CH_2), 1.52–1.45 (m, 2 H, CH_2), 1.40–1.31 (m, 2 H, CH_2), 0.94–0.91 (m, 3 H, CH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C=O), 39.0 (CH_2), 38.7 (CH_2), 38.3 (CH_2), 31.7 (CH_2), 20.1 (CH_2), 13.7 (CH_3). HRMS (ESI) m/z Calcd. for $C_7H_{17}N_2O$ $[M+H]^+$: 145.1341; Found: 145.1335.

3-Amino-*N*-neopentylpropanamide (26f)



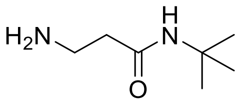
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and 2,2-dimethylpropan-1-amine (420 µL, 3.57 mmol) to afford amine **26f** as a pale yellow amorphous solid (201 mg, 42%). R_f 0.25 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3318, 2953, 2868, 1645, 1547, 1463, 1365, 1303, 1208. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (bs, 1 H, NH), 3.08 (d, *J* = 6.1 Hz, 2 H, NHC*H*$_2$), 3.03 (t, *J* = 5.8 Hz, 2 H, CH_2), 2.34 (t, *J* = 5.8 Hz, 2 H, CH_2), 0.92 (s, 9 H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C=O), 50.4 (CH_2), 38.5 (CH_2), 38.4 (CH_2), 31.7 ($C_q(CH_3)_3$), 27.3 ($C(CH_3)_3$). HRMS (ESI) m/z Calcd. for $C_8H_{19}N_2O$ $[M+H]^+$: 159.1497; Found: 159.1491.

3-Amino-*N*-isopropylpropanamide (26g)



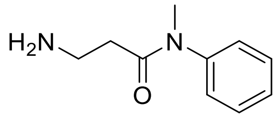
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and propan-2-amine (515 µL, 6.00 mmol) to afford amine **26g** as a pale yellow amorphous solid (120 mg, 31%). R_f 0.25 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3303, 3025, 2970, 2933, 1637 (C=O), 1568, 1531, 1450, 1359, 1174, 1128. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (b s, 1 H, NH), 4.08 (hept, *J* = 6.7 Hz, 1 H, C*H*(CH_3)$_2$), 3.01 (t, *J* = 5.9 Hz, 2 H, CH_2), 2.29 (t, *J* = 5.9 Hz, 1 H, CH_2), 1.16 (d, *J* = 6.7 Hz, 6 H, CH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C=O), 41.1 (*C*H(CH_3)$_2$), 38.8 (CH_2), 38.3 (CH_2), 22.8 (CH(*C*H$_3$)$_2$). HRMS (ESI) m/z Calcd. for $C_6H_{15}N_2O$ $[M+H]^+$: 131.1184; Found: 131.1180.

3-Amino-*N*-(*tert*-butyl)propanamide (26h)



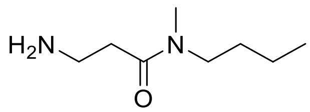
Triethylamine (2.10 mL, 15.0 mmol) was added to a stirred solution of 3-((*tert*-butoxycarbonyl)amino)propanoic acid (1.04 g, 5.50 mmol), 2-chloro-1-methylpyridinium iodide (3.65 g, 15.0 mmol), 2-methylpropan-2-amine (525 µL, 5.00 mmol) in CH_2Cl_2 (50 mL) and the reaction was stirred at 25 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium bicarbonate solution, dried concentrated and purified by flash column chromatography (silca, 80% diethyl ether/pentane) to afford the Boc intermediate. HCl was added (3.75 mL, 15 mmol, 4 M in dioxane) and the reaction stirred at rt until complete by TLC. 1 M aqueous NaOH was added and the free amine extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and solvent removed under reduced pressure to afford amine **26h** as an off-white wax (535 mg, 74%). R_f 0.14 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3298, 3074, 2967, 1643 (C=O), 1548, 1454, 1391, 1362, 1224, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (bs, 1 H, NH), 2.99 (t, *J* = 5.6 Hz, 2 H, CH_2), 2.26–2.23 (m, 2 H, CH_2), 1.36 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C=O), 51.0 (*C*(CH_3)$_3$), 39.2 (CH_2), 38.2 (CH_2), 28.8 (C(*C*H$_3$)$_3$). HRMS (ESI) m/z Calcd. for $C_7H_{17}N_2O$ $[M+H]^+$: 145.1341; Found: 145.1340.

3-Amino-*N*-methyl-*N*-phenylpropanamide (26i)



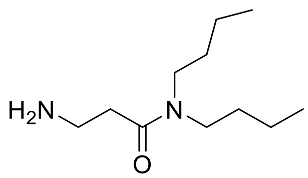
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and *N*-methylaniline (650 µL, 6.00 mmol) to afford amine **26i** as a brown oil (229 mg, 43%). R_f 0.30 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3369, 2937, 1644 (C=O), 1593, 1495, 1274, 1117. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2 H, Ph-H), 7.36–7.32 (m, 1 H, Ph-H), 7.19–7.18 (m, 2 H, Ph-H), 3.27 (s, 3 H, CH_3), 2.90 (t, *J* = 6.1 Hz, 2 H, CH_2), 2.22 (t, *J* = 6.1 Hz, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (C=O), 143.8 (Ph-C_q), 129.8 (Ph-C), 127.8 (Ph-C), 127.4 (Ph-C), 38.2 (CH_2), 37.5 (CH_2), 37.1 (CH_3). HRMS (ESI) m/z Calcd. for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1184; Found: 179.1177.

3-Amino-*N*-butyl-*N*-methylpropanamide (26j)



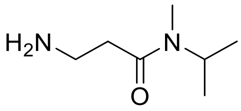
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and *N*-methylbutan-1-amine (710 µL, 6.00 mmol) to afford amine **26j** as a yellow oil (301 mg, 63%). R_f 0.23 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 2957, 2931, 2872, 1631 (s, C=O), 1459, 1402, 1296, 1130. HT (100 °C) ^{1}H NMR (400 MHz, DMSO) δ 3.28 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.88 (bs, 3 H, NCH_3), 2.79 (t, *J* = 6.5 Hz, 2 H, CH_2), 2.37 (t, *J* = 6.5 Hz, 2 H, CH_2), 1.52–1.45 (m, 2 H, CH_2), 1.34–1.25 (m, 2 H, CH_2), 0.92 (t, *J* = 7.3 Hz, 3 H, CH_3). HT (100 °C) ^{13}C NMR (101 MHz, DMSO) δ 170.6 (C=O), 48.2 (CH_2), 46.0 (CH_2), 37.6 (CH_2), 36.1 (CH_2), 29.0 (NCH_3), 18.9 (CH_2), 12.9 (CH_3). HRMS (ESI) m/z Calcd. for $C_8H_{19}N_2O$ $[M+H]^+$: 159.1497; Found: 159.1489.

3-Amino-*N,N*-dibutylpropanamide (26k)



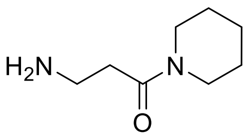
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and dibutylamine (1.02 mL, 6.00 mmol) to afford amine **26k** as a yellow oil (461 mg, 51%). R_f 0.15 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 2957, 2930, 2872, 1632 (C=O), 1456, 1426, 1375, 1214, 1131. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33–3.29 (m, 2 H, CH_2), 3.23–3.19 (m, 2 H, CH_2), 3.00 (t, *J* = 6.0 Hz, 2 H, CH_2), 2.46 (t, *J* = 6.0 Hz, 1 H, CH_2), 1.58–1.46 (m, 4 H, 2 × CH_2), 1.35–1.28 (m, 4 H, 2 × CH_2), 0.97–0.90 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C=O), 47.6 (CH_2), 45.6 (CH_2), 38.2 (CH_2), 36.1 (CH_2), 31.1 (CH_2), 29.9 (CH_2), 20.3 (CH_2), 20.1 (CH_2), 13.8 (CH_3), 13.8 (CH_3). HRMS (ESI) m/z Calcd. for $C_{11}H_{25}N_2O$ $[M+H]^+$: 201.1967; Found: 201.1966.

3-Amino-*N*-isopropyl-*N*-methylpropanamide (26l)



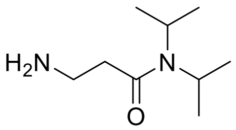
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and *N*-methylpropan-2-amine (625 µL, 6.00 mmol) to afford amine **26l** as a yellow oil (127 mg, 29%). R_f 0.25 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3365, 2971, 1620 (C=O), 1458, 1407, 1115. HT (100 °C) ^{1}H NMR (400 MHz, DMSO) δ 4.46 (bs, 1 H, C*H*(CH_3)$_2$), 2.79 (t, *J* = 6.5 Hz, 2 H, CH_2), 2.74 (bs, 3 H, NCH_3), 2.37 (t, *J* = 6.5 Hz, 2 H, CH_2), 1.09 (d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$). HT (100 °C) ^{13}C NMR (101 MHz, DMSO) δ 170.2 (C=O), 44.6 (*C*H(CH_3)$_2$), 37.7 (CH_2), 36.7 (CH_2), 26.9 (NCH_3), 19.0 (CH(*C*H$_3$)$_2$). HRMS (ESI) m/z Calcd. for $C_7H_{17}N_2O$ $[M+H]^+$: 145.1341; Found: 145.1337.

3-Amino-1-(piperidin-1-yl)propan-1-one (26m)



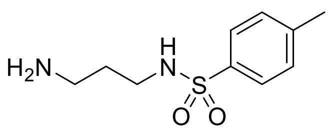
General procedure K was followed using 3-((*tert*-butoxycarbonyl)amino)propanoic acid (553 mg, 3.00 mmol) and piperidine (593 µL, 6.00 mmol) to afford amine **26m** as a yellow oil (343 mg, 73%). R_f 0.15 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3367, 2932, 2855, 1623 (C=O), 1440, 1251, 1226, 1136, 1122. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57–3.54 (m, 2 H, CH_2), 3.40–3.38 (m, 2 H, CH_2), 3.00 (t, *J* = 6.0 Hz, 1 H, CH_2), 2.46 (t, *J* = 6.0 Hz, 1 H, CH_2), 1.66–1.51 (m, 8 H, 3 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C=O), 46.4 (CH_2), 42.5 (CH_2), 38.1 (CH_2), 36.3 (CH_2), 26.4 (CH_2), 25.5 (CH_2), 24.5 (CH_2). HRMS (ESI) m/z Calcd. for $C_8H_{17}N_2O$ $[M+H]^+$: 157.1341; Found: 157.1339.

3-Amino-*N,N*-diisopropylpropanamide (26n)



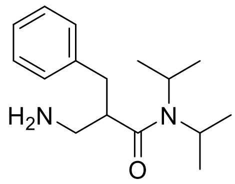
Triethylamine (4.20 mL, 30.0 mmol) was added to a stirred solution of 3-((*tert*-butoxycarbonyl)amino)propanoic acid (2.10 g, 11.0 mmol), 2-chloro-1-methylpyridinium iodide (7.70 g, 30.0 mmol), diisopropylamine (1.40 mL, 10.0 mmol) in CH_2Cl_2 (100 mL) and the reaction was stirred at 25 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium bicarbonate solution, dried concentrated and purified by flash column chromatography (silca, 80% diethyl ether/pentane) to afford the Boc intermediate. HCl was added (7.50 mL, 30 mmol, 4 M in dioxane) and the reaction stirred at rt untill complete by TLC. 1 M aqueous NaOH was added and the free amine extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and solvent removed under reduced pressure to afford amine **26n** as a yellow oil (1.25 g, 81%). R_f 0.22 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3368, 2967, 2932, 1618 (C=O), 1444, 1370, 1300, 1134, 1043. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (dt, *J* = 13.5, 6.7 Hz, 1 H, C*H*(CH_3)$_2$), 3.48 (bs, 1 H, C*H*(CH_3)$_2$), 2.99 (t, *J* = 6.0 Hz, 2 H, CH_2), 2.45 (t, *J* = 6.0 Hz, 2 H, CH_2), 1.39 (d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$), 1.20 (d, *J* = 6.7 Hz, 6 H, CH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C=O), 48.1 (*C*H(CH_3)$_2$), 45.6 (*C*H(CH_3)$_2$), 38.0 (CH_2), 37.6 (CH_2), 20.8 (CH(*C*H$_3$)$_2$), 20.7 (CH(*C*H$_3$)$_2$). HRMS (ESI) m/z Calcd. for $C_9H_{21}N_2O$ $[M+H]^+$: 173.1654; Found: 173.1647.

***N*-(3-Aminopropyl)-4-methylbenzenesulfonamide (27)**



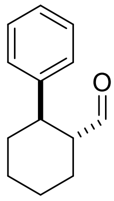
Tosyl chloride (2.85 g, 15 mmol) was added portionwise over a period of 1 h to a stirred solution of propylenediamine (12.5 mL, 150 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 h then warmed to 25 °C and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 and extracted with 1 M aqueous HCl. The combined aqueous extracts were basified to pH 10 with ground NaOH and the product extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford sulfonamide **27** as a white solid (1.73 g, 51%). R_f 0.06 (20% (1% NH_3 in MeOH)/CH_2Cl_2). mp = 115–119 °C (lit = 112–113 °C)[160]. IR (film)/cm^{-1} 2176 (br, N-H), 1653, 1503, 1414, 1390, 1327, 1007. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.31 (d, *J* = 8.1 Hz, 2 H, Ar-H), 3.09–3.06 (m, 2 H, CH_2), 2.81–2.78 (m, 2 H, CH_2), 2.43 (s, 3 H, Ar-CH_3) 1.62–1.56 (m, 2 H. CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (Ar-C_q), 137.1 (Ar-C_q), 129.6 (2 × Ar-C), 127.1 (2 × Ar-C), 43.0 (CH_2), 40.9 (CH_2), 30.8 (CH_2), 21.5 (Ar-CH_3). Spectroscopic data for this compound is consistent with that shown in the literature.[161]

3-Amino-2-benzyl-*N*,*N*-diisopropylpropanamide (30)



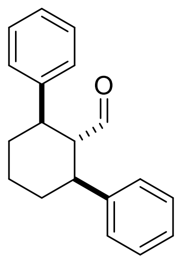
n-Butyllithium (2.12 mL, 4.80 mmol, 2.26 M in hexanes) was added dropwise to a stirred solution of diisopropylamine (673 µL, 4.80 mmol) in THF (6.0 mL) at -78 °C and the reaction was warmed to 0 °C and stirred for 30 minutes. The resulting LDA solution was cooled to -78 °C and *tert*-butyl (3-(diisopropylamino)-3-oxopropyl)carbamate **(2n-Boc)** (545 mg, 2.00 mmol) in THF (1.5 mL) was added dropwise and the reaction was stirred for 1 h. Benzyl bromide (952 µL, 8.00 mmol) was added dropwise and the reaction was heated to 0 °C and stirred for 2 h. The reaction was quenched by addition of saturated aqueous ammonium chloride solution and the product extracted with EtOAc, dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 20–40% Et_2O:Pentane) afforded over (also *N*-) benzylated intermediate (708 mg, 1.56 mmol, 78%) to which HCl was added (3.90 mL, 15.6 mmol, 4 M solution in dioxane) and the reaction was stirred until complete by TLC. 1 M aqueous NaOH was added and the free amine extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and solvent removed under reduced pressure to afford the un-boc-protected *N*-benzylated intermediate (524 mg, 95%). *N*-Debenzylation was achieved from hydrogenation with Pd/C (52 mg, 10 wt%) and a H_2 balloon in MeOH (3 mL) for 24 h followed by filtration through Celite and evaporation of the solvent under reduced pressure, affording benzyl amide analogue **30** (380 mg, 97%, 72% over 3 steps). Rf = 0.67 (20% (1% NH_3 in MeOH)/CH_2Cl_2). IR (film)/cm^{-1} 3485, 3370, 2969, 2932, 1594 (C=O), 1453, 1359, 1333, 1314, 1206, 1137, 1060, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2 H, Ph-H), 7.21–7.17 (m, 3 H, Ph-H), 3.89 (m, 1 H, C*H*(CH_3)$_2$), 3.42–3.21 (m, 1 H, C*H*(CH_3)$_2$), 3.14–3.01 (m, 2 H, CH + C(H)*H*), 2.92 (dd, *J* = 13.0, 8.9 Hz, 1 H, C(*H*)H), 2.80 (dd, *J* = 11.8, 4.0 Hz, 1 H, C(H)*H*), 2.72 (dd, *J* = 13.0, 5.2 Hz, 1 H, C(*H*)H), 1.39 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.32 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.10 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.67 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C=O), 139.4 (Ph-C_q), 129.2 (Ph-C), 128.4 (Ph-C), 126.3 (Ph-C), 48.6 (*C*H(CH_3)$_2$), 47.3 (*C*H(CH_3)$_2$), 46.0 (CH), 45.0 (CH_2), 37.3 (PhCH_2), 21.3 (CH_3), 20.9 (CH_3), 20.5 (CH_3), 20.2 (CH_3). HRMS (EI^+) m/z Calcd. for $C_{16}H_{26}N_2O$ $[M]^+$: 262.2045; Found: 262.2049.

***trans*-2-Phenylcyclohexane-1-carbaldehyde (23-mono)**



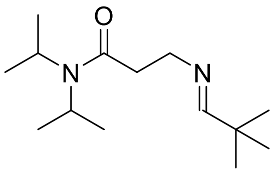
Cyclohexanecarboxaldehyde (106 µL, 0.80 mmol), 3-amino-*N*-(*tert*-butyl)propanamide (14.4 mg, 0.10 mmol), iodobenzene (44 µL, 0.40 mmol), palladium chloride (7.1 mg, 10 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), xylenes (0.2 mL), acetic acid (1.34 mL) and HFIP (4.0 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 80 °C for 72 h. The reaction was allowed to cool to room temperature, water was added and the product was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, 0.5-1% acetone/pentane) afforded arylated aldehyde **23-mono** as a colourless oil (3 mg, 4%). Rf = 0.36 (2.5% acetone/pentane). IR (film)/cm^{-1} 2926, 2855, 1722 (s, C=O), 1409, 1446. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 3.0 Hz, 1 H, CHO), 7.33–7.27 (m, 2 H, Ph-H), 7.26–7.17 (m, 3 H, Ph-H), 2.75 (td, *J* = 11.6, 3.6 Hz, 1 H, PhCH), 2.65–2.56 (m, 1 H, CHOC*H*), 2.07–1.88 (m, 4 H, 2 × CH_2), 1.69 – 1.38 (m, 4 H, 2 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7 (CHO), 144.1 (Ph-C_q), 128.7 (Ph-C), 127.4 (Ph-C), 126.6 (Ph-C), 55.3 (*C*HCHO), 45.2 (PhCH), 34.9 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 24.9 (CH_2). Spectroscopic data for this compound is consistent with that shown in the literature.[84]

***trans*-2,6-Diphenylcyclohexane-1-carbaldehyde (23-di)**



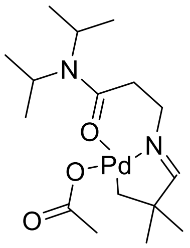
Cyclohexanecarboxaldehyde (53 µL, 0.40 mmol), 3-amino-*N*-(*tert*-butyl)propanamide (14.4 mg, 0.10 mmol), iodobenzene (135 µL, 1.20 mmol), palladium chloride (7.1 mg, 10 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), KF (35 mg, 0.60 mmol), xylenes (0.2 mL), acetic acid (1.34 mL) and HFIP (4.0 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 80 °C for 72 h. The reaction was allowed to cool to room temperature, water was added and the product was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, 20% CH_2Cl_2/pentane then 2% acetone/pentane) afforded arylated aldehyde **23-di** as an off-white solid (6 mg, 6%). Rf = 0.25 (2.5% acetone/pentane). IR (film)/cm^{-1} 2922, 2851, 1714 (C=O), 1490, 1453, 1028. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 3.6 Hz, 1 H, CHO), 7.33–7.27 (m, 4 H, Ph-H), 7.26–7.17 (m, 6 H, Ph-H), 3.09–3.00 (m, 1 H, CHOC*H*), 2.94 (td, *J* = 10.5, 3.8 Hz, 2 H, PhCH), 2.06–1.95 (m, 2 H, CH_2), 1.72–1.62 (m, 4 H, 2 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3 (CHO), 143.3 (Ph-C_q), 128.7 (Ph-C), 127.4 (Ph-C), 126.8 (Ph-C), 60.7 (*C*HCHO), 45.8 (2 × PhCH), 34.4 (2 × CH_2), 26.3 (CH_2). HRMS (pAPCI) m/z Calcd. for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587; Found: 265.1589.

(*E*)-3-((2,2-Dimethylpropylidene)amino)-*N,N*-diisopropylpropanamide (31)



General procedure C was followed using 3-amino-*N,N*-diisopropylpropanamide **27n** (1.00 g, 5.80 mmol) to afford imine **31** as an off-white gum (1.34 g, 96%) as a mixture of major and minor stereoisomers (15.5:1). NMR data quoted for the major isomer only. IR (film)/cm^{-1} 2963, 2870, 1636 (C=O), 1442, 1367, 1216, 1133, 1043. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 1.2 Hz, 1 H, N=CH), 4.09–3.98 (m, 1 H, C*H*(CH_3)$_2$), 3.67 (td, *J* = 7.2, 1.2 Hz, 2 H, C=NCH_2), 3.59–3.44 (m, 1 H, C*H*(CH_3)$_2$), 2.59 (t, *J* = 7.2 Hz, 2 H, CH_2), 1.36 (d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$), 1.20 (d, *J* = 6.7 Hz, 6 H, CH(C*H*$_3$)$_2$), 1.05 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (CH=N), 170.1 (C=O), 57.3 (2 × *C*H(CH_3)$_2$), 45.6 (CH=N*C*H$_2$), 36.0 (C_q(CH_3)$_3$), 35.9 (O=C*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 21.1 (CH(*C*H$_3$)$_2$), 20.7 (CH(*C*H$_3$)$_2$).

31-Pd-monomer

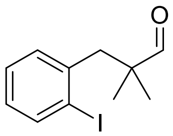


Palladium acetate (700 mg, 3.12 mmol) was added to a stirred solution of *(E)*-3-((2,2-dimethylpropylidene)amino)-*N,N*-diisopropylpropanamide (**31**) (750 mg, 3.12 mmol) in CH_3CN (10.4 mL) and the reaction was stirred at 60 °C for 3 h. Toluene (25 mL) was added and the reaction was filtered through Celite and concentrated to afford the crude palladacycle **31-Pd-monomer** (1.24 g, 98%). IR (film)/cm^{-1} 2963, 2933, 1628 (C=O), 1580 (s), 1442, 1401, 1330, 1211, 1043. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1 H, N=CH), 4.15–4.05 (m, 1 H, C*H*(CH_3)$_2$), 3.58–3.46 (m, 3 H, C=NCH_2 + C*H*(CH_3)$_2$), 2.83–2.63 (m, 2 H, O=CCH_2), 2.39–2.14 (m, 2 H, Pd-CH_2), 1.87 (s, 3 H, O=CCH_3), 1.39–1.16 (m, 18 H, 2 × CH(C*H*$_3$)$_2$ + C(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3 (N=CH), 179.8 (C=O, acetate), 169.1 (C=O), 56.5 (*C*H(CH_3)$_2$), 49.9 (C_q(CH_3)$_2$), 48.2 (*C*H(CH_3)$_2$), 45.7 (C=N*C*H$_2$), 34.1 (O=C*C*H$_2$), 32.9 (PdCH_2), 24.1 (O=C*C*H$_3$), 21.1 (C(*C*H$_3$)$_2$), 20.6 (2 × CH(*C*H$_3$)$_2$). HRMS (pNSI) m/z Calcd. for $C_{14}H_{27}N_2O^{102}Pd$ [M-OAc]$^+$: 341.1174; Found: 341.1182.

5.2.3 Compounds for Chapter 3.4: Intramolecular Annulation for Indane Synthesis

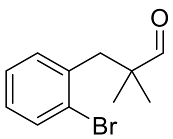
General Procedure L: Benzyl bromide (1.1 equiv) and aldehyde (1.0 equiv) were dissolved in the minimum amount of benzene and the resulting solution was added dropwise to a stirred suspension of ground sodium hydroxide pellets (1.0 equiv) and tetrabutylammonium iodide (10 mol%) in benzene (650 µL) at 25 °C under an argon atmosphere and the reaction was heated to 60 °C for 20 h. The reaction mixture was diluted with water and the crude product extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (2.5–5% Et_2O/pentane) afforded the title aldehydes.

3-(2-Iodophenyl)-2,2-dimethylpropanal (32)



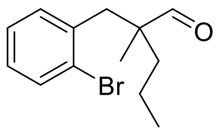
General procedure L was followed using 1-(Bromomethyl)-2-iodobenzene (1.63 g, 5.5 mmol) and isobutyraldehyde (456 µL, 5.0 mmol) to afford aldehyde **32** as a colorless oil (868 mg, 55%). R_f 0.25 (5% Et_2O/pentane). IR (film)/cm^{-1} 2969, 2929, 1723 (C=O), 1463, 1433, 1364, 1008. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H, CHO), 7.85 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar-H), 7.26 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-H), 7.15 (dd, *J* = 7.7, 1.7 Hz, 1 H, Ar-H), 6.93–6.88 (m, 1 H, Ar-H), 3.08 (s, 2 H, CH_2), 1.15 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 140.4 (Ar-C_q), 140.0 (Ar-C), 130.7 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 102.7 (Ar-C_q) 48.0 ($C_q(CH_3)_2$), 46.2 (CH_2), 21.6 ($C(CH_3)_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[162]

3-(2-Bromophenyl)-2,2-dimethylpropanal (33)



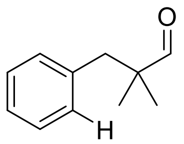
General procedure L was followed using 1-(bromomethyl)-2-bromobenzene (2.75 g, 11 mmol) and isobutyraldehyde (913 µL, 10 mmol) to afford aldehyde **33** as a colorless oil (1.26 g, 47%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2968, 2930, 2698, 1722 (C=O), 1467, 1438, 1027. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H, CHO), 7.56 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-H), 7.23 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-H), 7.16 (dd, *J* = 7.7, 1.8 Hz, 1 H, Ar-H), 7.11–7.07 (m, 1 H, Ar-H), 3.05 (s, 2 H, CH_2), 1.13 (s, 6 H, $C(CH_3)$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (CHO), 136.9 (Ar-C_q), 133.2 (Ar-C), 132.0 (Ar-C), 128.3 (Ar-C), 127.2 (Ar-C), 125.7 (Ar-C_q), 47.7 ($C_q(CH_3)_2$), 41.7 (CH_2), 21.5 ($C(CH_3)_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[163]

2-(2-Bromobenzyl)-2-methylpentanal (34)



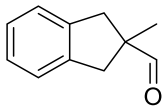
General procedure L was followed using 1-(Bromomethyl)-2-bromobenzene (823 mg, 3.30 mmol) and 2-methylpentanal (372 µL, 3.00 mmol) to afford aldehyde **34** as a colorless oil (273 mg, 36%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 2959, 2932, 2872, 2700, 1723 (C=O), 1467, 1438, 1022. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 7.55 (dd, *J* = 7.9, 1.3 Hz, 1 H, Ar-H), 7.22 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-H), 7.13 (dd, *J* = 7.5, 1.8 Hz, 1 H, Ar-H), 7.07 (ddd, *J* = 7.9, 7.5, 1.8 Hz, 1 H, Ar-H), 3.13 (d, *J* = 14.0 Hz, 1 H, C(*H*)H), 2.99 (d, *J* = 14.0 Hz, 1 H, C(H)*H*), 1.68 (ddd, *J* = 13.8, 12.2, 4.7 Hz, 1 H, C(*H*)H), 1.50 (ddd, *J* = 13.8, 12.4, 4.7 Hz, 1 H, C(H)*H*), 1.42–1.31 (m, 1 H, C(*H*)H), 1.29–1.18 (m, 1 H, C(H)*H*), 1.05 (s, 3 H, CH_3), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8 (CHO), 137.0 (Ar-C_q), 133.2 (Ar-C), 132.0 (Ar-C), 128.2 (Ar-C), 127.2 (Ar-C), 125.8 (Ar-C_q), 51.2 (C_q(CHO)), 40.8 (ArCH_2), 38.7 (CH_2), 17.6 (CH_2), 17.5 (CH_3), 14.7 (CH_3). HRMS (ESI) m/z Calcd. for $C_{13}H_{18}O^{79}Br$ [M+H]$^+$: 269.0541; Found: 269.0537.

2,2-Dimethyl-3-phenylpropanal (35)



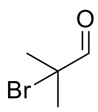
General procedure L was followed using (bromomethyl)benzene (363 µL, 3.3 mmol) and isobutyraldehyde (274 µL, 3.0 mmol) to afford aldehyde **35** as a colorless oil (267 mg, 50%). R_f 0.31 (5% Et_2O/pentane). IR (film)/cm^{-1} 3029, 2969, 2699, 1722 (s, C=O), 1454, 1397. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1 H, CHO), 7.31–7.21 (m, 3 H, Ar-H), 7.12–7.10 (m, 2 H, Ar-H), 2.79 (s, 2 H, CH_2), 1.06 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (CHO), 136.9 (Ar-C_q), 130.2 (2 × Ar-C), 128.1 (2 × Ar-C), 126.5 (Ar-C), 46.9 ($C_q(CH_3)_2$), 43.2 (CH_2), 21.4 ($C(CH_3)_2$). Spectroscopic data for this compound is consistent with that shown in the literature.[164]

2-Methyl-2,3-dihydro-1H-indene-2-carbaldehyde (36)



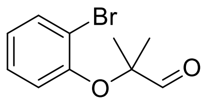
3-(2-Bromophenyl)-2,2-dimethylpropanal **33** (97 mg, 0.40 mmol), 2-methoxyethan-1-amine **1x** (8.7 µL, 0.10 mmol), palladium acetate (4.5 mg, 5 mol%), silver trifluoroacetate (220 mg, 1.00 mmol), acetic acid (0.4 mL) and HFIP (0.4 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 18 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash chromatography (silica, 30% CH_2Cl_2/pentane) afforded cyclised aldehyde **36** (26 mg, 41%) as a pale yellow oil. R_f 0.28 (30% CH_2Cl_2/pentane). IR (film)/cm^{-1} 3025, 2970, 1724 (s, C=O), 1457, 1433, 1370, 1231, 1217, 1023. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1 H, CHO), 7.25–7.15 (m, 4 H, Ar-H), 3.38 (d, *J* = 15.8 Hz, 2 H, C(*H*)H), 2.78 (d, *J* = 15.8 Hz, 2 H, C(H)*H*), 1.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (CHO), 140.9 (2 × Ar-C_q), 126.8 (2 × Ar-C), 124.7 (2 × Ar-C), 54.3 (C_q(CH_3)), 40.9 (2 × CH_2), 20.9 (CH_3). Spectroscopic data for this compound is consistent with that shown in the literature.[114]

2-Bromo-2-methylpropanal (37-alk-Br)



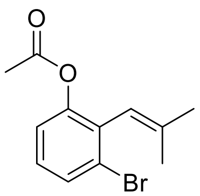
Bromine (1.66 g, 10.4 mmol) in Et_2O (5 mL) was added dropwise to a stirred solution of isobutyraldehyde (2 mL, 21.9 mmol) and 1,4-dioxane (1.02 mL, 12.0 mmol) in Et_2O (15 mL) at 0 °C and the reaction was stirred for 30 minutes. 10% Aqueous sodium thiosulfate was added (10 mL) and the reaction was stirred for 30 minutes. The product was extracted with Et_2O and the combined organic extracts were washed with 0% aqueous sodium thiosulfate, dried ($MgSO_4$) and carefully concentrated under reduced pressure to afford the crude brominated aldehyde **37-alk-Br** (1.36 g, 87%, approximately 20% purity) which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1 H, CHO), 1.82 (s, 6 H, $C(CH_3)_2$). Spectroscopic data for this compound (^{1}H NMR) is consistent with that shown in the literature.[165]

2-(2-Bromophenoxy)-2-methylpropanal (37)



2-Bromophenol (232 µL, 2.00 mmol) and potassium carbonate (332 mg, 2.4 mmol) were stirred in THF (10 mL) at rt for 10 minutes. 2-Bromo-2-methylpropanal **37-alk-Br** (1 mL, approximately 20% pure) was added dropwise and the reaction was refluxed overnight. Water was added and the product extracted with Et_2O. The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 5-10% Et_2O/Pentane) afforded the aldehyde **37** as a colourless oil (158 mg, 32%). R_f 0.24 (10% Et_2O/pentane). IR (film)/cm^{-1} 2982, 2808, 1736 (s, C=O), 1583, 1471, 1236, 1144, 1031. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1 H, CHO), 7.58 (dd, *J* = 8.1, 1.6 Hz, 1 H, Ar-H), 7.20 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1 H, Ar-H), 6.96–6.92 (m, 1 H, Ar-H), 6.85 (dd, *J* = 8.2, 1.4 Hz, 1 H, Ar-H), 1.48 (s, 6H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (CHO), 152.2 (Ar-C_q), 133.8 (Ar-C), 128.2 (Ar-C), 124.4 (Ar-C), 120.5 (Ar-C), 116.8 (Ar-C_q), 85.0 ($\mathit{C}(CH_3)_2$), 21.8 ($C(\mathit{C}H_3)_2$). HRMS (EI$^+$) m/z Calcd. for $C_{10}H_{11}O_2{}^{79}Br$ [M]$^+$: 241.9942; Found: 241.9936.

3-Bromo-2-(2-methylprop-1-en-1-yl)phenyl acetate (39)



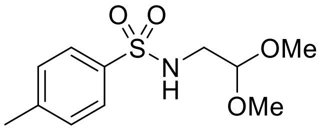
2-(2-Bromophenoxy)-2-methylpropanal **37** (97 mg, 0.40 mmol), 2-methoxyethan-1-amine (17.4 µL, 0.20 mmol), palladium acetate (4.9 mg, 5 mol%), silver trifluoroacetate (176 mg, 0.80 mmol), acetic acid (0.4 mL) and HFIP (0.4 mL) were combined in a flame dried microwave vial. The vial was purged with argon, sealed and heated to 130 °C for 18 h. The reaction was allowed to cool to room temperature, dissolved in CH_2Cl_2, filtered through a short plug of silica, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash chromatography (silica 0-10% Et_2O/Pentane) afforded alkene **39** as a pale yellow oil. R_f 0.13 (10% Et_2O/pentane). IR (film)/cm^{-1} 2982, 1736 (s, C=O), 1605, 1466, 1449, 1372, 1225 (s), 1111. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.0, 1.1 Hz, 1 H, Ar-H), 7.32 (d, *J* = 7.5 Hz, 1 H, Ar-H), 6.81 (t, *J* = 7.7 Hz, 1 H, Ar-H), 5.99 (s, 1H, C=CH), 2.10 (s, 3 H, OAc), 1.53 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (C=O), 157.1 (Ar-C_q), 134.1 (Ar-C), 126.4 (Ar-C_q), 126.1 (Ar-C), 121.9 (Ar-C), 103.5 (Ar-C_q), 88.9 (*C*=CH), 79.3 (C=*C*H), 26.1 (OAc), 20.9 (CH_3), 20.9 (CH_3). HRMS (EI$^+$) m/z Calcd. for $C_{12}H_{13}O_3Br$ [M]$^+$: 284.0048; Found: 284.0056 (observed mass corresponds to structure with additional O atom between the aromatic and alkene).

5.2.4 Compounds for Chapter 3.4: Arylation of Amines

*Preparation of directing groups (**46a**, **46e**, **46j-m**, **47**).*

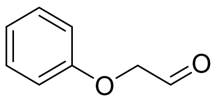
All other examples were commercially available.

N-(2,2-Dimethoxyethyl)-4-methylbenzenesulfonamide (46a)



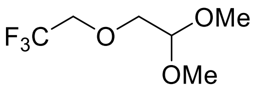
Tosyl chloride (955 mg, 5.00 mmol) was added to a stirred solution of 2,2-dimethoxyethan-1-amine (544 μL, 5.00 mmol) and triethylamine (2.10 mL, 15.0 mmol) in CH_2Cl_2 (1.07 mL). The reaction mixture was diluted with CH_2Cl_2, and the organic phase was washed with water and brine, dried (Na_2SO_4) filtered and solvent removed under reduced pressure to afford acetal **46a** as a colourless oil (1.25 g, 100%). R_f 0.33 (40% Et_2O/pentane). IR (film)/cm^{-1} 3287, 3187, 2936, 2838, 1598, 1454, 1437, 1376, 1318, 1306, 1158, 1088, 1080, 1054, 1040. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.74 (m, 2 H, Ar-H), 7.33–7.31 (m, 2 H, Ar-H), 4.59 (t, *J* = 5.9 Hz, 1 H, NH), 4.34 (t, *J* = 5.6 Hz, 1 H, CH), 3.34 (s, 6 H, CH(OC*H*$_3$)$_2$), 3.04 (t, *J* = 5.9 Hz, 2 H, NHC*H*$_2$), 2.44 (s, 3 H, Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, CDCl3) δ 143.6 (Ar-C_q), 136.7 (Ar-C_q) 129.8 (2 × Ar-C), 127.1 (2 × Ar-C), 102.6 (*C*H(OCH_3)$_2$), 54.7 (CH(O*C*H$_3$)$_2$), 44.5 (NHCH_2), 21.5 (Ar-CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[166]

2-Phenoxyacetaldehyde (47)



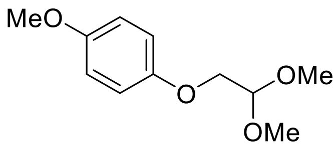
(2,2-Dimethoxyethoxy)benzene **46d** was added to a stirred solution of 1 M aqueous HCl (625 μL, 0.63 mmol) and AcOH (1.25 mL, 21.8 mmol) in EtOH (5.0 mL) and the reaction was refluxed for 3 h. The solvent was removed under reduced pressure, saturated aqueous sodium bicarbonate was added and the product extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 20% Et_2O/Pentane) afforded aldehyde **47** as a colourless oil (101 mg, 74%). R_f: 0.16 (20% Et_2O/pentane). IR (film)/cm^{-1} 1737 (C=O), 1598, 1494, 1291, 1242, 1048. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (t, *J* = 1.0 Hz, 1 H, CHO), 7.36–7.31 (m, 2 H, Ph-H), 7.05–7.02 (m, 1 H, Ph-H), 6.93–6.91 (m, 2 H, Ph-H), 4.59 (d, *J* = 1.0 Hz, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5 (CHO), 157.6 (Ph-C_q), 129.8 (Ph-C), 122.0 (Ph-C), 114.5 (Ph-C), 72.6 (OCH_2). Spectroscopic data for this compound (^{1}H NMR),[167] (^{13}C NMR, IR)[168] is consistent with that shown in the literature.

2-(2,2-Dimethoxyethoxy)-1,1,1-trifluoroethane (46e)



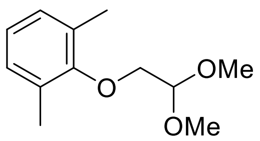
Sodium hydride (48 mg, 1.20 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 2,2,2-trifluoroethan-1-ol (87.0 μL, 1.20 mmol) in DMF (1.0 mL) at 0 °C and the reaction was allowed to warm to rt and stirred for 5 minutes. 2-Bromo-1,1-dimethoxyethane (118 μL, 1.0 mmol) was added and the reaction was stirred at 70 °C overnight. Water was added and the product extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/pentane) afforded acetal **46e** as a colourless oil (36 mg, 19%). R_f 0.11 (10% Et_2O/pentane). IR (film)/cm^{-1} 2942, 1738, 1277, 1154, 1122, 1068, 964. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (t, *J* = 5.1 Hz, 1 H, C*H*($OCH_3)_2$), 3.92 (q, J_{C-F} = 8.7 Hz, 2 H, CF_3CH_2), 3.66 (d, *J* = 5.1 Hz, 2 H, CHCH_2), 3.42 (s, 6 H, CH(OC$H_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 123.9 (q, $^1J_{C-F}$ = 280 Hz, CF_3), 102.8 (*C*H($OCH_3)_2$), 68.5 (q, $^2J_{C-F}$ = 34.1 Hz, *C*H_2CF_3). 54.3 (OCH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.38. HRMS (APCI) m/z Calcd. for $C_6H_{12}F_3O_3$ $[M+H]^+$: 189.0733; Found: 189.0730.

1-(2,2-Dimethoxyethoxy)-4-methoxybenzene (46j)



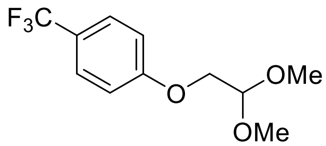
Sodium hydride (48 mg, 1.20 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 4-methoxyphenol (124 mg, 1.00 mmol) in DMF (3.3 mL) at 0 °C and the reaction was allowed to warm to rt and stirred for 5 minutes. 2-Bromo-1,1-dimethoxyethane (142 μL, 1.20 mmol) was added and the reaction was stirred at 120 °C overnight. Water was added and the product extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/pentane) afforded acetal **46j** as a colourless oil (154 mg, 73%). R_f 0.30 (20% Et_2O/pentane). IR (film)/cm^{-1} 2935, 2834, 1506, 1460, 1443, 1229, 1133, 1034, 1073. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–6.82 (m, 4 H, Ar-H), 4.71 (t, *J* = 5.2 Hz, 1 H, CH), 3.97 (d, *J* = 5.2 Hz, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.46 (s, 6 H, CH(OC$H_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (Ar-C_q), 152.7 (Ar-C_q), 115.7 (2 × Ar-C), 114.6 (2 × Ar-C), 102.2 (*C*H($OCH_3)_2$), 68.3 (OCH_2), 55.7 (Ar-OCH_3), 54.0 (2 × OCH_3). HRMS (APCI) m/z Calcd. for $C_{11}H_{17}O_4$ $[M+H]^+$: 213.1121; Found: 213.1119.

2-(2,2-Dimethoxyethoxy)-1,3-dimethylbenzene (46k)



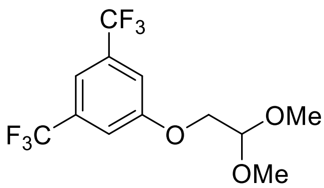
Sodium hydride (48 mg, 1.20 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 2,6-dimethylphenol (122 mg, 1.00 mmol) in DMF (3.3 mL) at 0 °C and the reaction was allowed to warm to rt and stirred for 5 minutes. 2-Bromo-1,1-dimethoxyethane (142 µL, 1.2 mmol) was added and the reaction was stirred at 120 °C overnight. Water was added and the product extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 5% Et_2O/pentane) afforded acetal **46k** as a colourless oil (140 mg, 62%). R_f 0.26 (10% Et_2O/pentane). IR (film)/cm^{-1} 2932, 2832, 1476, 1263, 1204, 1133, 1093, 1073, 1032. ^1H NMR (400 MHz, $CDCl_3$) δ 7.02–7.00 (m, 2 H, Ar-H), 6.95–6.91 (m, 1 H, Ar-H), 4.76 (t, *J* = 5.2 Hz, 1 H, CH), 3.85 (d, *J* = 5.2 Hz, 2 H, CH_2), 3.48 (s, 6 H, $CH(OC\mathit{H}_3)_2$), 2.31 (s, 6 H, 2 × Ar-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Ar-C_q), 130.7 (2 × Ar-C_q), 128.9 (Ar-C), 123.9 (Ar-C), 102.8 ($\mathit{C}H(OCH_3)_2$), 71.5 (OCH_2), 54.0 (2 × OCH_3), 16.2 (2 × Ar-CH_3). HRMS (EI^+) m/z Calcd. for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256; Found: 210.1267.

1-(2,2-Dimethoxyethoxy)-4-(trifluoromethyl)benzene (46l)



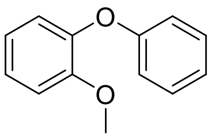
Cs_2CO_3 (2.40g, 7.5 mmol), NaI (7.5 mg, 0.05 mmol), 4-trifluoromethylphenol (810 mg, 5.00 mmol), 2-bromo-1,1-dimethoxyethane (1.20 mL, 10.0 mmol) and DMF (1.70 mL) were combined in a flame dried microwave vial, purged with argon and sealed. The reaction was heated to 65 °C overnight, allowed to cool to rt and filtered through a pad of Celite (washed with EtOAc). Water was added and the product extracted with EtOAc. The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/pentane) afforded acetal **46l** as a colourless oil (451 mg, 36%). R_f 0.20 (10% Et_2O/pentane). IR (film)/cm^{-1} 2942, 1615, 1591, 1519, 1324, 1310, 1259, 1159, 1108, 1067, 1045. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.00 (d, *J* = 8.5 Hz, 2 H, Ar-H), 4.74 (t, *J* = 5.1 Hz, 1 H, CH), 4.05 (d, *J* = 5.1 Hz, 2 H, CH_2), 3.48 (s, 6 H, $CH(OC\mathit{H}_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (Ar-C_q), 126.9 (q, $^3J_{C\text{-}F}$ = 4 Hz, 2 × Ar-C), 124.35 (q, $^1J_{C\text{-}F}$ = 271 Hz, CF_3), 123.32 (q, $^2J_{C\text{-}F}$ = 33 Hz, Ar-C_q), 114.6 (2 × Ar-C), 102.0 ($\mathit{C}H(OCH_3)_2$), 67.8 (OCH_2), 54.3 (2 × OCH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.58. HRMS (EI^+) m/z Calcd. for $C_{11}H_{13}O_3F_3$ $[M]^+$: 250.0817; Found: 250.0827.

1-(2,2-Dimethoxyethoxy)-3,5-bis(trifluoromethyl)benzene (46m)



Cs_2CO_3 (2.40g, 7.5 mmol), NaI (7.5 mg, 0.05 mmol), 3,5-bis(trifluoromethyl)phenol (761 μL, 5.00 mmol), 2-bromo-1,1-dimethoxyethane (1.20 mL, 10.0 mmol) and DMF (1.70 mL) were combined in a flame dried microwave vial, purged with argon and sealed. The reaction was heated to 65 °C overnight, allowed to cool to room temperature and filtered through a pad of Celite (washed with EtOAc). Water was added and the product extracted with EtOAc. The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 5% Et_2O/pentane) afforded acetal **46m** as a colourless oil (322 mg, 20%). R_f 0.32 (10% Et_2O/pentane). IR (film)/cm^{-1} 2942, 2838, 1614, 1467, 1881, 1257, 1171, 1124, 1076, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H, Ar-H), 7.35 (s, 2 H, Ar-H), 4.74 (t, J = 5.1 Hz, 1 H, CH), 4.09 (d, J = 5.1 Hz, 2 H, CH_2), 3.49 (s, 6 H, CH(OCH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_q), 132.9 (dd, $^2J_{C\text{-}F}$ = 33 Hz, 2 × Ar-C_q), 123.10 (q, $^1J_{C\text{-}F}$ = 273 Hz, 2 × CF_3), 115.0 (q, $^3J_{C\text{-}F}$ = 4 Hz, Ar-C), 114.8 (q, $^3J_{C\text{-}F}$ = 4 Hz, Ar-C), 101.9 (*C*H(OCH_3)$_2$), 68.3 (OCH_2), 54.4 (CH(O*C*H_3)$_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.07. HRMS (APCI) m/z Calcd. for $C_{10}H_8F_6O$ [M-2OCH_3+H]$^+$: 259.0552; Found: 259.0563.

1-Methoxy-2-phenoxybenzene (L13)

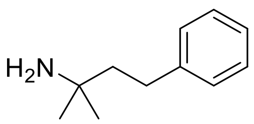


Phenol (117 mg, 0.5 mmol), 2-iodoanisole (56 mg, 0.60 mmol), copper(I) iodide (4.80 mg, 0.025 mmol), picolinic acid (6.15 mg, 0.05 mmol), K_3PO_4 (212 mg, 1.00 mmol) and DMSO (1.0 mL) were combined in a flame dried microwave vial. The reaction was capped and solvent bubbled with argon for 10 minutes then heated to 90 °C overnight. Water was added and the product extracted with EtOAc, dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, 2.5% Et_2O/pentane) afforded ether **L13** as a white solid (25.0 mg, 25%). R_f 0.26 (2.5% Et_2O/pentane). IR (film)/cm^{-1} 1596, 1580, 1489, 1455, 1298, 1259, 1219, 1174, 1150, 1110, 1019. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 3 H, Ar-H), 7.16–7.12 (m, 1 H, Ar-H), 7.07–6.91 (m, 5 H, Ph-H), 3.85 (s, 3 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (Ph-C_q), 151.5 (Ar-C_q), 145.1 (Ar-C_q), 129.5 (Ph-C), 124.8 (Ar-C), 122.4 (Ar-C), 121.11 (Ar-C), 121.09 (Ar-C), 117.2 (Ph-C), 112.9 (Ph-C), 56.0 (OCH_3). Spectroscopic data for this compound (^{1}H NMR)[169] is consistent with that shown in the literature.

*C(sp^3)–H Arylation of tert-amylamine **44** with aryl iodides (**45a**-**r**)*

General procedure M: AgTFA (132 mg, 0.60 mmol), $Pd(OPiv)_2$ (9.3 mg, 0.03 mmol, 10 mol%), aryl iodide (3.00 equiv), H_2O (27 µL, 1.50 mmol), amine (0.30 mmol), (2,2-dimethoxyethoxy)benzene **46d** (7.6 µL, 0.045 mmol), AcOH (1.25 mL) and HFIP (0.25 mL) were combined in a microwave vial. The vial was sealed and the reaction was stirred at 110 °C for 18 h. The reaction was allowed to cool to rt and filtered through a bed of Celite (eluting with diethyl ether). The product was extracted from the organic phase into 1 M aqueous HCl solution. The combined aqueous extracts were basified with saturated aqueous sodium hydroxide solution and the free amine extracted with CH_2Cl_2, dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford the title amines.

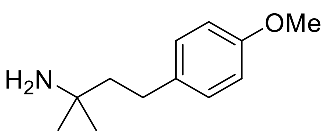
2-Methyl-4-phenylbutan-2-amine (45a)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford amine **45a** as a yellow oil (29 mg, 59%). IR (film)/cm^{-1} 3026, 2958, 1502, 1494, 1454, 1392, 1365, 1222, 1177, 1068, 1030. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.21–7.17 (m, 3 H, Ph-H), 2.68–2.64 (m, 2 H, CH_2), 1.71–1.66 (m, 2 H, CH_2), 1.18 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (Ph-C_q), 128.3 (Ph-C), 128.3 (Ph-C), 125.6 (Ph-C), 49.5 ($\mathit{C}(CH_3)_2$), 47.0 (CH_2), 31.1 (CH_2), 30.3 ($C(\mathit{C}H_3)_2$). Spectroscopic data for this compound (^{1}H NMR)[170] (^{13}C NMR, IR)[171] is consistent with the literature.

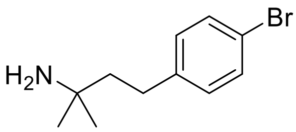
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45a** was obtained as a yellow oil (30 mg, 61%), data obtained was identical.

4-(4-Methoxyphenyl)-2-methylbutan-2-amine (45b)



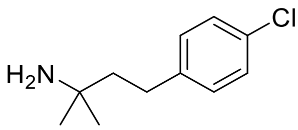
General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 4-iodoanisole (211 mg, 0.90 mmol) to afford amine **45b** as a brown oil (32 mg, 55%). IR (film)/cm^{-1} 2955, 1738, 1610, 1510, 1365, 1242, 1176, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.6 Hz, 2 H, Ar-H), 6.84 (d, J = 8.6 Hz, 2 H, Ar-H), 3.79 (s, 3 H, OCH_3), 2.62–2.58 (m, 2 H, CH_2), 1.67–1.63 (m, 2 H, CH_2), 1.35 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (Ar-C_q), 134.8 (Ar-C_q), 129.1 (2 × Ar-C), 113.8 (2 × Ar-C), 55.2 (OCH_3), 49.5 ($\mathit{C}(CH_3)_2$), 47.3 (CH_2), 30.4 ($C(\mathit{C}H_3)_2$), 30.1 (CH_2). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

4-(4-Bromophenyl)-2-methylbutan-2-amine (45c)



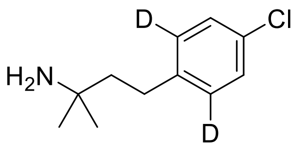
General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 1-bromo-4-iodobenzene (256 mg, 0.90 mmol) to afford amine **45c** as a brown oil (41 mg, 56%). IR (film)/cm^{-1} 2957, 1487, 1364, 1070, 1010. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2 H, Ar-H), 7.09–7.07 (m, 2 H, Ar-H), 2.62–2.59 (m, 2 H, CH_2), 1.66–1.62 (m, 2 H, CH_2), 1.43 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (Ar-C_q), 131.4 (2 × Ar-C), 130.1 (2 × Ar-C), 119.3 (Ar-C_q), 49.5 ($\mathit{C}(CH_3)_2$), 46.8 (CH_2), 30.5 (CH_2), 30.4 ($C(\mathit{C}H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

4-(4-Chlorophenyl)-2-methylbutan-2-amine (45d)



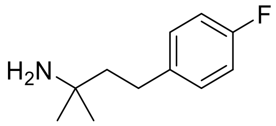
General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 1-chloro-4-iodobenzene (214 mg, 0.90 mmol) to afford amine **45d** as a yellow oil (33 mg, 56%). IR (film)/cm^{-1} 2957, 1738, 1490, 1365, 1228, 1217, 1092, 1014. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (m, 2 H, Ar-H), 7.13 (d, *J* = 8.4 Hz, 2 H, Ar-H), 2.65–2.61 (m, 2 H, CH_2), 1.67–1.62 (m, 2 H, CH_2), 1.46 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (Ar-C_q), 131.3 (Ar-C_q), 129.6 (2 × Ar-C), 128.4 (2 × Ar-C), 49.5 ($\mathit{C}(CH_3)_2$), 46.9 (CH_2), 30.44 (CH_2), 30.42 ($C(\mathit{C}H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97] On a 2.0 mmol scale, amine **45d** was afforded as a yellow oil (182 mg, 46%).

4-(4-Chlorophenyl-2,6-d2)-2-methylbutan-2-amine (D2-45d)



IR (film)/cm^{-1} 2958, 2926, 2861, 1579, 1445, 1366, 1260, 1102, 1018. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2 H, Ar-H), 2.66–2.61 (m, 2 H, CH_2), 1.67–1.63 (m, 2 H, CH_2), 1.50 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.4 (2 × Ar-CH), 49.5 ($C_q(CH_3)_2$), 46.9 (CH_2), 30.5 ($C(\mathit{C}H_3)_2$), 30.4 (CH_2). Disappearance of the ε-C in the ^{13}C NMR spectra of the deutero compared to the proteo amine (after full characterisation by HSQC and HMBC) enabled conclusive regioselectivity assignment. HRMS (ES) m/z Calcd. for $C_{11}H_{15}N^{35}ClD_2$ $[M+H]^+$: 200.1184; Found: 200.1175.

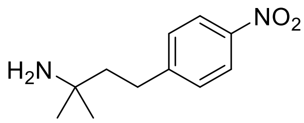
4-(4-Fluorophenyl)-2-methylbutan-2-amine (45e)



General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 1-fluoro-4-iodobenzene (104 μL, 0.90 mmol) to afford amine **45e** as a brown oil (20 mg, 37%). IR (film)/cm^{-1} 2959, 1600, 1508, 1365, 1219, 1156. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.13 (m, 2 H, Ar-C), 7.00–6.94 (m, 2 H, Ar-C), 2.66–2.61 (m, 2 H, CH_2), 1.67–1.63 (m, 2 H, CH_2), 1.42 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, $^{1}J_{C\text{-}F}$ = 243 Hz, Ar-C_q), 138.3 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, Ar-C_q), 129.5 (d, $^{3}J_{C\text{-}F}$ = 8 Hz, 2 × Ar-C), 115.0 (d, $^{2}J_{C\text{-}F}$ = 21 Hz, 2 × Ar-C), 49.5 (*C*$(CH_3)_2$), 47.1 (CH_2), 30.3 (C(*C*$H_3)_2$), 30.2 (CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.0. Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

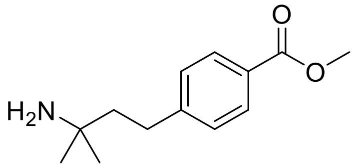
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45e** was obtained as a brown oil (25 mg, 46%), data obtained was identical.

2-Methyl-4-(4-nitrophenyl)butan-2-amine (45f)



General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 1-iodo-4-nitrobenzene (224 mg, 0.90 mmol) to afford amine **45f** as a brown solid (30 mg, 48%). IR (film)/cm^{-1} 2949, 1738, 1596, 1508, 1342, 1217, 1109. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.36 (d, *J* = 8.7 Hz, 2 H, Ar-H), 2.80–2.76 (m, 2 H, CH_2), 1.71–1.67 (m, 2 H, CH_2), 1.48 (bs, 2 H, NH_2), 1.20 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (Ar-C_q), 146.2 (Ar-C_q), 129.1 (2 × Ar-C), 123.7 (2 × Ar-C), 49.5 (*C*$(CH_3)_2$), 46.3 (CH_2), 31.1 (CH_2), 30.5 (C(*C*$H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

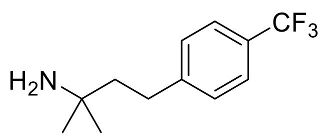
Methyl 4-(3-amino-3-methylbutyl)benzoate (45g)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and methyl 4-iodobenzoate (236 mg, 0.90 mmol) to afford amine **45g** as a brown oil (33 mg, 47%). IR (film)/cm^{-1} 2957, 1721 (s, C=O), 1608, 1433, 1271, 1175, 1108, 1015. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.27 (d, *J* = 8.3 Hz, 2 H, Ar-H), 3.91 (s, 3 H, OCH_3), 2.74–2.70 (m, 2 H, CH_2), 1.71–1.66 (m, 2 H, CH_2), 1.51 (bs, 2 H, NH_2), 1.19 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C=O), 148.4 (Ar-C_q), 129.7 (2 × Ar-C), 128.3 (2 × Ar-C), 127.7 (Ar-C_q), 52.0 (OCH_3), 49.5 (*C*$(CH_3)_2$), 46.6 (CH_2), 31.2 (CH_2), 30.4 (C(*C*$H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with the literature.[97]

Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45g** was obtained as a brown oil (30 mg, 45%), data obtained was identical.

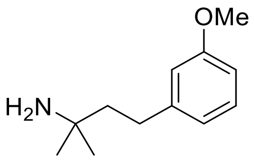
2-Methyl-4-(4-(trifluoromethyl)phenyl)butan-2-amine (45h)



General procedure M was followed using *tert*-amylamine 44 (35 µL, 0.30 mmol) and 1-iodo-4-(trifluoromethyl)benzene (132 µL, 0.90 mmol) to afford amine **45h** as a yellow oil (22 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2 H, Ar-H), 2.75–2.70 (m, 2 H, CH_2), 1.70–1.66 (m, 2 H, CH_2), 1.42 (bs, 2 H, NH_2), 1.19 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (Ar-C_q), 128.6 (2 × Ar-C), 128.1 (q, $^2J_{C\text{-}F}$ = 32 Hz, Ar-C_q), 125.3 (*q*, $^3J_{C\text{-}F}$ = 3 Hz, 2 × Ar-C), 124.3 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3) 49.5 (*C*$(CH_3)_2$), 46.6 (CH_2), 31.0 (CH_2), 30.4 (C(*C*$H_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.29. Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45h** was obtained as a yellow oil (28 mg, 40%), data obtained was identical.

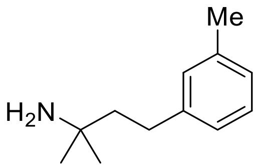
4-(3-Methoxyphenyl)-2-methylbutan-2-amine (45i)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 3-iodoanisole (107 µL, 0.90 mmol) to afford amine **45i** as a brown oil (27 mg, 47%). IR (film)/cm^{-1} 2958, 1600, 1583, 1488, 1465, 1454, 1434, 1365, 1257, 1151, 1042. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 1 H, Ar-H), 6.81–6.72 (m, 3 H, Ar-H), 3.81 (s, 3 H, OCH_3), 2.66–2.62 (m, 2 H, CH_2), 1.71–1.66 (m, 2 H, CH_2), 1.40 (bs, 2 H, NH_2), 1.18 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (Ar-C_q), 144.5 (Ar-C_q), 129.3 (Ar-C), 120.7 (Ar-C), 114.1 (Ar-C), 111.0 (Ar-C), 55.1 (OCH_3), 49.5 (*C*($CH_3)_2$), 46.9 (CH_2), 31.2 (CH_2), 30.4 (C(*C*$H_3)_2$). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{12}H_{20}NO$ [M+H]$^+$: 194.1545; Found: 194.1543.

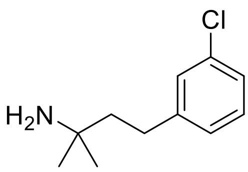
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45i** was obtained as a yellow oil (28 mg, 48%), data obtained was identical.

2-Methyl-4-(m-tolyl)butan-2-amine (45j)



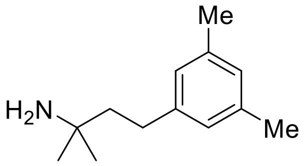
General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 1-iodo-3-methylbenzene (156 µL, 0.90 mmol) to afford amine **45j** as a brown oil (30 mg, 56%). IR (film)/cm^{-1} 2957, 2864, 1670, 1608, 1588, 1456, 1380, 1364, 1218. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.03–7.00 (m, 3 H, Ar-H), 2.65–2.60 (m, 2 H, CH_2), 2.34 (s, 3 H, Ar-CH_3), 1.70–1.65 (m, 2 H, CH_2), 1.41 (bs, 2 H, NH_2), 1.18 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (Ar-C_q), 137.9 (Ar-C_q), 129.1 (Ar-C), 128.3 (Ar-C), 126.4 (Ar-C), 125.3 (Ar-C), 49.5 (*C*($CH_3)_2$), 47.2 (CH_2), 31.0 (CH_2), 30.4 (C(*C*$H_3)_2$), 21.4 (Ar-CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

4-(3-Chlorophenyl)-2-methylbutan-2-amine (45k)



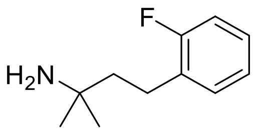
General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 1-chloro-3-iodobenzene (111 µL, 0.90 mmol) to afford amine **45k** as a brown oil (34 mg, 57%). IR (film)/cm^{-1} 2958, 2865, 1596, 1573, 1474, 1427, 1365, 1206, 1077. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 3 H, Ar-H), 7.09–7.07 (m, 1 H, Ar-H), 2.66–2.62 (m, 2 H, CH_2), 1.68–1.64 (m, 2 H, CH_2), 1.40 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (Ar-C_q), 134.1 (Ar-C_q), 129.6 (Ar-C), 128.4 (Ar-C), 126.5 (Ar-C), 125.9 (Ar-C), 49.5 (*C*($CH_3)_2$), 46.7 (CH_2), 30.8 (CH_2), 30.4 (C(*C*$H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

4-(3,5-Dimethylphenyl)-2-methylbutan-2-amine (45l)



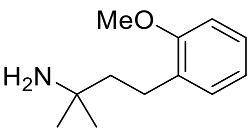
General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 1-iodo-3,5-dimethylbenzene (130 µL, 0.90 mmol) to afford amine **45l** as a yellow oil (31 mg, 54%). IR (film)/cm^{-1} 3013, 2956, 2918, 2864, 1605, 1466, 1380, 1364, 1036. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 3 H, Ar-H), 2.61–2.56 (m, 2 H, CH_2), 2.30 (s, 3 H, Ar-CH_3), 2.30 (s, 3 H, Ar-CH_3), 1.69–1.64 (m, 2 H, CH_2), 1.37 (bs, 2 H, NH_2), 1.17 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (Ar-C_q), 137.8 (2 × Ar-C_q), 127.3 (Ar-C), 126.1 (Ar-C), 49.6 (*C*$(CH_3)_2$), 47.3 (CH_2), 30.9 (CH_2), 30.4 (C(*C*$H_3)_2$), 21.2 (2 × Ar-CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{15}H_{20}N$ $[M+H]^+$: 192.1754; Found: 192.1752.

4-(2-Fluorophenyl)-2-methylbutan-2-amine (45m)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 1-fluoro-2-iodobenzene (115 µL, 0.90 mmol) to afford amine **45m** as a brown oil (20 mg, 37%). IR (film)/cm^{-1} 2959, 1584, 1491, 1455, 1365, 1227, 1181. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.14 (m, 2 H, Ar-H), 7.08–6.98 (m, 2 H, Ar-H), 2.71–2.67 (m, 2 H, CH_2), 1.69–1.64 (m, 2 H, CH_2), 1.47 (bs, 2 H, NH_2), 1.19 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, $^1J_{C-F}$ = 245 Hz, Ar-C_q), 130.4 (d, $^3J_{C-F}$ = 5 Hz, Ar-C), 129.6 (d, $^2J_{C-F}$ = 16 Hz, Ar-C_q), 127.4 (d, $^3J_{C-F}$ = 8 Hz, Ar-C), 124.0 (d, $^4J_{C-F}$ = 3 Hz, Ar-C), 115.2 (d, $^2J_{C-F}$ = 22 Hz, Ar-C), 49.6 (*C*$(CH_3)_2$), 45.5 (CH_2), 30.2 (C(*C*$H_3)_2$), 24.3 (CH_2). ^{19}F NMR (377 MHz, $CDCl_3$) δ -119.3. HRMS (TOF-ES$^+$) m/z Calcd. for $C_{11}H_{17}NF$ $[M+H]^+$: 182.1345; Found: 182.1352.

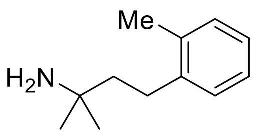
4-(2-Methoxyphenyl)-2-methylbutan-2-amine (45n)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 2-iodoanisole (105 µL, 0.90 mmol) to afford amine **45n** as a brown oil (22 mg, 38%). IR (film)/cm^{-1} 2957, 1599, 1493, 1463, 1241, 1029. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.14 (m, 2 H, Ar-H), 6.91–6.84 (m, 2 H, Ar–H), 3.83 (s, 3 H, OCH_3), 2.67–2.63 (m, 2 H, CH_2), 1.66–1.61 (m, 2 H, CH_2), 1.51 (bs, 2 H, NH_2), 1.18 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (Ar-C_q), 131.1 (Ar-C_q), 129.5 (Ar-C), 126.9 (Ar-C), 120.4 (Ar-C), 110.2 (Ar-C), 55.2 (OCH_3), 49.6 (CH_2), 45.2 (*C*$(CH_3)_2$), 30.2 (C(*C*$H_3)_2$), 25.3 (CH_2). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{12}H_{20}NO$ $[M+H]^+$: 194.1545; Found: 194.1552.

Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45n** was afforded as a yellow oil (23 mg, 47%), data obtained was identical.

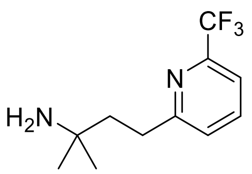
2-Methyl-4-(o-tolyl)butan-2-amine (45o)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 1-iodo-2-methylbenzene (115 µL, 0.90 mmol) to afford amine **45o** as a brown oil (7 mg, 13%). IR (film)/cm^{-1} 2961, 2925, 1666, 1605, 1458, 1366, 1259, 1101, 1031. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.11 (m, 4 H, Ar-H), 2.66–2.62 (m, 2 H, CH_2), 2.33 (s, 3 H, Ar-CH_3), 1.63–1.59 (m, 4 H, CH_2 + NH_2), 1.20 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (Ar-C_q), 135.7 (Ar-C_q), 130.2 (Ar-C), 128.7 (Ar-C), 126.0 (Ar-C), 125.9 (Ar-C), 49.6 ($\mathit{C}(CH_3)_2$), 45.8 (CH_2), 30.3 ($C(\mathit{C}H_3)_2$), 28.4 (CH_2), 19.2 (Ar-CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596; Found: 178.1590.

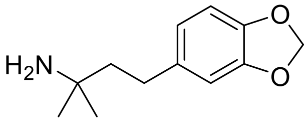
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45o** was obtained as a brown oil (14 mg, 26%), data obtained was identical.

2-Methyl-4-(6-(trifluoromethyl)pyridin-2-yl)butan-2-amine (45p)



General procedure M was followed using *tert*-amylamine **44** (35 µL, 0.30 mmol) and 2-iodo-6-(trifluoromethyl)pyridine (246 mg, 0.90 mmol) to afford amine **45p** as a brown oil (40 mg, 57%). IR (film)/cm^{-1} 2963, 1601, 1463, 1340, 1182, 1133, 1111, 1090. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 7.8 Hz, 1 H, Ar-H), 7.50 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.37 (d, *J* = 7.9 Hz, 1 H, Ar-H), 2.96–2.91 (m, 2 H, CH_2), 1.84–1.79 (m, 2 H, CH_2), 1.43 (bs, 2 H, NH_2), 1.19 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (Ar-C_q), 147.61 (q, $^2J_{C\text{-}F}$ = 34 Hz, Ar-C_q), 137.5 (Ar-C), 125.4 (Ar-C), 121.6 (q, $^1J_{C\text{-}F}$ = 274 Hz, CF_3), 117.6 (q, $^3J_{C\text{-}F}$ = 3 Hz, Ar-C), 49.5 ($\mathit{C}(CH_3)_2$), 44.4 (CH_2), 33.4 (CH_2), 30.4 ($C(\mathit{C}H_3)_2$). ^{19}F NMR (377 MHz, $CDCl_3$) δ -68.04. Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

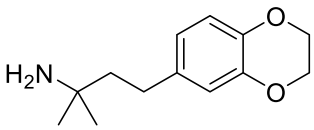
4-(Benzo[d][1,3]dioxol-5-yl)-2-methylbutan-2-amine (45q)



General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 5-iodobenzo[d][1,3]dioxole (110 μL, 0.90 mmol) to afford amine **45q** as a brown oil (22 mg, 35%). IR (film)/cm^{-1} 2958, 1502, 1488, 1440, 1364, 1245, 1187, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 – 6.63 (m, 3 H, Ar-H), 5.92 (s, 2 H, OCH_2), 2.60–2.55 (m, 2 H, CH_2), 1.65–1.61 (m, 2 H, CH_2), 1.43 (bs, 2 H, NH_2), 1.16 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (Ar-C_q), 145.4 (Ar-C_q), 136.6 (Ar-C_q), 120.8 (Ar-C), 108.8 (Ar-C), 108.1 (Ar-C), 100.7 (OCH_2), 49.4 ($\mathit{C}(CH_3)_2$), 47.3 (CH_2), 30.8 (CH_2), 30.4 ($C(\mathit{C}H_3)_2$). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1338; Found: 208.1333.

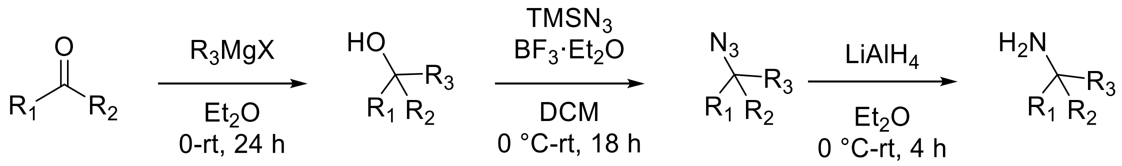
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **45q** was afforded as a brown oil (29 mg, 47%), data obtained was identical.

4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-methylbutan-2-amine (45r)



General procedure M was followed using *tert*-amylamine **44** (35 μL, 0.30 mmol) and 6-iodo-2,3-dihydrobenzo[b][1,4]dioxine (336 mg, 0.90 mmol) to afford amine **45r** as a yellow oil (37 mg, 56%). IR (film)/cm^{-1} 2960, 1589, 1507, 1458, 1283, 1257, 1067. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.2 Hz, 1 H, Ar-H), 6.71 (d, *J* = 2.0 Hz, 1 H, Ar-H), 6.67 (dd, *J* = 8.2, 2.0 Hz, 1 H, Ar-H), 4.24 (s, 4 H, 2 × OCH_2), 2.57–2.53 (m, 2 H, CH_2), 1.66–1.62 (m, 2 H, CH_2), 1.54 (bs, 2 H, NH_2), 1.16 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (Ar-C_q), 141.5 (Ar-C_q), 136.1 (Ar-C_q), 121.1 (Ar-C), 117.0 (Ar-C), 116.8 (Ar-C), 64.4 (OCH_2), 64.3 (OCH_2), 49.5 ($\mathit{C}(CH_3)_2$), 47.1 (CH_2), 30.32 ($C(\mathit{C}H_3)_2$), 30.27 (CH_2). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1494; Found: 222.1496.

*Preparation of amines (**49-53**)*



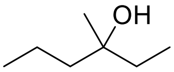
Procedure for the synthesis of amines *via* azide transfer based on preparation by Shi.[127] All other amines were commercially available.

General procedure N: Grignard reagent (15.0 mmol, 1.5 equiv) was added dropwise to a stirred solution of ketone (10 mmol, 1 equiv) in Et_2O (13.3 mL, 0.75 M) at 0 °C, the reaction was allowed to warm to rt and stirred for 18 h. The reaction was quenched by slow addition of saturated aqueous ammonium chloride solution and stirred for 10 minutes. The reaction was diluted with Et_2O and the organic phase was washed with water and brine, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford the crude alcohol which was used in the next step without further purification.

General procedure O: $TMSN_3$ (1.2 equiv in 2 mL CH_2Cl_2) was added to a stirred solution of alcohol (1 equiv) in CH_2Cl_2 (1.12 M). $BF_3{\cdot}Et_2O$ (1.2 equiv) was then added dropwise at 0 °C, the reaction was allowed to warm to rt and stirred for 18 h. The reaction was quenched by slow addition of saturated aqueous ammonium bicarbonate solution and stirred for 10 minutes. The reaction was diluted with CH_2Cl_2 and the organic phase was washed with water and brine, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford the crude azide which was used in the next step without further purification.

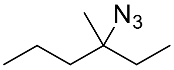
General procedure P: $LiAlH_4$ (1 equiv) was slowly added to a stirred solution of azide (1 equiv) in Et_2O (1.25 M) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by slow addition of $Na_2SO_4{\cdot}10H_2O$ at 0 °C until there was no further effervescence. The reaction mixture was filtered through Celite and the Celite was washed thoroughly with Et_2O (Caution: any unquenched $LiAlH_4$ on the Celite was quenched with water before disposal). The solvent removed under reduced pressure to afford the crude amine which was purified by vacuum distillation.

3-Methylhexan-3-ol (49-OH)



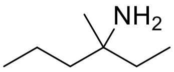
General procedure N was followed using methylmagnesium chloride (5.36 mL, 15 mmol, 2.8 M solution in Et_2O) and 3-hexanone (1.23 mL, 10.0 mmol) to afford tertiary alcohol **49-OH** as a colourless oil (1.11 g, 95%). R_f = 0.40 (40% Et_2O/pentane). IR (film)/cm^{-1} 3375 (br, OH), 2960, 2933, 2874, 1460, 1377, 1154. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.46–1.39 (m, 2 H, CH_2), 1.36–1.30 (m, 2 H, CH_2), 1.16 (bs, 1 H, OH), 1.15 (s, 3 H, CH_3), 0.95–0.88 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.9 (C_qOH), 43.8 (CH_2), 34.3 (CH_2), 26.4 (CH_3), 17.1 (CH_2), 14.7 (CH_3), 8.2 (CH_3). Spectroscopic data for this compound (^{1}H NMR, IR) is consistent with that shown in the literature.[172]

3-Azido-3-methylhexane (49-N3)



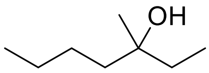
General procedure O was followed using 3-methylhexan-3-ol **49-OH** (1.00 g, 8.60 mmol) to afford tertiary azide **49-N3** as a colourless oil (1.21 g, 100%). R_f = 0.10 (40% Et_2O/pentane). IR (film)/cm^{-1} 2964, 2936, 2875, 2084 (N_3), 1462, 1381, 1251, 1145. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.52 (m, 2 H, CH_2), 1.50–1.45 (m, 2 H, CH_2), 1.41–1.33 (m, 2 H, CH_2), 1.21 (s, 3 H, CH_3), 0.93 (q, *J* = 7.4 Hz, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.6 (C_qN_3), 41.2 (CH_2), 32.0 (CH_2), 22.8 (CH_3), 17.2 (CH_2), 14.4 (CH_3), 8.3 (CH_3).

3-Methylhexan-3-amine (49)



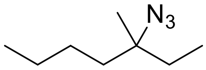
General procedure P was followed using 3-azido-3-methylhexane **49-N3** (1.21 g, 8.60 mmol) to afford amine **49** as a colourless oil (305 mg, 28%). IR (film)/cm^{-1} 2958, 2931, 2873, 1583, 1461, 1376, 1179. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.31–1.22 (m, 4 H, 2 × CH_2), 1.00 (s, 3 H, CH_3), 0.93–0.88 (m, 3 H, CH_3), 0.85 (t, *J* = 7.6 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.4 (C_qNH_2), 44.8 (CH_2), 35.1 (CH_2), 27.5 (CH_3), 17.1 (CH_2), 14.8 (CH_3), 8.2 (CH_3). Spectroscopic data for this compound (NMR) is consistent with that shown in the literature.[97]

3-Methylheptan-3-ol (50-OH)



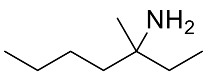
General procedure N was followed using methylmagnesium chloride (5.36 mL, 15 mmol, 2.8 M solution in Et_2O) and 3-heptanone (1.41 mL, 10.0 mmol) to afford tertiary alcohol **50-OH** as a colourless oil (1.33 g, 100%). R_f = 0.40 (40% Et_2O/pentane). IR (film)/cm^{-1} 3371 (br, OH), 2961, 2932, 2882, 1738, 1460, 1376, 1217, 1151. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.47–1.42 (m, 2 H, CH_2), 1.35–1.29 (m, 4 H, 2 × CH_2), 1.16 (bs, 1 H, OH), 1.15 (s, 3 H, CH_3), 0.94–0.88 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.9 (C_qOH), 41.0 (CH_2), 34.2 (CH_2), 26.4 (CH_3), 26.1 (CH_2), 23.3 (CH_2), 14.1 (CH_3), 8.2 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

3-Azido-3-methylheptane (50-N3)



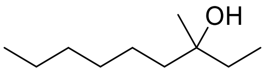
General procedure O was followed using 3-methylheptan-3-ol **50-OH** (1.27 g, 9.75 mmol) to afford tertiary azide **50-N3** as a colourless oil (1.33 g, 88%). R_f = 0.10 (40% Et_2O/pentane). IR (film)/cm^{-1} 2963, 2935, 2864, 2085 (N_3), 1462, 1380, 1251. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (qd, *J* = 7.7, 0.9 Hz, 2 H, CH_2), 1.52–1.47 (m, 2 H, CH_2), 1.22 (s, 3 H, CH_3), 1.34–1.30 (m, 4 H, 2 × CH_2), 0.95–0.90 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.5 (C_qN_3), 38.6 (CH_2), 32.0 (CH_2), 26.1 (CH_2), 23.1 (CH_2), 22.8 (CH_3), 14.0 (CH_3), 8.3 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

3-Methylheptan-3-amine (50)



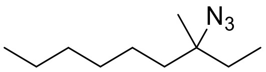
General procedure P was followed using 3-azido-3-methylheptane **50-N3** (1.30 g, 8.37 mmol) to afford amine **50** as a colourless oil (305 mg, 28%). IR (film)/cm^{-1} 2958, 2929, 2860, 1593, 1460, 1376, 1175. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.32–1.20 (m, 8 H, 3 × CH_2 + NH_2), 1.00 (s, 3 H, CH_3), 0.91 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.85 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.3 (C_qNH_2), 41.9 (CH_2), 35.0 (CH_2), 27.5 (CH_3), 26.2 (CH_2), 23.4 (CH_2), 14.1 (CH_3), 8.2 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

3-Methylnonan-3-ol (51-OH)



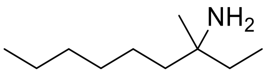
General procedure N was followed using methylmagnesium chloride (5.36 mL, 15 mmol, 2.8 M solution in Et_2O) and 3-nonanone (1.73 mL, 10.0 mmol) to afford tertiary alcohol **51-OH** as a colourless oil (1.31 g, 83%). R_f = 0.40 (40% Et_2O/pentane). IR (film)/cm^{-1} 3368 (br, OH), 2961, 2929, 2858, 1738, 1460, 1375, 1148. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.46–1.42 (m, 2 H, CH_2), 1.36–1.26 (m, 8 H, 4 × CH_2), 1.17 (bs, 1 H, OH), 1.14 (s, 3 H, CH_3), 0.91–0.88 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.9 (C_qOH), 41.4 (CH_2), 34.2 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 26.4 (CH_3), 23.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 8.2 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

3-Azido-3-methylnonane (51-N3)



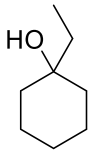
General procedure O was followed using 3-methylnonan-3-ol **51-OH** (1.27 g, 8.02 mmol) to afford tertiary azide **51-N3** as a colourless oil (1.39 g, 95%). R_f = 0.10 (40% Et_2O/pentane). IR (film)/cm^{-1} 2959, 2931, 2859, 2086 (N_3), 1738, 1461, 1378, 1251. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.51–1.45 (m, 2 H, CH_2), 1.38–1.24 (m, 8 H, 4 × CH_2), 1.21 (s, 3 H, CH_3), 0.94–0.88 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, CDCl3) δ 64.6 (C_qN_3), 38.9 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_2), 14.0 (CH_3), 8.3 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

3-Methylnonan-3-amine (51)



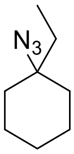
General procedure P was followed using 3-azido-3-methylnonane **51-N3** (1.34 g, 7.31 mmol) to afford amine **51** as a colourless oil (600 mg, 52%). IR (film)/cm^{-1} 2958, 2926, 2855, 1610, 1460, 1375, 1173. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.32–1.24 (m, 10 H, 5 × CH_2), 1.18 (bs, 2 H, NH_2), 1.01 (s, 3 H, CH_3), 0.90–0.84 (m, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.4 (C_qNH_2), 42.3 (CH_2), 35.1 (CH_2), 31.9 (CH_2), 30.1 (CH_2), 27.6 (CH_3), 23.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 8.2 (CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{10}H_{24}N$ $[M+H]^+$: 158.1909; Found: 158.1902. Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

1-Ethylcyclohexan-1-ol (52-OH)



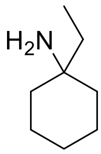
General procedure N was followed using ethylmagnesium bromide (6.00 mL, 15 mmol, 2.5 M solution in Et_2O) and cyclohexanone (1.04 mL, 10 mmol) to afford tertiary alcohol **52-OH** as a colourless oil (1.15 g, 90%). R_f = 0.40 (40% Et_2O/pentane). IR (film)/cm^{-1} 3377 (br, OH), 2926, 2856, 1447, 1168, 1123. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.38 (m, 12 H, 6 × CH_2), 1.15 (bs, 1 H, OH), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.4 (C_qOH), 36.9 (2 × CH_2), 34.7 (CH_2), 25.9 (CH_2), 22.2 (2 × CH_2), 7.2 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[40]

1-Azido-1-ethylcyclohexane (52-N3)



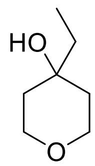
General procedure O was followed using 1-ethylcyclohexan-1-ol **52-OH** (1.10 g, 8.60 mmol) to afford tertiary azide **52-N3** as a colourless oil (1.27 g, 97%). R_f = 0.10 (40% Et_2O/pentane). IR (film)/cm^{-1} 2931, 2971, 2094 (N_3), 1447, 1257, 1157, 1149. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70–1.65 (m, 2 H, 2 × C(*H*)H), 1.62–1.51 (m, 7 H, 3 × CH_2 + C(H)*H*), 1.39–1.32 (m, 2 H, CH_2), 1.30–1.21 (m, 1 H, C(H)*H*), 0.95 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.4 (C_q-N_3), 34.2 (2 × CH_2), 32.8 (CH_2), 25.5 (CH_2), 22.2 (2 × CH_2), 7.7 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[127]

1-Ethylcyclohexan-1-amine (52)



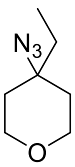
General procedure P was followed using 1-azido-1-ethylcyclohexane **52-N3** (1.23 g, 8.03 mmol) to afford amine **52** as a colourless oil (685 mg, 67%). IR (film)/cm^{-1} 2964, 2921, 2849, 1596, 1449. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47–1.26 (m, 12 H, 6 × CH_2), 1.19 (bs, 2 H, NH_2), 0.86 (q, *J* = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 50.4 ($C_q$$NH_2$), 38.2 (2 × CH_2), 34.9 (CH_2), 26.1 (CH_2), 22.3 (2 × CH_2), 7.2 (CH_3). Spectroscopic data for this compound (NMR) is consistent with that shown in the literature.[97]

4-Ethyltetrahydro-2H-pyran-4-ol (53-OH)



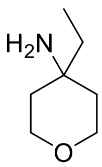
General procedure N was followed using ethylmagnesium bromide (6.00 mL, 15 mmol, 2.5 M solution in Et_2O) and tetrahydro-4H-pyran-4-one (0.92 mL, 10 mmol) to afford tertiary alcohol **53-OH** as a colourless oil (673 mg, 52%). R_f = 0.16 (60% Et_2O/pentane). IR (film)/cm^{-1} 3396 (br, OH), 2944, 2868, 1464, 1388, 1238, 1159, 1096, 1021. ^1H NMR (400 MHz, $CDCl_3$) δ 3.81–3.73 (m, 4 H, 2 × OCH_2), 1.72–1.64 (m, 2 H, 2 × C(*H*)H), 1.56–1.44 (m, 4 H, 2 × C(H)*H* + CH_2), 1.17 (bs, 1 H, OH), 0.93 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.0 (C_qOH), 63.9 (2 × OCH_2), 37.1 (2 × CH_2), 35.7 (CH_2), 6.7 (CH_3). HRMS (APCI) m/z Calcd. for $C_7H_{15}O_2$ $[M+H]^+$: 131.1067; Found: 131.1069.

4-Azido-4-ethyltetrahydro-2H-pyran (53-N3)



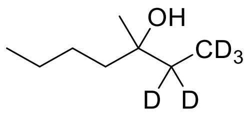
General procedure O was followed using 4-ethyltetrahydro-2H-pyran-4-ol **53-OH** (630 mg, 4.84 mmol) to afford tertiary azide **53-N3** as a pale yellow oil (750 mg, 100%). R_f = 0.16 (10% Et_2O/pentane). IR (film)/cm^{-1} 2958, 2858, 2098 (N_3), 1382, 1257, 1159, 1104, 1020. ^1H NMR (400 MHz, $CDCl_3$) δ 3.81–3.77 (m, 2 H, 2 × OC(*H*)H), 3.70–3.63 (m, 2 H, 2 × OC(H)*H*), 1.69–1.59 (m, 6 H, 3 × CH_2), 0.99 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.6 (C_qN_3), 63.9 (2 × OCH_2), 34.3 (2 × CH_2), 33.1 (CH_2), 7.3 (CH_3). HRMS (APCI) m/z Calcd. for $C_7H_{12}N_3O$ $[M-H]^-$: 154.0975; Found: 154.0973.

4-Ethyltetrahydro-2H-pyran-4-amine (53)



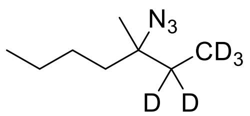
General procedure D was followed using 4-azido-4-ethyltetrahydro-2H-pyran **53-N3** (750 mg, 4.84 mmol) to afford amine **53** as a pale yellow oil (53 mg, 8%). Due to low yield, amine was purified by flash column chromatography (20% MeOH/CH_2Cl_2) not distillation. R_f = 0.18 (20% MeOH/CH_2Cl_2). IR (film)/cm^{-1} 3370 (br, NH_2), 2960, 2938, 2863, 1601, 1462, 1237, 1180, 1107, 1079, 1016. ^1H NMR (400 MHz, $CDCl_3$) δ 3.80–3.68 (m, 4 H, 2 × CH_2), 1.67–1.60 (m, 4 H, CH_2 + NH_2), 1.47 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.40–1.35 (m, 2 H, 2 × C(H)*H*), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.9 (2 × OCH_2), 49.0 (C_qNH_2), 37.8 (2 × CH_2), 35.7 (CH_2), 6.8 (CH_3). HRMS (ES) m/z Calcd. for $C_7H_{16}NO$ $[M+H]^+$: 130.1232; Found: 130.1234.

3-Methylheptan-1,1,1,2,2-d$_5$-3-ol (D5-50-OH)



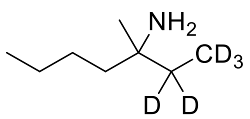
General procedure N was followed using (ethyl-d$_5$)magnesium bromide (6.25 mL, 12.5 mmol, 2.0 M solution in Et_2O, prepared from 1-bromoethane-1,1,2,2,2-d$_5$ (933 µL, 12.5 mmol), magnesium turnings (304 mg, 12.5 mL) in Et_2O (6.25 mL) using standard techniques) and hexan-2-one (1.23 mL, 10.0 mmol). Product was impure after workup (contained aldol by-products) and so the product was further purified by flash column chromatography (silica, 10% Et_2O/pentane) followed by vacuum distillation to afford tertiary alcohol **D5-50-OH** as a colourless oil (512 mg, 38%). R_f = 0.26 (20% Et_2O/pentane). IR (film)/cm^{-1} 3441 (Br, OH), 2957, 2933, 1701, 1465, 1469, 1375, 1144. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46–1.42 (m, 2 H, CH_2), 1.34–1.29 (m, 4 H, 2 × CH_2), 1.15 (s, 3 H, CH_3), 0.92 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.8 (C_qOH), 41.0 (CH_2), 26.4 (CH_3), 26.1 (CH_2), 23.3 (CH_2), 14.1 (CH_3).

3-Azido-3-methylheptane-1,1,1,2,2-d$_5$ (D5-50-N3)



General procedure O was followed using 3-methylheptan-1,1,1,2,2-d$_5$-3-ol **D5-50-OH** (512 mg, 3.79 mmol) to afford tertiary azide **D5-50-N3** as a colourless oil (607 mg, 100%). R_f = 0.10 (40% Et_2O/pentane). IR (film)/cm^{-1} 2960, 2935, 2864, 2093 (N_3), 1254, 1131. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.47 (m, 2 H, CH_2), 1.34–1.30 (m, 4 H, 2 × CH_2), 1.21 (s, 3 H, CH_3), 0.93 (t, *J* = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.4 (C_qN_3), 38.6 (CH_2), 26.1 (CH_2), 23.1 (CH_2), 22.8 (CH_3), 14.0 (CH_3).

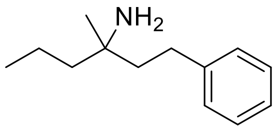
3-Methylheptan-1,1,1,2,2-d$_5$-3-amine (D5-50)



General procedure P was followed using 3-azido-3-methylheptane-1,1,1,2,2-d$_5$ **D5-50-N3** (607 mg, 3.79 mmol) to afford amine **D5-50** as a colourless oil (213 mg, 40%). IR (film)/cm^{-1} 2957, 2929, 2860, 2221, 1395, 1466, 1374 1057. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34–1.18 (m, 8 H, 3 × CH_2 + NH_2), 1.01 (s, 3 H, CH_3), 0.91 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.2 (C_qNH_2), 42.0 (CH_2), 27.5 (CH_3), 26.2 (CH_2), 23.4 (CH_2), 14.1 (CH_3). HRMS (ES) m/z Calcd. for $C_8H_{16}ND_5$ $[M+H]^+$: 135.1910; Found: 135.1906.

*C(sp^3)–H Arylation of Amines (**54**-**69**)*

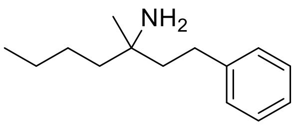
3-Methyl-1-phenylhexan-3-amine (54)



General procedure M was followed using 3-methylhexane-3-amine **49** (35 mg, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford arylated amine **54** as a brown oil (22 mg, 38%). IR (film)/cm^{-1} 2956, 2929, 2870, 1495, 1454, 103. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.21–7.17 (m, 3 H, Ph-H), 2.65–2.61 (m, 2 H, CH_2), 1.68–1.63 (m, 2 H, CH_2), 1.44–1.32 (m, 6 H, 2 × CH_2 + NH_2), 1.12 (s, 3 H, CH_3), 0.95 (t, J = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (Ph-C_q), 128.4 (Ph-C), 128.3 (Ph-C), 125.6 (Ph-C), 51.5 (C_qNH_2), 45.4 (CH_2), 44.9 (CH_2), 30.6 (CH_2), 28.1 (CH_3), 17.2 (CH_2), 14.8 (CH_3). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

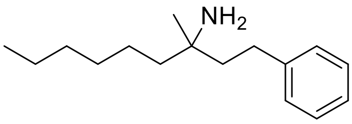
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **54** was afforded as a brown oil (28 mg, 49%), data obtained was identical.

3-Methyl-1-phenylheptan-3-amine (55)



General procedure M was followed using 3-methylheptane-3-amine **50** (39 mg, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford arylated amine **55** as a yellow oil (33 mg, 54%). IR (film)/cm^{-1} 2955, 2928, 2859, 1495, 1454, 1376. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.22–7.16 (m, 3 H, Ph-H), 2.66–2.61 (m, 2 H, CH_2), 1.68–1.64 (m, 2 H, CH_2), 1.44–1.25 (m, 8 H, 3 × CH_2 + NH_2), 1.12 (s, 3 H, CH_3), 0.94 (t, J = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (Ph-C_q), 128.4 (Ph-C), 128.3 (Ph-C), 125.7 (Ph-C), 51.4 (C_qNH_2), 44.8 (CH_2), 42.7 (CH_2), 30.6 (CH_2), 28.1 (CH_3), 26.2 (CH_2), 23.4 (CH_2), 14.1 (CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{14}H_{24}N$ $[M+H]^+$: 206.1909; Found: 206.1919. Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

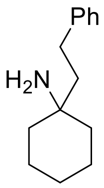
3-Methyl-1-phenylnonan-3-amine (56)



General procedure M was followed using 3-methylnonane-3-amine **51** (47 mg, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford arylated amine **56** as a yellow oil (13 mg, 19%). IR (film)/cm^{-1} 2955, 2927, 2856, 1670, 1454, 1375. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.21–7.17 (m, 3 H, Ph-H), 2.65–2.61 (m, 2 H, CH_2), 1.68–1.63 (m, 2 H, CH_2), 1.44–1.37 (m, 2 H, NH_2), 1.36–1.25 (m, 10 H, 5 × CH_2), 1.12 (s, 3 H, CH_3), 0.92–0.86 (m, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (Ph-C_q), 128.4 (Ph-C), 128.3 (Ph-C), 125.7 (Ph-C), 51.5 (C_qNH_2), 44.8 (CH_2), 42.9 (CH_2), 31.9, (CH_2) 30.6 (CH_2), 30.0 (CH_2), 28.1 (CH_3), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3). Spectroscopic data for this compound (NMR) is consistent with that shown in the literature.[40]

Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **56** was afforded as a yellow oil (16 mg, 23%), data obtained was identical.

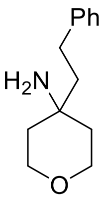
1-Phenethylcyclohexan-1-amine (57)



General procedure M was followed using 1-ethylcyclohexan-1-amine **52** (38 mg, 0.30 mmol) to afford arylated amine **57** as a brown oil (19 mg, 31%). IR (film)/cm^{-1} 2923, 2854, 1496, 1452, 1058, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, Ph-H), 7.23–7.17 (m, 3 H, Ph-H), 2.68–2.64 (m, 2 H, CH_2), 1.70–1.66 (m, 2 H, CH_2), 1.58–1.36 (m, 12 H, 5 × CH_2 + NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (Ph-C_q), 128.4 (4 × Ph-C), 125.6 (Ph-C), 50.6 (C_q-NH_2), 38.8 (2 × CH_2), 29.5 (CH_2), 26.0 (CH_2), 22.3 (3 × CH_2). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[97]

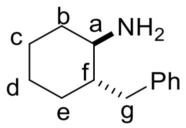
Using CF_3-acetal **46l** (12 mg, 0.045 mmol), amine **57** was afforded as a brown oil (25 mg, 41%), data obtained was identical.

4-Phenethyltetrahydro-2H-pyran-4-amine (58)



General procedure M was followed using 4-ethyltetrahydro-2H-pyran-4-amine **53** (39 mg, 0.30 mmol) to afford arylated amine **58** as a brown oil (24 mg, 39%). IR (film)/cm^{-1} 2935, 2861, 1602, 1454, 1236, 1104, 1019, 1032. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H, Ph-H), 7.22–7.18 (m, 3 H, Ph-H), 3.82–3.71 (m, 4 H, 2 × OCH_2), 2.71–2.66 (m, 2 H, CH_2), 1.76–1.68 (m, 4 H, CH_2 + 2 × C(*H*)H), 1.46–1.41 (m, 4 H, 2 × C(H)*H* + NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (Ph-C_q), 128.5 (Ph-C), 128.3 (Ph-C), 125.8 (Ph-C), 64.0 (2 × OCH_2), 48.6 (C_q-NH_2), 46.0 (CH_2), 38.7 (2 × CH_2), 29.1 (CH_2). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{13}H_{20}NO$ [M+H]$^+$: 206.1545; Found: 206.1547.

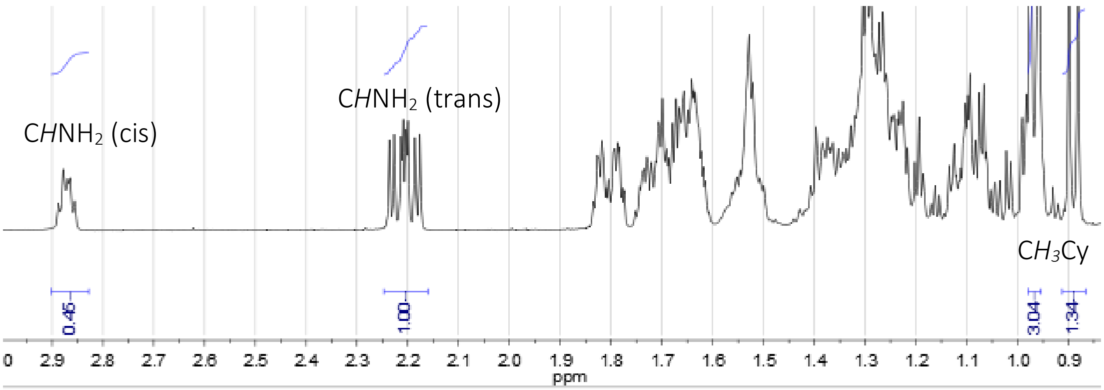
***trans*-2-Benzylcyclohexan-1-amine (60)**



General procedure M was followed using *cis/trans*-2-methylcyclohexan-1-amine **59** (40 µL, 0.30 mmol, approx 3:7 *cis*:*trans*) and iodobenzene (101 µL, 0.90 mmol) to afford arylated *trans*-amine **60** as a yellow oil (19 mg, 33%). IR (film)/cm^{-1} 3324, 2920, 2852, 1606, 1582, 1551, 1493, 1445, 1284. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2 H, Ph-H), 7.21–7.16 (m, 3 H, Ph-H), 3.17 (dd, *J* = 13.2, 3.8 Hz, 1 H, PhCH^g(H)), 2.41 (td, *J* = 10.2, 4.0 Hz, 1 H, CH^aNH$_2$), 2.24 (dd, *J* = 13.2, 9.8 Hz, 1 H, PhCH(H^g)), 1.89–1.85 (m, 1 H, CH^c(H)), 1.72–1.66 (m, 1 H, CH^b(H)), 1.63–1.54 (m, 2 H, CH^e(H) + CH^d(H)), 1.45–1.03 (m, 6 H, CH^f + CH(H^b) + CH(H^c) + CH(H^d) + NH$_2$), 0.94–0.83 (m, 1 H, CH(H^e)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (Ph-C$_q$), 129.3 (Ph-C), 128.1 (Ph-C), 125.6 (Ph-C), 54.9 (C^{a}HNH$_2$), 47.6 (C^{f}H), 39.5 (PhC^{g}H$_2$), 36.8 (C^{b}H$_2$), 30.4 (C^{e}H$_2$), 25.8 (CH$_2$), 25.5 (CH$_2$). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{13}H_{20}N$ [M+H]$^+$: 190.1596; Found: 190.1599.

H^a exhibits 2 large *trans* diaxial H–H splitting (10 Hz, b_{ax} and f_{ax}) and one small cis axial-equatorial splitting (4.0 Hz, b_{eq}) consistent with proposed *trans* stereochemistry with a di-equatorial conformation of the substituents.

Isomeric ratio of the starting material 59:



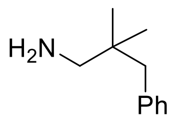
cis/trans Assigned by chemical shift, *J* values and literature NMR for a *trans*-enantiomer.[173]

Calculated ratio: *cis*:*trans* 3:7

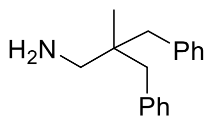
General procedure Q (to avoid alpha oxidation): AgTFA (99 mg, 0.45 mmol), $Pd(OPiv)_2$ (9.3 mg, 0.03 mmol, 10 mol%), iodobenzene (3.00 equiv), H_2O (27 µL, 1.50 mmol), amine (0.30 mmol), (2,2-dimethoxyethoxy)benzene **46d** (7.6 µL, 0.045 mmol), AcOH (1.25 mL) and HFIP (0.25 mL) were combined in a microwave vial. The vial was sealed and the reaction was stirred at 110 °C for 3 h. The reaction was allowed to cool to rt and filtered through a bed of Celite which was washed with Et_2O. The product was extracted from the organic phase into 1 M aqueous HCl solution. The combined aqueous extracts were basified with saturated aqueous sodium hydroxide solution, and the free amine extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the title amines.

2,2-Dimethyl-3-phenylpropan-1-amine (62-mono) and 2-benzyl-2-methyl-3-phenylpropan-1-amine (62-di)

General procedure Q was followed using 2,2-dimethylpropan-1-amine (35 µL, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford a (3.55:1) mixture of monoarylated amine **62-mono** (11 mg, 22%) and diarylated amine **62-di** (6 mg, 8%) as a brown oil. IR (film)/cm^{-1} 3027, 2955, 1484, 1452, 1369. ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 138.7, 130.7, 130.5, 127.8, 127.7, 125.9, 125.8, 52.6, 48.5, 45.7, 44.3, 39.6, 35.9, 27.2, 24.5, 21.9.



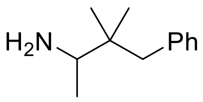
2,2-Dimethyl-3-phenylpropan-1-amine (62-mono): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2 H, Ph-H), 7.27–7.19 (m, 1 H, Ph-H), 7.18–7.11 (m, 2 H, Ph-H), 2.54 (s, 2 H, CH_2), 2.49 (s, 2 H, CH_2), 0.86 (s, 6 H, $C(CH_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[174]



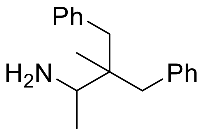
2-Benzyl-2-methyl-3-phenylpropan-1-amine (62-di): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.27 (m, 4 H, Ph-H), 7.27–7.19 (m, 2 H, Ph-H), 7.18–7.11 (m, 4 H, Ph-H), 2.71 (d, *J* = 13.1 Hz, 2 H, 2 × C*H*(H)), 2.60 (d, *J* = 13.2 Hz, 2 H, 2 × CH(*H*)), 2.45 (s, 2 H, CH_2), 0.79 (s, 3 H, CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{17}H_{22}N$ $[M+H]^+$: 240.1752; Found: 240.1745.

3,3-Dimethyl-4-phenylbutan-2-amine (63-mono) and 3-benzyl-3-methyl-4-phenylbutan-2-amine (63-di)

General procedure Q was followed using 3,3-dimethylbutan-2-amine (40 μL, 0.30 mmol) and iodobenzene (101 μL, 0.90 mmol) to afford a (1.25:1) mixture of monoarylated amine **63-mono** (10 mg, 19%) and diarylated amine **63-di** (11 mg, 14%) as a yellow oil. IR (film)/cm^{-1} 3026, 2962, 2872, 1601, 1494, 1452, 1375, 1031. ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 138.9, 130.9, 130.8, 130.7, 127.8, 127.7, 125.9, 125.8, 54.4, 50.9, 44.6, 41.6, 41.5, 41.3, 38.1, 23.1, 22.5, 22.2, 18.5.



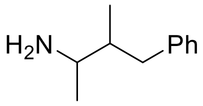
3,3-Dimethyl-4-phenylbutan-2-amine (63-mono): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2 H, Ph-H), 7.26–7.19 (m, 1 H, Ph-H), 7.19–7.14 (m, 2 H, Ph-H), 2.79 (q, *J* = 6.6 Hz, 1 H, CH), 2.70 (s, 2 H, CH_2), 1.09 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.85 (s, 3 H, CH_3). 0.84 (s, 3 H, CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596; Found: 178.1588.



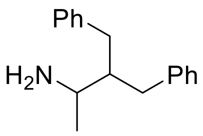
3-Benzyl-3-methyl-4-phenylbutan-2-amine (63-di): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 4 H, Ph-H), 7.26–7.19 (m, 2 H, Ph-H), 7.19–7.14 (m, 4 H, Ph-H), 2.90 (d, *J* = 13.2 Hz, 1 H, C*H*(H)), 2.72 (q, *J* = 6.6 Hz, 1 H, CH), 2.63 (d, *J* = 12.9 Hz, 1 H, C*H*(H)), 2.53 (d, *J* = 12.9 Hz, 1 H, CH(*H*)), 2.44 (d, *J* = 13.1 Hz, 1 H CH(*H*)), 1.15 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.82 (s, 3 H, CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{18}H_{24}N$ $[M+H]^+$: 254.1909; Found: 254.1914.

3-Methyl-4-phenylbutan-2-amine (64-mono) and 3-benzyl-4-phenylbutan-2-amine (64-di)

General procedure Q was followed using 3-methylbutan-2-amine (35 µL, 0.30 mmol) and iodobenzene (101 µL, 0.90 mmol) to afford a (2:1) mixture of monoarylated amine **64-mono** (11 mg, 22%) and diarylated amine **64-di** (8 mg, 11%) as a brown oil. IR (film)/cm^{-1} 3025, 2962, 2926, 1669, 1600, 1494, 1452, 1374, 1029. ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 129.1, 129.0, 128.3, 128.2, 125.8, 125.7, 50.5, 46.7, 42.4, 39.7, 35.7, 20.1, 19.5, 14.4.



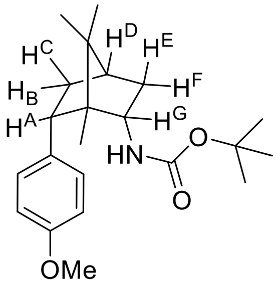
3-Methyl-4-phenylbutan-2-amine (64-mono): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2 H, Ph-H), 7.21–7.12 (m, 3 H, Ph-H), 2.88 (dt, *J* = 12.7, 6.4 Hz, 1 H, C*H*NH_2), 2.80 (dd, *J* = 13.3, 5.1 Hz, 1 H, PhC(*H*)H), 2.33 (dd, *J* = 13.3, 9.5 Hz, 1 H, PhC(H)*H*), 1.76–1.68 (m, 1 H, C*H*CH_3), 1.09 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.83 (d, *J* = 6.8 Hz, 3 H, CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{11}H_{18}N$ [M+H]$^+$: 164.1439; Found: 164.1438.



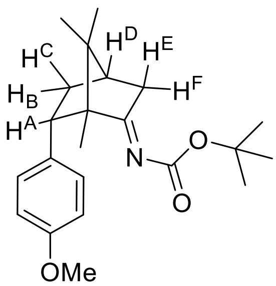
3-Benzyl-4-phenylbutan-2-amine (64-di): δ 7.35–7.25 (m, 4 H, Ph-H), 7.21–7.12 (m, 6 H, Ph-H), 2.99–2.92 (m, 1 H, C*H*NH_2), 2.77–2.72 (m, 1 H, PhC(*H*)H), 2.63 (dd, *J* = 13.8, 7.0 Hz, 1 H, PhC(*H*)H), 2.55 (dd, *J* = 13.8, 7.5 Hz, 1 H, PhC(H)*H*), 2.48 (dd, *J* = 13.7, 7.3 Hz, 1 H, PhC(H)*H*), 2.03–1.96 (m, 1 H, CH), 1.11 (d, *J* = 6.4 Hz, 3 H, CH_3). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{17}H_{22}N$ [M+H]$^+$: 240.1752; Found: 240.1750.

***tert*-Butyl ((*1S,2S,4R,6S*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)carbamate (66) and *tert*-butyl ((*1S*,*4R*,*6S*,*E*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)carbamate (67)**

AgTFA (132 mg, 0.60 mmol), $Pd(OPiv)_2$ (9.3 mg, 0.03 mmol, 10 mol%), 4-iodoanisole (210 mg, 0.90 mmol), H_2O (27 µL, 1.50 mmol), (R)-(+)-bornylamine (46 mg, 0.30 mmol), (2,2-dimethoxyethoxy)benzene (7.6 µL, 0.045 mmol), AcOH (1.25 mL) and HFIP (0.25 mL) were combined in a microwave vial. The vial was sealed, and the reaction was stirred at 110 °C for 18 h. The reaction was allowed to cool to room temperature, filtered through a bed of Celite which was washed with Et_2O. The product was extracted from the organic phase into 1 M aqueous HCl solution. The combined aqueous extracts were basified with saturated aqueous sodium hydroxide solution, and the free amine extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent removed under reduced pressure. To the crude material was added di-*tert*-butyl dicarbonate (1 equiv), triethylamine (2 equiv) and CH_2Cl_2 (0.3 M) and the reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2, and saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts dried (Na_2SO_4), filtered and solvent removed under reduced pressure. The mixture of Boc protected products were purified by column chromatography (silica, 5% EtOAc/pentane) to afford arylated amine **66** as an off-white solid (6 mg, 6%) followed by arylated imine **67** as a white solid (6 mg, 6%).

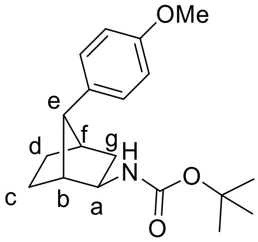


***tert*-Butyl ((*1S,2S,4R,6S*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)carbamate (66):** R_f = 0.44 (10% (EtOAc/Pentane). IR (film)/cm^{-1} 3431, 2955, 2096, 1719, 1688, 1511, 1451, 1376, 1240, 1164, 1100, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.9 Hz, 2 H, Ar-H), 6.91 (d, *J* = 8.9 Hz, 2 H, Ar-H), 4.17 (d, *J* = 9.6 Hz, 1 H, NH), 3.97–3.90 (m, 1 H, H^G), 3.82 (s, 3 H, OCH_3), 3.22 (dd, *J* = 12.1, 5.4 Hz, 1 H, H^A), 2.45–2.37 (m, 1 H, H^E), 2.24–2.16 (m, 1 H, H^C)), 1.92 (dd, *J* = 13.2, 5.8 Hz, 1 H, H^B), 1.84 (t, *J* = 4.6 Hz, 1 H, H^D), 1.24 (s, 9 H, $C(CH_3)_3$), 1.13–1.04 (m, 1 H, H^F), 1.04 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q), 155.8 (C=O), 134.3 (Ar-C_q), 129.1 (2 × Ar-C), 114.0 (2 × Ar-C), 78.0 (*C*$O(CH_3)_3$), 55.6 (CH^G), 55.2 (OCH_3), 53.9 (*C*(CH_3)), 50.5 (*C*$(CH_3)_2$), 46.6 (CH^A), 43.5 (CH^D), 37.0 ($CH^{EF}{}_2$), 32.3 ($CH^{BC}{}_2$), 28.1 (C(*C*$H_3)_3$), 20.1 (CH_3), 19.6 (CH_3), 13.6 (C(*C*H_3)). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{22}H_{34}NO_3$ $[M+H]^+$: 360.2539; Found: 360.2550.



***tert*-Butyl ((*1S,4R,6S,E*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)carbamate (67):** R_f = 0.35 (10% (EtOAc/Pentane). IR (film)/cm^{-1} 3431, 2955, 2096, 1719, 1688, 1511, 1451, 1376, 1240, 1164, 1100, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98–6.96 (m, 2 H, Ar-H), 6.82–6.80 (m, 2 H, Ar-H), 3.78 (s, 3 H, OCH_3), 3.17 (dd, *J* = 11.6, 5.5 Hz, 1 H, H^A), 2.70–2.63 (m, 1 H, H^E), 2.50–2.42 (m, 1 H, H^C), 2.21 (d, *J* = 17.8 Hz, 1 H, H^F), 2.08 (t, *J* = 4.5 Hz, 1 H, H^D), 1.57–1.55 (m, 1 H, H^B), 1.53 (s, 9 H, $C(CH_3)_3$), 1.13 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 0.83 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2 (C=N), 162.2 (C=O), 158.3 (Ar-C_q), 132.2 (Ar-C_q), 130.2 (2 × Ar-C), 113.3 (2 × Ar-C), 81.2 (*C*$O(CH_3)_3$), 59.5 (*C*(CH_3)), 55.1 (OCH_3), 50.0 (*C*$(CH_3)_2$), 48.7 (CH^A), 42.2 (CH^D), 37.2 ($CH^{EF}{}_2$), 34.9 ($CH^{BC}{}_2$), 28.1 (C(*C*$H_3)_3$), 20.3 (CH_3), 19.0 (CH_3), 9.5 (C(*C*H_3)). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{22}H_{32}NO_3$ $[M+H]^+$: 358.2382; Found: 358.2399.

***tert*-Butyl ((*1R,2R,4R,7S*)-7-(4-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl)carbamate (69)**

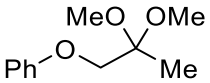


AgTFA (132 mg, 0.60 mmol), $Pd(OPiv)_2$ (9.3 mg, 0.03 mmol, 10 mol%), 4-iodoanisole (210 mg, 0.90 mmol), H_2O (27 µL, 1.50 mmol), exo-2-aminonorbornane **68** (36 µL, 0.30 mmol), (2,2-dimethoxyethoxy)benzene (7.6 µL, 0.045 mmol), AcOH (1.25 mL) and HFIP (0.25 mL) were combined in a microwave vial. The vial was sealed, and the reaction was stirred at 110 °C for 18 h. The reaction was allowed to cool to room temperature, filtered through a bed of Celite which was washed with Et_2O. The product was extracted from the organic phase into 1 M aqueous HCl solution. The combined aqueous extracts were basified with saturated aqueous sodium hydroxide solution, and the free amine extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent removed under reduced pressure. To the crude material was added di-*tert*-butyl dicarbonate (1 equiv), triethylamine (2 equiv) and CH_2Cl_2 (0.3 M) and the reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2, and saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts dried (Na_2SO_4), filtered and solvent removed under reduced pressure. The mixture of Boc protected products were purified by column chromatography (silica, 5% EtOAc/pentane) to afford arylated amine **69** as a pale yellow solid (3 mg, 3%). R_f = 0.27 (10% (EtOAc/Pentane). IR (film)/cm^{-1} 3442, 2969, 2954, 1700 (s, C=O), 1610, 1495, 1365, 1346, 1243, 1229, 1160, 1070, 1034, 1020. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 2 H, Ar-H), 6.87–6.85 (m, 2 H, Ar-H), 3.81 (s, 3 H, OCH_3), 3.63–3.58 (m, 2 H, NH + CH^aNH), 2.91 (s, 1 H, CH^e), 2.71–2.69 (m, 2H, 2 × CH^{f+b}), 1.88–1.83 (m, 1 H, CH^g(H)), 1.79–1.65 (m, 2 H, 2 × C$H^{d/c}$(H)), 1.45–1.39 (m, 2 H, 2 × CH($H^{g + d/c}$)), 1.35 (s, 9 H, $C(CH_3)_3$), 1.31–1.22 (m, 1 H, CH($H^{d/c}$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (Ar-C_q), 155.1 (C=O), 132.3 (Ar-C_q), 129.2 (2 × Ar-C), 113.8 (2 × Ar-C), 78.6 (*C*O$(CH_3)_3$) 55.3 (OCH_3), 54.5 (C^aH), 51.8 (C^eH), 46.3 (C^bH), 37.9 (C^gH_2), 37.8 (C^fH), 28.5 ($C^{d/c}H_2$), 28.4 (C$(CH_3)_3$), 28.0 ($C^{d/c}H_2$). HRMS (TOF-ES$^+$) m/z Calcd. for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2069; Found: 318.2079.

*Preparation of additives for structural comparison of the optimal directing group **70-73, 76**)*

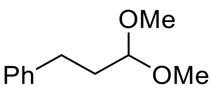
Additives **74** and **75** were commercially available.

(2,2-Dimethoxypropoxy)benzene (70)



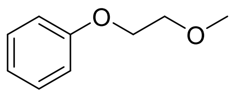
Trimethoxymethane (164 µL, 1.50 mmol) was added to a stirred solution of 1-phenoxypropan-2-one (150 µL, 1.00 mmol) and 4-methylbenzenesulfonic acid monohydrate (1.9 mg, 0.01 mmol) in MeOH (10 mL) and the reaction was heated to 60 °C overnight. The reaction was allowed to cool to rt, $MgSO_4$ was added, the mixture was filtered and solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/Pentane) afforded acetal **70** as a colourless oil (196 mg, 100%) R_f 0.29 (10% Et_2O/pentane). IR (film)/cm^{-1} 2944, 2831, 1600, 1588, 1496, 1475, 1374, 1235, 1119, 1083, 1060. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2 H, Ph-H), 7.00–6.95 (m, 3 H, Ph-H), 3.92 (s, 2 H, CH_2), 3.29 (s, 6 H, $CH(OC\textit{H}_3)_2$), 1.49 (s, 3 H CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ph-C_q), 129.4 (Ph-C), 121.1 (Ph-C), 114.7 (Ph-C), 99.9 ($\textit{C}H(OCH_3)_2$), 68.7 (CH_2), 48.4 (2 × OCH_3), 20.3 (CH_3). HRMS (EI$^+$) m/z Calcd. for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099; Found: 196.1108.

(3,3-Dimethoxypropyl)benzene (71)



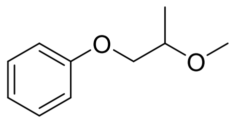
4-Methylbenzenesulfonic acid monohydrate (380 mg, 0.20 mmol) in MeOH (2.0 mL) was added to a stirred solution of 3-phenylpropanal (2.60 mL, 20.0 mmol) and trimethoxymethane (3.30 mL, 30.0 mmol) in MeOH (4.0 mL) containing a small amount of 3 Å molecular sieves and the reaction was stirred at 25 °C for 2 h. The reaction was diluted with Et_2O, saturated aqueous sodium bicarbonate was added and the product extracted with Et_2O, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Vacuum distillation afforded acetal **71** as a colourless oil (468 mg, 13%) R_f 0.32 (10% Et_2O/pentane). IR (film)/cm^{-1} 2951, 2829, 1496, 1454, 1191, 1171, 1123, 1051. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, Ph-H), 7.22–7.18 (m, 3 H, Ph-H), 4.38 (t, J = 5.7 Hz, 1 H, CH), 3.35 (s, 6 H, $CH(OC\textit{H}_3)_2$), 2.71–2.67 (m, 2 H, CH_2), 1.97–1.91 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (Ph-C_q), 128.4 (Ph-C), 125.9 (Ph-C), 103.7 ($\textit{C}H(OCH_3)_2$), 52.7 ($CH(O\textit{C}H_3)_2$), 34.1 (CH_2), 30.9 (CH_2). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[175]

(2-Methoxyethoxy)benzene (72)



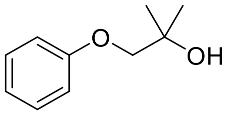
Sodium hydride (48 mg, 1.20 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 2-phenoxyethan-1-ol (251 µL, 2.00 mmol) in THF (6.7 mL) at 0 °C and the reaction was stirred for 15 minutes. Iodomethane (131 µL, 2.10 mmol) was added and the reaction was stirred at rt overnight. Water was added and the product extracted with Et_2O, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/Pentane) afforded the methyl ether **72** as a colourless oil (158 mg, 32%). R_f 0.21 (10% Et_2O/pentane). IR (film)/cm^{-1} 2926, 2878, 2819, 1598, 1587, 1495, 1453, 1243, 1126, 1060, 1033. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2 H, Ph-H), 6.98–6.92 (m, 3 H, Ph-H), 4.14–4.12 (m, 2 H, CH_2), 3.77–3.75 (m, 2 H, CH_2), 3.46 (s, 3 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ph-C_q), 129.4 (Ph-C), 120.9 (Ph-C), 114.6 (Ph-C), 71.1 (OCH_2), 67.1 (OCH_2), 59.2 (OCH_3). Spectroscopic data for this compound (^{1}H NMR, IR) is consistent with that shown in the literature.[176]

(2-Methoxypropoxy)benzene (73)



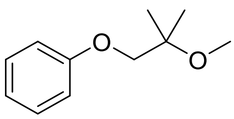
Sodium hydride (40 mg, 1.00 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 2-methyl-1-phenoxypropan-2-ol (83 mg, 0.50 mmol) in THF (1.0 mL) at 0 °C and the reaction was allowed to warm to rt and stirred for 1 h. Iodomethane (93 µL, 1.5 mmol) was added and the reaction was stirred at rt overnight. Water was added and the product extracted with Et_2O, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/Pentane) afforded ether **73** as a colourless oil (66 mg, 79%). R_f 0.32 (20% Et_2O/pentane). IR (film)/cm^{-1} 2976, 2930, 2877, 2824, 1599, 1587, 1495, 1455, 1290, 1242, 1079, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H, Ph-H), 6.98–6.91 (m, 3 H, Ph-H), 4.00 (dd, J = 9.7, 5.8 Hz, 1 H, C(*H*)H), 3.90 (dd, J = 9.7, 4.5 Hz, 1 H, C(H)*H*), 3.77–3.70 (m, 1 H, CH), 3.47 (s, 3 H, OCH_3), 1.29 (d, J = 6.3 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (Ph-C_q), 129.4 (Ph-C), 120.8 (Ph-C), 114.6 (Ph-C), 75.3 (CH), 71.3 (CH_2), 57.0 (OCH_3), 16.7 (CH_3). HRMS (ESI) m/z Calcd. for $C_{10}H_{15}O_2$ $[M+H]^+$: 167.1072; Found: 167.1064.

2-Methyl-1-phenoxypropan-2-ol (76-OH)



2,2-Dimethyloxirane (266 µL, 3.00 mmol), phenol (94 mg, 1.00 mmol), K_2CO_3 (276 mg, 2.00 mmol) and DMF (1 mL) were combined in a microwave vial, sealed and heated to 150 °C in a microwave reactor for 30 minutes. Water was added and the product extracted with EtOAc, dried ($MgSO_4$), filtered and solvent removed under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded alcohol **76-OH** as a colourless oil (174 mg, 87%). R_f 0.26 (20% Et_2O/pentane). IR (film)/cm^{-1} 3400, 2974, 2930, 2871, 1599, 1587, 1495, 1456, 1230, 1170, 1044. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2 H, Ph-H), 7.00–6.93 (m, 3 H, Ph-H), 3.81 (s, 2 H, CH_2), 2.22 (bs, 1 H, OH), 1.36 (s, 6 H, $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ph-C_q), 129.5 (Ph-C), 121.1 (PhC), 114.6 (Ph-C), 75.9 (CH_2), 70.1 ($\textit{C}(CH_3)_2$), 26.1 ($C(\textit{C}H_3)_2$). Spectroscopic data for this compound (NMR, IR) is consistent with that shown in the literature.[177]

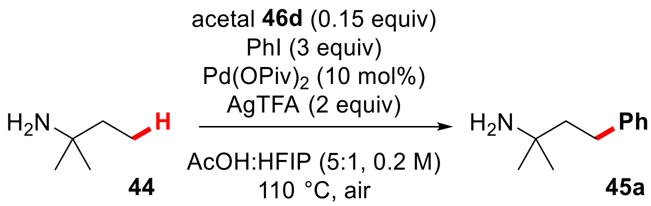
(2-Methoxy-2-methylpropoxy)benzene (76)



Sodium hydride (40 mg, 1.00 mmol as 60% dispersion in mineral oil) was added to a stirred solution of 2-methyl-1-phenoxypropan-2-ol **76-OH** (83 mg, 0.50 mmol) in THF (1.0 mL) at 0 °C and the reaction was allowed to warm to rt and stirred for 1 h. Iodomethane (93 µL, 1.5 mmol) was added and the reaction was stirred at rt overnight. Water was added and the product extracted with Et_2O, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, 10% Et_2O/Pentane) afforded ether **76** as a colourless oil (76 mg, 84%). R_f 0.32 (20% Et_2O/pentane). IR (film)/cm^{-1} 2975, 2936, 2829, 1599, 1587, 1496, 1471, 1364, 1238, 1184, 1170, 1080, 1048. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H, Ph-H), 6.98–6.93 (m, 3 H, Ph-H), 3.84 (s, 2 H, CH_2), 3.32 (s, 3 H, OCH_3), 1.32 (s, 6 H. $C(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (Ph-C_q), 129.4 (Ph-C), 120.8 (Ph-C), 114.6 (Ph-C), 74.3 ($\textit{C}_q(CH_3)_2$), 73.6 (OCH_2), 49.9 (OCH_3), 22.4 ($C(\textit{C}H_3)_2$). HRMS (EI^+) m/z Calcd. for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150; Found: 180.1157.

5.3 Procedures and raw data for kinetic experiments

General procedure for kinetic experiments



Each data point shown represents a discrete, worked up reaction following the procedure outlined below.

AgTFA (66 mg, 0.30 mmol), $Pd(OPiv)_2$ (4.7 mg, 0.015 mmol, 10 mol%), iodobenzene (50.5 µL, 0.45 mmol), H_2O (13.5 µL, 0.75 mmol), *tert*-amylamine **44** (17.5 µL, 0.15 mmol), (2,2-dimethoxyethoxy)benzene **46d** (3.8 µL, 0.0225 mmol), AcOH (0.625 mL) and HFIP (0.125 mL) were combined in a microwave vial. The vial was sealed, and the reaction was stirred at 110 °C for 18 h. The reaction was allowed to cool to room temperature, was diluted with CH_2Cl_2 and filtered through a bed of Celite which was then washed with CH_2Cl_2. The solvent was removed under reduced pressure and 10–20 mg of accurately weighed 1,3,5-trimethoxybenzene was added, the residue was fully dissolved in $CDCl_3$ and the yield of the arylated product (**2a**) was calculated by ^{1}H NMR by comparison to the internal standard.

Concentrations were calculated given the total volume of liquids in parent reaction: 0.8218 mL, changes in this value between experiments were deemed negligible.

Raw data for kinetic experiments

P = arylated product **45a**; RSM = recovered starting material, *tert*-amylamine **44**

time/h	[RSM]/ M	[P]/M
0.25	0.146	0.013
0.5	0.128	0.035
1	0.078	0.073
2	0.062	0.089
3	0.040	0.095
6	0.029	0.104
12	0.031	0.091
18	0.033	0.100
24	0.042	0.093

Table 5.1: Raw data for control reaction. (Figure 3.21)

	[P] for catalyst loading/M		
time/h	**5 mol%**	**7.5 mol%**	**15 mol%**
0.25	0.005476	0.010952	0.021903
0.50	0.020078	0.021903	0.062059
1	0.040156	0.051107	0.091263
2	0.071185	0.07301	0.10404
3	0.080312	0.083962	0.096739

Table 5.2: Raw data for different catalyst concentrations. (Figure 3.22)

	t[cat]^x											
	for catalyst order = 0.5 (t[cat]$^{0.5}$)				for catalyst order = 1.0 (t[cat]^1)				for catalyst order = 2.0 (t[cat]^2)			
time/h	**5 mol%**	**7.5 mol%**	**10 mol%**	**15 mol%**	**5 mol%**	**7.5 mol%**	**10 mol%**	**15 mol%**	**5 mol%**	**7.5 mol%**	**10 mol%**	**15 mol%**
0.25	0.0239	0.0293	0.0338	0.0414	2.28E-03	6.85E-03	4.56E-03	3.42E-03	2.08E-05	4.68E-05	8.33E-05	1.87E-04
0.50	0.0478	0.0585	0.0676	0.0827	4.56E-03	1.37E-02	9.13E-03	6.85E-03	4.16E-05	9.37E-05	1.67E-04	3.75E-04
1	0.0955	0.1170	0.1351	0.1655	9.13E-03	2.74E-02	1.83E-02	1.37E-02	8.33E-05	1.87E-04	3.33E-04	7.50E-04
2	0.1911	0.2340	0.2702	0.3309	1.83E-02	5.48E-02	3.65E-02	2.74E-02	1.67E-04	3.75E-04	6.66E-04	1.50E-03
3	0.2866	0.3510	0.4053	0.4964	2.74E-02	8.21E-02	5.48E-02	4.11E-02	2.50E-04	5.62E-04	1.00E-03	2.25E-03

Table 5.3: Normalised time data different catalyst concentrations at orders of 0.5, 1.0 and 2. (Figure 3.23)

	[P] for acetal loading/M		
time/h	none	5 mol%	25 mol%
0.25		0.013	0.013
0.50	0.007	0.040	0.046
1	0.022	0.069	0.080
2	0.037	0.093	0.099
3	0.047	0.102	0.102
6	0.060	0.095	0.102

time (h)	[P]/M for CF_3-Acetal 46l	[P]/M for di-CF_3-Acetal 46m
0.25	0.011	
0.5	0.031	0.013
0.75	0.053	
1	0.078	0.020
2	0.089	0.057
3	0.111	0.058
6		0.073

Table 5.4: Raw data for different acetal loadings. (Figure 3.24) Right: **Table 5.5:** Raw data for rate of CF_3 acetal 4**6l** and di-CF3 acetal **46m** promoted arylation. (Figure 3.25)

	[P] for different excess experiments/M					
time/h	B	B2	C	C2	D	D2
0.25	0.022	0.012	0.018	0.011	0.015	0.011
0.50	0.031	0.034	0.031	0.029	0.038	0.033
0.75	0.048	0.045	0.055	0.038	0.046	0.049
1	0.062	0.054	0.062	0.053	0.058	0.053
2	0.083	0.059	0.082	0.077	0.075	0.051
3	0.081	0.057	0.091	0.080	0.077	0.053

Table 5.6: Raw data for different excess experiments. (Figures 3.27, 3.28 and 3.30)

Time/ h	[P] 4-OMe	[P] 4-Cl
0.25	0.011	0.009
0.5	0.035	0.031
0.75	0.053	0.047
1	0.069	0.062
2	0.077	0.082

Table 5.7: Raw data for rate amine arylation with different aryl iodides. (Figure 3.29)

		[P]/M			
time/ h	**adjusted time/h**	**Same excess t = 1 h**	→	**Same excess t = 1 h [P] adjusted**	**same excess t = 1 h + product 45a**
0.25	**1.25**	0.011		0.084	0.078
0.5	**1.5**	0.033		0.106	0.075
1	**2**	0.048		0.121	0.088
2	**3**	0.065		0.138	0.093
3	**4**	0.072		0.145	0.104

Table 5.8: Raw data for same excess experiments, for [P] adjustment, a value of 0.073 M of product **45a** was added to each observed value. Where product was added, 0.073 M of product **45a** was added to each reaction with all other reagents (for each point), which is included in this value. (Figure 3.31)

Time/ h	[P] 4-OMe	[P] 4-Cl
0	0	0
0.25	0.018	0.007
0.5	0.040	0.013
1	0.077	0.037
2	0.084	0.042
3	0.082	0.046

Table 5.9: Raw data for KIE study.

5. References

1 H. J. H. Fenton, *J. Chem. Soc., Trans.*, 1894, **65**, 899–910.

2 M. S. Kharasch and H. S. Isbell, *J. Am. Chem. Soc.*, 1931, **53**, 3053–3059.

3 A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879–2932.

4 R. G. Bergman, *Nature*, 2007, **446**, 391–393.

5 S. Rousseaux, S. I. Gorelsky, B. K. W. Chung and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 10692–10705.

6 J. R. Clark, K. Feng, A. Sookezian and M. C. White, *Nat. Chem.*, 2018, **10**, 583–591.

7 W. N. Palmer, J. V. Obligacion, I. Pappas and P. J. Chirik, *J. Am. Chem. Soc.*, 2016, **138**, 766–769.

8 M. C. White, *Science*, 2012, **335**, 807–809.

9 D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749–823.

10 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295.

11 G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11726–11743.

12 D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238.

13 B. J. Li, S. D. Yang and Z.-J. Shi, *Synlett*, 2008, 949–957.

14 J. Yang, *Org. Biomol. Chem.*, 2015, **13**, 1930–1941.

15 S. De Sarkar, W. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1461–1479.

16 R. Das, G. S. Kumar and M. Kapur, *Eur. J. Org. Chem.*, 2017, 5439–5459.

17 D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118–1126.

18 P. Wang, M. E. Farmer, X. Huo, P. Jain, P. Shen, M. Ishoey, J. E. Bradner, S. R. Wisniewski, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 9269–9276.

19 X. Hu, J. Liu, L. Wang, F. Huang, C.-Z. Sun and D.-Z. Chen, *Org. Chem. Front.*, 2018, **5**, 1670–1678.

20 D. Shabashov and O. Daugulis, *Org. Lett.*, 2005, **7**, 3657–3659.

21 L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542–9543.

22 R.-Y. Zhu, L.-Y. Liu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 12394–12397.

23 B. D. Dangel, K. Godula, S. W. Youn, B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2002, **124**, 11856–11857.

24 V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155.

25 D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965–3972.

26 M. Corbet and F. De Campo, *Angew. Chem. Int. Ed.*, 2013, **52**, 9896–9898.

27 Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898–901.

28 D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965–3972.

29 B. Gopalakrishnan, S. A. Babu and R. Padmavathi, *Tetrahedron*, 2015, **71**, 8333–8349.

30 J. Roane and O. Daugulis, *J. Am. Chem. Soc.*, 2016, **138**, 4601–4607.

31 Z. Liu, Y. Wang, Z. Wang, T. Zeng, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 11261–11270.

32 M. Berger, R. Chauhan, C. A. B. Rodrigues and N. Maulide, *Chem. Eur. J.*, 2016, **22**, 16805–16808.

33 G. He, S.-Y. Zhang, W. A. Nack, Q. Li and G. Chen, *Angew. Chem. Int. Ed.*, 2013, **52**, 11124–11128.

34 N. Rodríguez, J. a. Romero-Revilla, M. Á. Fernández-Ibáñez and J. C. Carretero, *Chem. Sci.*, 2013, **4**, 175–179.

35 Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2013, **52**, 13588–13592.

36 M. Fan and D. Ma, *Angew. Chem. Int. Ed.*, 2013, **52**, 12152–12155.

37 J. Peng, C. Chen and C. Xi, *Chem. Sci.*, 2016, **7**, 1383–1387.

38 Y. Xu and G. Dong, *Chem. Sci.*, 2018, **9**, 1424–1432.

39 D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308.

40 M. Kapoor, D. Liu and M. C. Young, *J. Am. Chem. Soc.*, 2018, **140**, 6818–6822.

41 R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, *Angew. Chem. Int. Ed.*, 2003, **42**, 112–114.

42 R. B. Bedford and M. E. Limmert, *J. Org. Chem.*, 2003, **68**, 8669–8682.

43 S. Oi, S. Watanabe, S. Fukita and Y. Inoue, *Tetrahedron Lett.*, 2003, **44**, 8665–8668.

44 R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. Lewis-Alleyne, P. D. Long, D. Polo-Cerón and S. Prashar, *Chem. Commun.*, 2008, 990–992.

45 R. B. Bedford, M. F. Haddow, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.*, 2009, **7**, 3119–3127.

46 J. C. Lewis, J. Wu, R. G. Bergman and J. A. Ellman, *Organometallics*, 2005, **24**, 5737–5746.

47 M. C. Carrión and D. J. Cole-Hamilton, *Chem. Commun.*, 2006, 4527–4529.

48 J.-F. Yang, R.-H. Wang, Y.-X. Wang, W.-W. Yao, Q.-S. Liu and M. Ye, *Angew. Chem. Int. Ed.*, 2016, **55**, 14116–14120.

49 Q.-S. Liu, D.-Y. Wang, J.-F. Yang, Z.-Y. Ma and M. Ye, *Tetrahedron*, 2017, **73**, 3591–3595.

50 F. Mo and G. Dong, *Science*, 2014, **345**, 68–72.

51 F. Mo, H. N. Lim and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 15518–15527.

52 H. Jiang and A. Studer, *Angew. Chem. Int. Ed.*, 2018, **57**, 1692–1696.

53 Q. Lu and F. Glorius, *Angew. Chem. Int. Ed.*, 2017, **56**, 49–51.

54 C.-H. Jun, H. Lee and J.-B. Hong, *J. Org. Chem.*, 1997, **62**, 1200–1201.

55 C.-H. Jun, D.-Y. Lee and J.-B. Hong, *Tetrahedron Lett.*, 1997, **38**, 6673–6676.

56 C.-H. Jun, D.-Y. Lee, H. Lee and J.-B. Hong, *Angew. Chem.*, 2000, **39**, 3070–3072.

57 C.-H. Jun, H. Lee, J. B. Hong and B. Il Kwon, *Angew. Chem. Int. Ed.*, 2002, **41**, 2146–2147.

58 N. R. Vautravers, D. D. Regent and B. Breit, *Chem. Commun.*, 2011, **47**, 6635–6637.

59 E. V. Beletskiy, C. Sudheer and C. J. Douglas, *J. Org. Chem.*, 2012, **77**, 5884–5893.

60 F. Yang, K. Rauch, K. Kettelhoit and L. Ackermann, *Angew. Chem. Int. Ed.*, 2014, **53**, 11285–11288.

61 D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Org. Lett.*, 2006, **8**, 2523–2526.

62 P. W. Tan, N. A. B. Juwaini and J. Seayad, *Org. Lett.*, 2013, **15**, 5166–5169.

63 W. Hu, Q. Zheng, S. Sun and J. Cheng, *Chem. Commun.*, 2017, **53**, 6263–6266.

64 J. Shen, X. Liu, L. Wang, Q. Chen and M. He, *Synth. Commun.*, 2018, **48**, 1354–1362.

65 X. Wang, S. Song and N. Jiao, *Chin. J. Chem.*, 2018, **36**, 213–216.

66 X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 888–896.

67 D. Mu, X. Wang, G. Chen and G. He, *J. Org. Chem.*, 2017, **82**, 4497–4503.

68 Y. F. Zhang, B. Wu and Z.-J. Shi, *Chem. Eur. J.*, 2016, **22**, 17808–17812.

69 O. Rasheed and F.-L. Zhang, *Synlett*, 2018, **29**, 1033–1036.

70 F. Li, Y. Zhou, H. Yang, D. Liu, B. Sun and F.-L. Zhang, *Org. Lett.*, 2018, **20**, 146–149.

71 M. Y. Zhang and R. A. Barrow, *J. Org. Chem.*, 2018, **83**, 6776–6782.

72 D.-Y. Wang, S.-H. Guo, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao and Y.-Q. Wang, *Org. Lett.*, 2018, **20**, 1794–1797.

73 D. Mu, G. He and G. Chen, *Chem. Asian J.*, 2018, **13**, 2423–2426.

74 X.-Y. Chen, S. Ozturk and E. J. Sorensen, *Org. Lett.*, 2017, **19**, 1140–1143.

75 B. Li, K. Seth, B. Niu, L. Pan, H. Yang and H. Ge, *Angew. Chem. Int. Ed.*, 2018, **57**, 3401–3405.

76 X.-Y. Chen, S. Ozturk and E. J. Sorensen, *Org. Lett.*, 2017, **19**, 6280–6283.

77 X.-Y. Chen and E. J. Sorensen, *J. Am. Chem. Soc.*, 2018, **140**, 2789–2792.

78 Q.-J. Yao, S. Zhang, B.-B. Zhan and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2017, **56**, 6617–6621.

79 G. Liao, Q.-J. Yao, Z.-Z. Zhang, Y.-J. Wu, D.-Y. Huang and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2018, **57**, 3661–3665.

80 F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252–256.

81 F. Ma, M. Lei and L. Hu, *Org. Lett.*, 2016, **18**, 2708–2711.

82 H. Park, K. Yoo, B. Jung and M. Kim, *Tetrahedron*, 2018, **74**, 2048–2055.

83 H. Park, P. Verma, K. Hong and J.-Q. Yu, *Nat. Chem.*, 2018, **10**, 755–762.

84 K. Yang, Q. Li, Y. Liu, G. Li and H. Ge, *J. Am. Chem. Soc.*, 2016, **138**, 12775–12778.

85 C.-H. Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung and Y.-H. Kim, *Chem. Eur. J.*, 2002, **8**, 485–492.

86 Y. Kuninobu, Y. Nishina, M. Shouho and K. Takai, *Angew. Chem. Int. Ed.*, 2006, **45**, 2766–2768.

87 J. Xu, Y. Liu, Y. Wang, Y. Li, X. Xu and Z. Jin, *Org. Lett.*, 2017, **19**, 1562–1565.

88 J. Xu, Y. Liu, J. Zhang, X. Xu and Z. Jin, *Chem. Commun.*, 2018, **54**, 689–692.

89 K. Hong, H. Park and J.-Q. Yu, *ACS Catal.*, 2017, **7**, 6938–6941.

90 L. Pan, K. Yang, G. Li and H. Ge, *Chem. Commun.*, 2018, **54**, 2759–2762.

91 J. Vicente, I. Saura-Llamas, M. G. Palin, P. G. Jones and M. C. Ramírez de Arellano, *Organometallics*, 1997, **16**, 826–833.

92 J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216.

93 J. F. Hartwig, S. Richards, D. Barañano and F. Paul, *J. Am. Chem. Soc.*, 1996, **118**, 3626–3633.

94 J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224.

95 Y. Xu, M. C. Young, C. Wang, D. M. Magness and G. Dong, *Angew. Chem. Int. Ed.*, 2016, **55**, 9084–9087.

96 Y. Xu, M. C. Young, C. Wang, D. M. Magness and G. Dong, *Angew. Chem. Int. Ed.*, 2016, **55**, 9084–9087.

97 Y. Liu and H. Ge, *Nat. Chem.*, 2016, **9**, 26–32.

98 Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14554–14557.

99 H. Lin, C. Wang, T. D. Bannister and T. M. Kamenecka, *Chem. Eur. J.*, 2018, **24**, 9535–9541.

100 A. Yada, W. Liao, Y. Sato and M. Murakami, *Angew. Chem. Int. Ed.*, 2017, **56**, 1073–1076.

101 S. St John-Campbell and J. A. J. A. Bull, *Org. Biomol. Chem.*, 2018, **16**, 4582–4595.

102 H. Tang, X.-R. Huang, J. Yao and H. Chen, *J. Org. Chem.*, 2015, **80**, 4672–4682.

103 D. P. Affron and J. A. Bull, *Eur. J. Org. Chem*, 2016, 139–149.

104 I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, **1**, 0088.

105 L. Menabue and M. Saladini, *Inorg. Chem.*, 1991, **30**, 1651–1655.

106 J. Sanmartín, F. Novio, A. M. García-Deibe, M. Fondo, N. Ocampo and M. R. Bermejo, *Eur. J. Inorg. Chem.*, 2008, 1719–1726.

107 J. Sanmartín-Matalobos, C. Portela-García, M. Fondo, A. M. García-Deibe and A. L. Llamas-Saiz, *J. Coord. Chem.*, 2016, **69**, 1358–1370.

108 S. St John-Campbell, A. J. P. White and J. A. Bull, *Chem. Sci.*, 2017, **8**, 4840–4847.

109 Y. Yang, G. Chen, X. Hong, J.-Q. Yu and K. N. Houk, *J. Am. Chem. Soc.*, 2017, **139**, 8514–8521.

110 B. Gabriele, R. Mancuso and L. Veltri, *Chem. Eur. J.*, 2016, **22**, 5056–5094.

111 A. R. O. Venning, P. T. Bohan and E. J. Alexanian, *J. Am. Chem. Soc.*, 2015, **137**, 3731–3734.

112 Á. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis and R. Martin, *J. Am. Chem. Soc.*, 2016, **138**, 6384–6387.

113 N. Martin, C. Pierre, M. Davi, R. Jazzar and O. Baudoin, *Chem. Eur. J.*, 2012, **18**, 4480–4484.

114 B. Winter and S. Gallo-Flückiger, *Helv. Chim. Acta*, 2005, **88**, 3118–3127.

115 X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094–5115.

116 G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11726–11743.

117 A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129–133.

118 A. P. Smalley and M. J. Gaunt, *J. Am. Chem. Soc.*, 2015, **137**, 10632–10641.

119 D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2005, **44**, 4302–4320.

120 J. Zakrzewski, A. P. Smalley, M. A. Kabeshov, M. J. Gaunt and A. A. Lapkin, *Angew. Chem. Int. Ed.*, 2016, **55**, 8878–8883.

121 A. P. Smalley, J. D. Cuthbertson and M. J. Gaunt, *J. Am. Chem. Soc.*, 2017, **139**, 1412–1415.

122 M. J. Gaunt, M. Nappi, C. He, W. Whitehurst and B. Chappell, *Angew. Chem. Int. Ed.*, 2018, 3178–3182.

123 D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley and M. J. Gaunt, *Science*, 2016, **354**, 851–857.

124 C. He and M. J. Gaunt, *Angew. Chem. Int. Ed.*, 2015, **54**, 15840–15844.

125 J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer and M. J. Gaunt, *Nat. Chem.*, 2015, **7**, 1009–1016.

126 C. He and M. J. Gaunt, *Chem. Sci.*, 2017, **8**, 3586–3592.

127 K. Chen, D. Wang, Z.-W. Li, Z. Liu, F. Pan, Y.-F. Zhang and Z.-J. Shi, *Org. Chem. Front.*, 2017, **4**, 2097–2101.

128 A. K. Ou, *MSci Report Imperial College London*, 2017.

129 Y. Tanji, N. Mitsutake, T. Fujihara and Y. Tsuji, *Angew. Chem. Int. Ed.*, 2018, **57**, 10314–10317.

130 M. Largeron, *Eur. J. Org. Chem.*, 2013, **2013**, 5225–5235.

131 J. Sheng, Y. Guo and J. Wu, *Tetrahedron*, 2013, **69**, 6495–6499.

132 R. D. Baxter, D. Sale, K. M. Engle, J.-Q. Yu and D. G. Blackmond, *J. Am. Chem. Soc.*,

2012, **134**, 4600–4606.

133 J. Burés, *Angew. Chem. Int. Ed.*, 2016, **55**, 2028–2031.

134 J. Burés, *Angew. Chem. Int. Ed.*, 2016, **55**, 16084–16087.

135 S. St John-Campbell, A. K. Ou and J. A. Bull, *Chem. Eur. J.*, , DOI:10.1002/chem.201804515.

136 ICH-3D-quality, 0013-Guideline for elemental impurities Q3D.

137 D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, 1934, 1303–1305.

138 J. Wu, X.-L. Hou and L.-X. Dai, *J. Org. Chem.*, 2000, **65**, 1344–1348.

139 R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2002, **67**, 674–683.

140 J. Tan, W. Tang, Y. Sun, Z. Jiang, F. Chen, L. Xu, Q. Fan and J. Xiao, *Tetrahedron*, 2011, **67**, 6206–6213.

141 M. S. Abdel-Maksoud, M.-R. Kim, M. I. El-Gamal, M. M. Gamal El-Din, J. Tae, H. S. Choi, K.-T. Lee, K. H. Yoo and C.-H. Oh, *Eur. J. Med. Chem.*, 2015, **95**, 453–463.

142 S. K. Mangawa, S. K. Bagh, K. Sharma and S. K. Awasthi, *Tetrahedron Lett.*, 2015, **56**, 1960–1963.

143 R. M. Lopez and G. C. Fu, *Tetrahedron*, 1997, **53**, 16349–16354.

144 P.-X. Ling, S.-L. Fang, X.-S. Yin, K. Chen, B.-Z. Sun and B.-F. Shi, *Chem. Eur. J.*, 2015, **21**, 17503–17507.

145 W. J. Ryan, W. K. Banner, J. L. Wiley, B. R. Martin and R. K. Razdan, *J. Med. Chem.*, 1997, **40**, 3617–3625.

146 H. Fujioka, A. Goto, K. Otake, O. Kubo, Y. Sawama and T. Maegawa, *Chem. Commun.*, 2011, **47**, 9894.

147 S. H. Christensen, T. Holm and R. Madsen, *Tetrahedron*, 2014, **70**, 4942–4946.

148 L.-P. B. Beaulieu, D. S. Roman, F. Vallée and A. B. Charette, *Chem. Commun.*, 2012, **48**, 8249.

149 P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao and S. Chiba, *Angew. Chem. Int. Ed.*, 2016, **55**, 3719–3723.

150 S. Takano, M. Akiyama, S. Sato and K. Ogasawara, *Chem. Lett.*, 1983, **12**, 1593–1596.

151 E. L. Eliel, L. Clawson and D. E. Knox, *J. Org. Chem.*, 1985, **50**, 2707–2711.

152 M. A. Blanchette, M. S. Malamas, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, S. Masamune, M. Kageyama and T. Tamura, *J. Org. Chem.*, 1989, **54**, 2817–2825.

153 Y. Yang, J. Wang and M. Kayser, *Tetrahedron: Asymmetry*, 2007, **18**, 2021–2029.

154 M. Motoi, H. Suda, K. Shimamura, S. Nagahara, M. Takei and S. Kanoh, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1653–1659.

155 N. Harada, J. Yasuhara, Y. Motoyama, O. Fujimura, T. Tsuji, T. Takahashi, Y. Takahashi and H. Nagashima, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 26–39.

156 Y. Nishimoto, M. Yasuda and A. Baba, *Org. Lett.*, 2007, **9**, 4931–4934.

157 A. R. Martin and L. A. Gharat, *Heterocycles*, 1996, **43**, 185.

158 Y.-F. Zhang, H.-W. Zhao, H. Wang, J.-B. Wei and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2015, **54**, 13686–13690.

159 H. G. Khorana, *J. Chem. Soc.*, 1952, 2081.

160 F. Veznik, A. Guggisberg and M. Hesse, *Helv. Chim. Acta*, 1991, **74**, 654–661.

161 V. del Solar, A. Quiñones-Lombraña, S. Cabrera, J. M. Padrón, C. Ríos-Luci, A. Alvarez-Valdés, C. Navarro-Ranninger and J. Alemán, *J. Inorg. Biochem.*, 2013, **127**, 128–140.

162 B. Milde, M. Leibeling, M. Pawliczek, J. Grunenberg, P. G. Jones and D. B. Werz, *Angew. Chem. Int. Ed.*, 2015, **54**, 1331–1335.

163 P. Álvarez-Bercedo, A. Flores-Gaspar, A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 466–467.

164 G. A. Molander, E. M. Sommers and S. R. Baker, *J. Org. Chem.*, 2006, **71**, 1563–1568.

165 M. D. Rausch, *J. Org. Chem.*, 1974, **39**, 1787–1788.

166 D. L. Boger, C. E. Brotherton and M. D. Kelley, *Tetrahedron*, 1981, **37**, 3977–3980.

167 H. C. Arndt and S. A. Carroll, *Synthesis*, 1979, **1979**, 202–204.

168 Y. S. Hon, Y. C. Wong, C. P. Chang and C. H. Hsieh, *Tetrahedron*, 2007, **63**, 11325–11340.

169 D. Ma and Q. Cai, *Org. Lett.*, 2003, **5**, 3799–3802.

170 U. Wannagat, V. Damrath and U. Harder, *Monatsh. Chem.*, 1994, **1169**, 1159–1169.

171 M. Rueping, C. Vila and U. Uria, *Org. Lett.*, 2012, **14**, 768–771.

172 A. J. M. Janssen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, 1991, **47**, 7645–7662.

173 S. Marino, D. Stachurska-Buczek, D. Huggins, B. Krywult, C. Sheehan, T. Nguyen, N. Choi, J. Parsons, P. Griffiths, I. James, A. Bray, J. White and R. Boyce, *Molecules*, 2004, **9**, 405–426.

174 X. Sun, X. Wen, Y. Chen, C. Shi, C. Gao, Y. Wu, L. Wang, X. Yang and H. Sun, *Eur. J. Med. Chem.*, 2015, **103**, 269–288.

175 Y.-S. Hon, C.-F. Lee, R.-J. Chen and Y.-F. Huang, *Synth. Commun.*, 2003, **33**, 2829–2842.

176 A. Wada, S. Kanatomo and S. Nagai, *Chem. Pharm. Bull.*, 1985, **33**, 1016–1022.

177 P. S. Dragovich, T. J. Prins and R. Zhou, *J. Org. Chem.*, 1995, **60**, 4922–4924.

178 S. St John-Campbell, A. J. P. White and J. A. Bull, *Chem. Sci.*, 2017, **8**, 4840–4847.

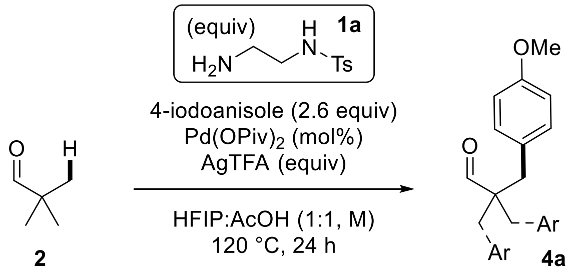
Appendix 1: Design of Experiment (DOE) Optimisation

DOE enables the variation of multiple continuous factors simultaneously, giving information about how the variables may affect one another and potentially resulting in an improved yield and better understanding of the reaction. MODDE software was used for the DOE study, exploring the following factors in the indicated ranges (Figure A1.1).

	Name	Abbr.	Units	Type	Settings	Transform	Precision
1	**DG**	DG	equiv	Quantitative	0.2 to 0.8	None	0.015
2	**Ag**	Ag	equiv	Quantitative	1 to 3	None	0.05
3	**Pd**	Pd	mol%	Quantitative	5 to 15	None	0.25
4	**Conc**	Conc	M	Quantitative	0.1 to 0.5	None	0.01
		Double-click here	to add	a new factor			

Figure A1.1: Screenshot of select factors for DOE optimisation and ranges explored for each

It was decided that the amount of aryl iodide in the reaction would be fixed. The combination of these four factors lead to the software predicting a CCF (face centred cubic) model for optimisation whereby all extremes and midpoints would need to be performed experimentally to understand the effect of all factors and possibly predict an optimum set of conditions. The results of each experiment are shown in Table A1.1.



Exp No	Exp Name	Run Order	DG (equiv)	Ag (equiv)	Pd (mol%)	Conc (M)	Total yield (%)
1	N1	6	0.2	1	5	0.1	0.1
2	N2	15	0.8	1	5	0.1	0.1
3	N3	1	0.2	3	5	0.1	24
4	N4	2	0.8	3	5	0.1	24
5	N5	27	0.2	1	15	0.1	0.1
6	N6	21	0.8	1	15	0.1	0.1
7	N7	26	0.2	3	15	0.1	19
8	N8	9	0.8	3	15	0.1	29
9	N9	8	0.2	1	5	0.5	20
10	N10	14	0.8	1	5	0.5	10
11	N11	25	0.2	3	5	0.5	25
12	N12	4	0.8	3	5	0.5	28
13	N13	24	0.2	1	15	0.5	14
14	N14	10	0.8	1	15	0.5	23
15	N15	3	0.2	3	15	0.5	16
16	N16	22	0.8	3	15	0.5	32
17	N17	13	0.2	2	10	0.3	24
18	N18	19	0.8	2	10	0.3	36
19	N19	7	0.5	1	10	0.3	19
20	N20	18	0.5	3	10	0.3	32
21	N21	20	0.5	2	5	0.3	25
22	N22	16	0.5	2	15	0.3	33
23	N23	12	0.5	2	10	0.1	25
24	N24	11	0.5	2	10	0.5	31
25	N25	23	0.5	2	10	0.3	27
26	N26	17	0.5	2	10	0.3	32
27	N27	5	0.5	2	10	0.3	27

Table A1.1: DOE results. [a]Yields determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The results were conducted in the 'run order' to minimise systematic errors. Repeats of a single experiment were included in the software as a measure of reproducibility. These results gave the following summary of fit plot (Figure A1.2).

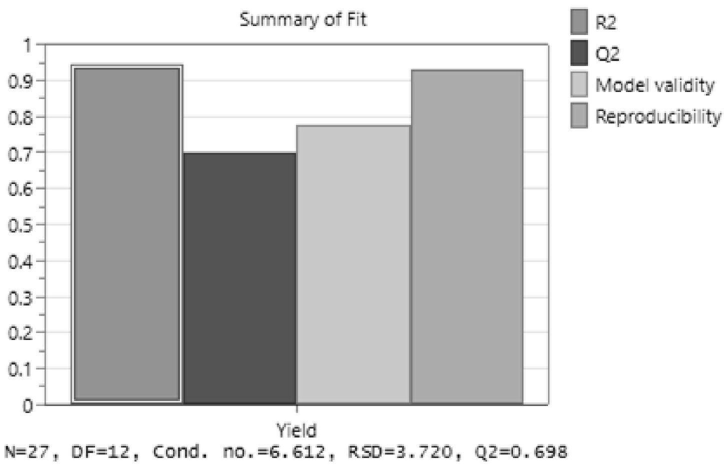


Figure A1.2: Screenshot of summary of fit plot for DOE experiments

The plot shows an extremely high model fit (R2), future prediction accuracy (Q2), model validity and reproducibility. This plot gives confidence that the model works well for the reaction and can be used to predict yields given amounts of all the components in the ranges as outlined in Figure A1.1.

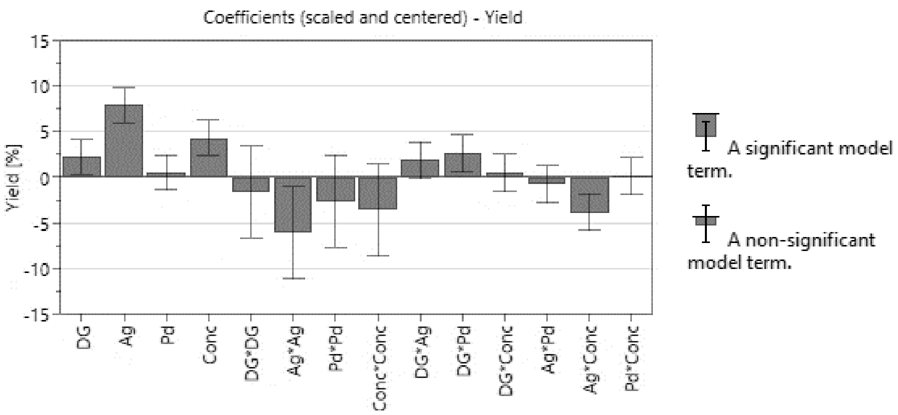


Figure A1.3: Coefficients of factors

The coefficients shown in figure A1.3 allow us to visualise the most important components of the reaction that lead to changes in yield. As shown in the key, factors with a large value and smaller error bar are most significant. The graph shows that the most important factors are the equivalents of silver and the solvent concentration, as well as the combination of these factors working together. The amount of palladium appears unimportant whereas the amount of directing group appears to only have a small amount of significance. The prediction software did not propose a set of conditions in the ranges used that would provide a greater total yield of the arylated aldehyde.

Appendix 2: Crystal Structure Data for 3a-Pd-dimer

Crystals suitable for X-ray analysis were grown by vapour diffusion of pentane into a concentrated CH_2Cl_2 solution at 25 °C.

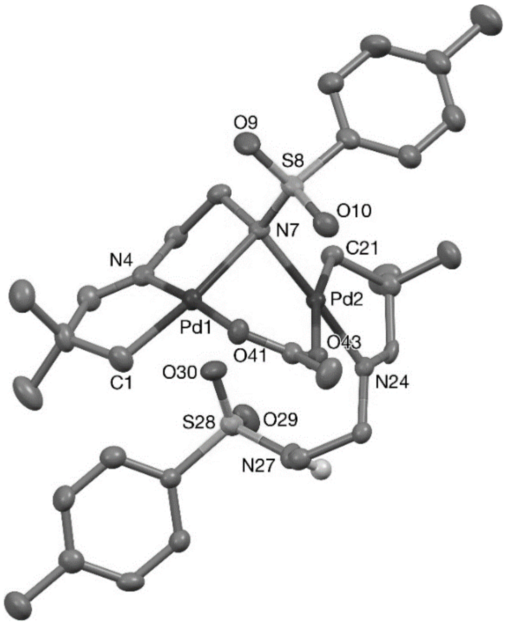


Figure A2.1: The crystal structure of **2a-Pd-dimer** (50% probability ellipsoids).

The X-ray crystal structure of 2a-Pd-dimer

Crystal data for **2a-Pd-dimer**: $C_{30}H_{44}N_4O_6Pd_2S_2$, M = 833.61, monoclinic, $P2_1/n$ (no. 14), a = 13.3652(4), b = 18.9012(7), c = 14.5561(5) Å, β = 104.314(4)°, V = 3563.0(2) Å^3, Z = 4, D_c = 1.554 g cm^{-3}, μ(Mo-Kα) = 1.171 mm^{-1}, T = 173 K, colourless tablets, Agilent Xcalibur 3 E diffractometer; 7079 independent measured reflections (R_{int} = 0.0243), F^2 refinement,[X1,X2] R_1(obs) = 0.0345, wR_2(all) = 0.0736, 5616 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 57°], 408 parameters. CCDC 1534094. For bond lengths, angles and CIF see: *Chem Sci,* **2017**, 4840.[178]

The N27–H hydrogen atom in the structure of **2a-Pd-dimer** was located from a Δ*F* map and refined freely subject to an N–H distance constraint of 0.90 Å.

References

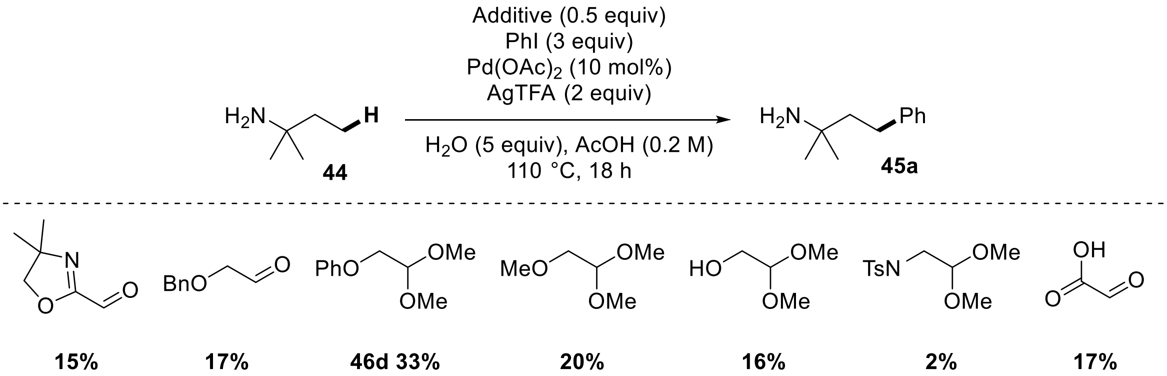
[X1] SHELXTL v5.1, Bruker AXS, Madison, WI, 1998.

[X2] SHELX-2013, G.M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3-8.

Appendix 3: Initial Amine Arylation Results by Alex Ou

Inspired by the developed methodology for aldehyde arylation (Section 3.1), MSci Student Alex Ou started to investigate transient *exo*-imines for the direct C(sp^3)–H arylation of aliphatic amines.

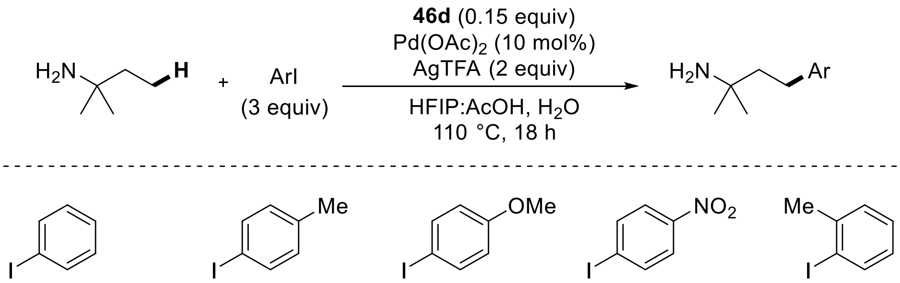
He sought to investigate the potential aldehyde structures that could promote amine functionalisation, and so under conditions developed by Ge,[97] screened some potential TDGs, using *tert*-amylamine as the model substrate (Scheme A3.1). In many cases acetals were used due to their commercial availability compared to the related aldehydes, and all yields are isolated following an acid/base work up of the free amine product.



Scheme A3.1: Screen of TDG's for amine arylation as performed by Alex Ou

Although a control reaction was not conducted, with 0.5 equivalents of the additive, each reaction formed the arylated product in low to moderate yields. An oxazoline aldehyde gave a 15% yield, with similar yields observed for O-benzyl, O-methyl, alcohol examples, but also Ge's Glyoxylic acid. A low yield was seen for an *N*-tosyl acetal. Phenoxyacetaldehyde dimethyl acetal was identified as the optimal candidate at this early stage.

It was identified that lowering the loading of the acetal additive led to improved yields, with a 60% yield observed at 0.15 equivalents of the phenoxy acetal. With the optimal loading of the acetal, some scope of the aryl iodides was conducted (Scheme A3.2).



60% **60%** **58%** **42%** **trace**

Scheme A3.2: Aryl iodide scope of amine arylation as performed by Alex Ou

4-Methyl and 4-methoxy substituents didn't influence the reaction yield, however a 4-nitro substituent led to a decreased amount of product formation. Hindered 2-methyliodobenzene was an incompatible coupling partner. Cyclopropylmethanamine, cyclohexylmethanamine and butan-2-amine were tested for the amine scope, but none gave any reactivity.