Novel One-Pot Multi-Reaction Methods for the Synthesis of Carbocyclic and Heterocyclic Compounds

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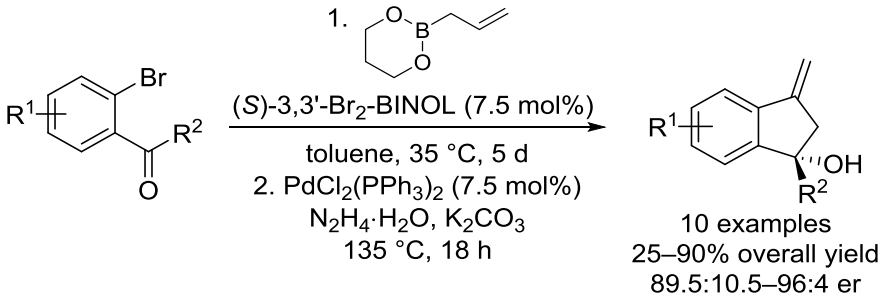
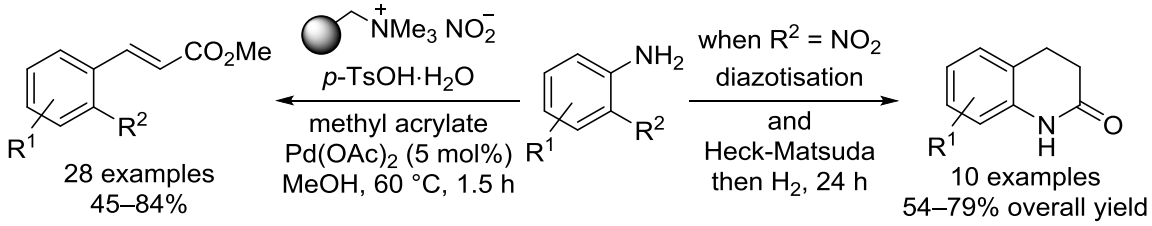
Abstract

The first section describes the development of an asymmetric one-pot synthesis of 1-alkylindan-1-ols involving an enantioselective allylboration of 2'-bromoaryl alkyl ketones followed by an intramolecular Mizoroki-Heck cyclisation. The synthetic utility of the chiral 1-alkylindan-1-ol scaffold was demonstrated using the ozonolysis product indanone in diastereoselective reductive reactions.



The second section describes the development of a rapid, one-pot tandem diazotisation and Heck-Matsuda reaction for the synthesis of methyl (*E*)-cinnamates *via* stable aryl diazonium tosylate salts. This process was then altered to allow the one-pot multistep synthesis of 3,4-dihydroquinolin-2-ones. This methodology was used for the total synthesis of a sodium channel modulator.



The third section describes a one-pot diazotisation-intramolecular cyclisation process for the synthesis of 1*H*-benzotriazoles and the regioselective preparation of N_1-substituted benzotriazoles, including a series of biologically active compounds.

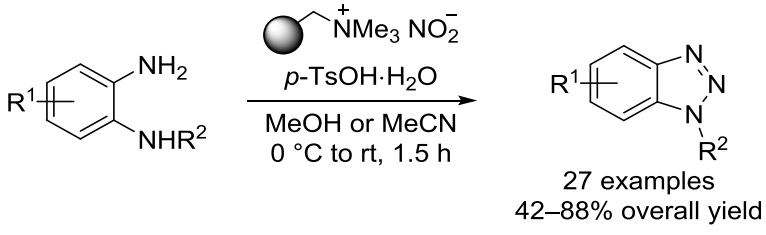


Table of Contents

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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Réka Julianna Faggyas and has not been submitted for any other degree at the University of Glasgow or any other institution. The work upon which it is based was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr Andrew Sutherland between October 2015 and March 2019. Aspects of the work described herein have previously been published elsewhere as listed below.

Réka J. Faggyas, Ewen D. D. Calder, Claire Wilson and Andrew Sutherland, One-Pot Asymmetric Synthesis of Alkylidene 1-Alkylindan-1-ols Using Brønsted Acid and Palladium Catalysis, *J. Org. Chem.*, 2017, **82**, 11585–11593.

Réka J. Faggyas, Megan Grace, Lewis Williams and Andrew Sutherland, Multibond Forming Tandem Reactions of Anilines *via* Stable Aryl Diazonium Salts: One-Pot Synthesis of 3,4-Dihydroquinolin-2-ones, *J. Org. Chem.*, 2018, **83**, 12595–12608.

Réka J. Faggyas, Nikki L. Sloan, Ned Buijs and Andrew Sutherland, Synthesis of Structurally Diverse Benzotriazoles *via* Rapid Diazotization and Intramolecular Cyclization of 1,2-Aryldiamines, *Eur. J. Org. Chem.*, 2019, **2019**, 5344–5353.

Martyn C. Henry, Rochelle McGrory, **Réka J. Faggyas**, Mohamed A. B. Mostafa and Andrew Sutherland, One-pot *ortho*-Amination of Aryl C–H Bonds Using Consecutive Iron and Copper Catalysis, *Org. Biomol. Chem.*, 2019, **17**, 4629–4639.

Signature _____

Printed name Réka J. Faggyas

Abbreviations

Δ	Reflux
Ac	Acetyl
Ar	Aromatic
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
[BMIM]NTf_2	1-Butyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bz	Benzoyl
Cat	Catalyst
Cbz	Benzyloxycarbonyl
CI	Chemical Ionisation
COSY	Correlation spectroscopy
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
dppf	Diphenylphosphinoferrocene

dr	Diastereomeric Ratio
DSC	Differential Scanning Calorimetry
EDG	Electron-donating Group
ee	Enantiomeric Excess
EI	Electron Impact
endo	*Endo* Ring Closure or Endocyclic
equiv.	Equivalents
er	Enantiomeric Ratio
ESI	Electrospray Ionisation
Et	Ethyl
EWG	Electron-widrawing Group
exo	*Exo* Ring Closure or Exocyclic
FTIR	Fourier Transform Infrared
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IC_{50}	Half Maximal Inhibitory Concentration
i-PrOH	Isopropyl Alcohol
m-	*Meta*-
M	Molar
Me	Methyl
MeCN	Acetonitrile
min	Minute(s)
mp	Melting Point

NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
o-	*Ortho*-
oct	Octet
p-	*Para*-
Ph	Phenyl
Pin	Pinacol
PMP	1,2,2,6,6-Pentamethylpiperidine
ppm	Parts Per Million
q	Quartet
quin	Quintet
rt	Room Temperature
s	Singlet
sept	Septet
SPECT	Single-Photon Emission Computed Tomography
t	Triplet (NMR) or Retention Time (HPLC)
tert	Tertiary
t-BuOH	*tert*-Butyl Alcohol
TFA	Trifluoroacetic acid
TfO	Trifluoromethanesulfonate
THF	Tetrahydrofuran

TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Ts	*para*-Toluenesulfonyl
UV	Ultraviolet
μW	Microwave

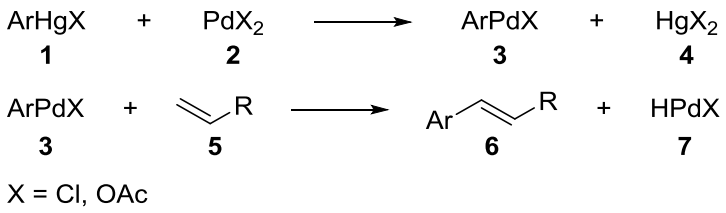
1.0 Introduction

Palladium-catalysed transformations are one of the most important classes of transition metal-catalysed reactions in organic synthesis.[1–3] This is especially true for carbon-carbon bond formation, which is usually the key step in the preparation of fine chemicals, or the synthesis of pharmaceutically active compounds and natural products. The significance of palladium chemistry is highlighted by the number of reactions developed by synthetic organic chemists in the past 50 years.[3] Among the most significant examples is the palladium-catalysed arylation of olefins, which enabled the formation of a new carbon-carbon bond and was independently discovered and reported by Mizoroki and Heck in the early 1970s.[4,5] Since then, the scope of palladium-catalysed transformations has increased exceedingly, leading to a wide-range of cross-coupling reactions, such as the Negishi, Sonogashira, Stille, Suzuki-Miyaura and Buchwald-Hartwig couplings. As a consequence, palladium catalysis has become a fundamental and versatile tool for organic synthesis and was celebrated worldwide in 2010, when the Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.[6] They all equally shared the prize for their outstanding contribution in the discovery and development of palladium-catalysed cross-couplings.

1.1 The Mizoroki-Heck reaction

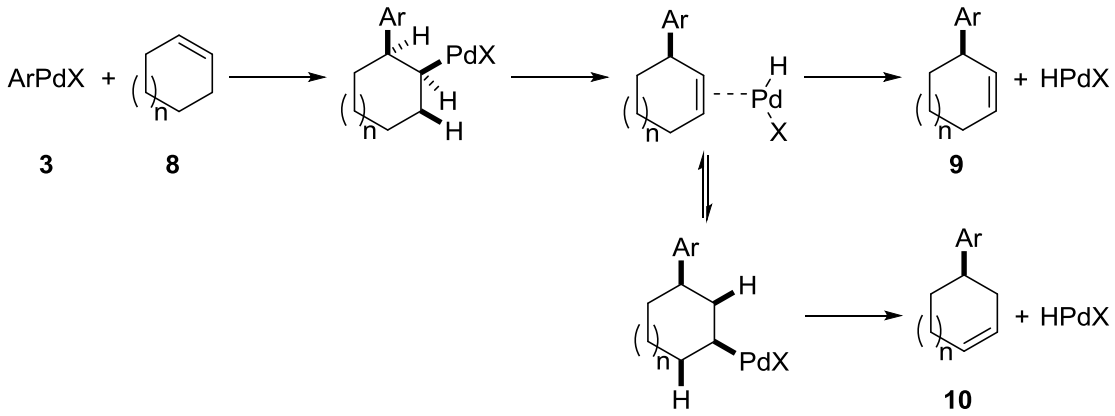
In 1968, Heck published six consecutive single-author papers which demonstrated the comprehensive scope of olefin arylation in the presence of transition metal complexes, especially palladium-based salts (Scheme 1).[7–12] This was achieved by using arylpalladium salts **3**, prepared *in situ* by transmetallation of organomercury compounds **1** with palladium(II) complexes **2** (eg. $LiPdCl_3$). The reactions were reported as air and water stable, and a wide range of substituted alkenes were able to react with arylpalladium salts such as acrylates, allylic alcohols and allylic halides.[7–9] The reactions required a stoichiometric amount of **2** which was reduced to Pd(0) during the reaction. Using copper(II) chloride as an additive meant that, the process could be carried out with a catalytic amount of palladium(II). The $CuCl_2$ served as a palladium reoxidant and, enabled the

transmetallation or direct palladation to occur. The next year, Heck also reported that the formation of the major *E*-alkene product **6** in the olefin arylation occurred *via* a mechanism which involved the *syn*-addition of **3** to the olefin **5** followed by *syn* β-hydride elimination of the hydridopalladium complex **7**.[13] It was believed that complex **7** decomposed to Pd and HX after the reaction, but was also capable of reducing the starting material olefin.



Scheme 1: Heck's general procedure for olefin arylation

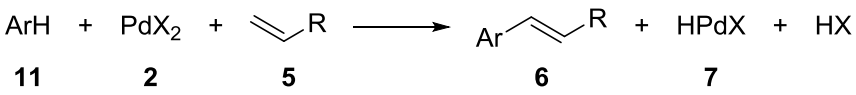
In coupling reactions of cyclic alkenes **8** in which no *syn* β-hydride was available, a *syn* β'-hydride elimination occurred to give alkene **9** (Scheme 2).[14] Isomerisation of the new C-C bond was also possible *via syn* re-addition of HPdX in the reverse direction, followed by a *syn* β'-hydride elimination to give product **10**. This redox-relay process is also known as palladium chain-walking.[15]



Scheme 2: Arylation of cyclic alkenes

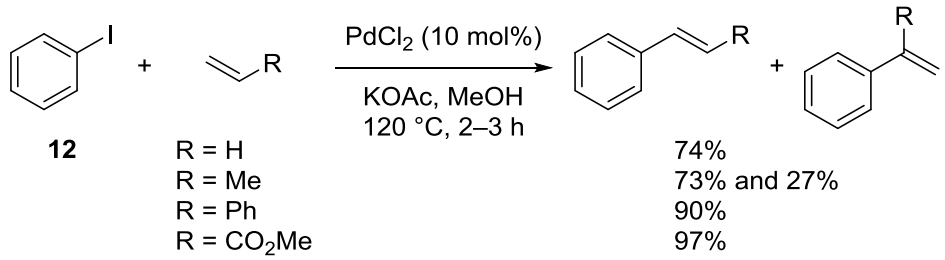
In an independent series of publications, Moritani and Fujiwara described similar vinylic substitutions which utilise the organopalladium precursor **2** *via* the direct electrophilic palladation of arenes **11** (Scheme 3).[16–18] These reactions also

employed **2** in stoichiometric amount initially, before a process using a catalytic amount of palladium was also developed by the addition of Pd(0) reoxidants.[18]



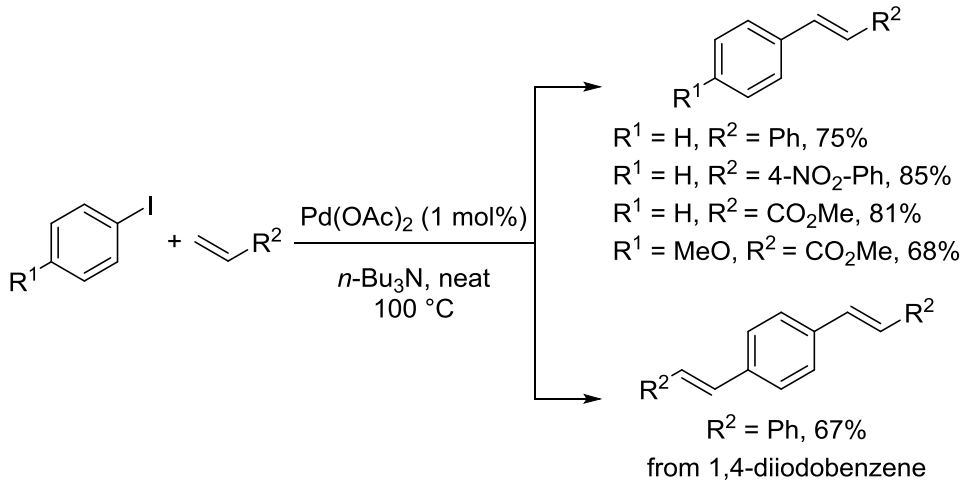
Scheme 3: Olefin arylation of unactivated arenes

In the next few years, a series of major improvements were carried out, which ultimately led to the Mizoroki-Heck reaction known today. In 1971, Mizoroki *et al.*, reported the first base-mediated palladium-catalysed arylation of alkenes (Scheme 4).[4] The preliminary results were obtained by using iodobenzene (**12**) and various alkene coupling partners. The reactions including ethylene, styrene and methyl acrylate mostly gave *E*-alkenes as major products in the presence of $PdCl_2$ and potassium acetate. However, coupling of **12** with propylene gave a 3:1 mixture of both 1,2- and 1,1-disubstituted products. Although, no comments were made on the mechanism of the reaction, it was proposed that the active form of the catalyst was *in situ* formed palladium(0) nanoparticles.



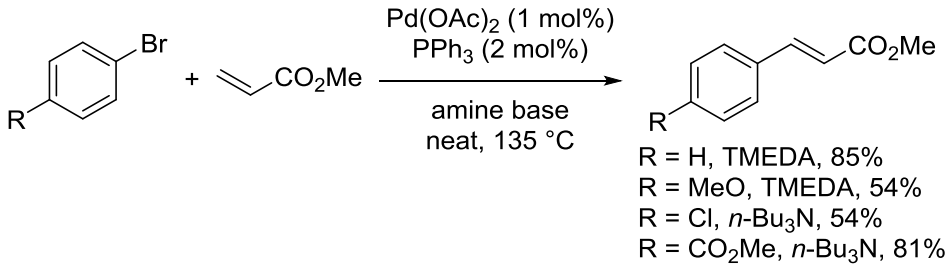
Scheme 4: Mizoroki's base-mediated catalytic cross-coupling reaction

In 1972, Heck independently found that the olefin vinylic substitution reaction with methyl acrylate and styrene could be carried out in the presence of a catalytic amount of $Pd(OAc)_2$ and *n*-Bu_3N as base (Scheme 5).[5] A range of aryl iodides (less toxic than the previously studied organomercury compounds) were found to be suitable substrates for the reaction and proceeded without the need of a Pd(0) reoxidant.



Scheme 5: Heck's base-mediated catalytic cross-coupling reaction

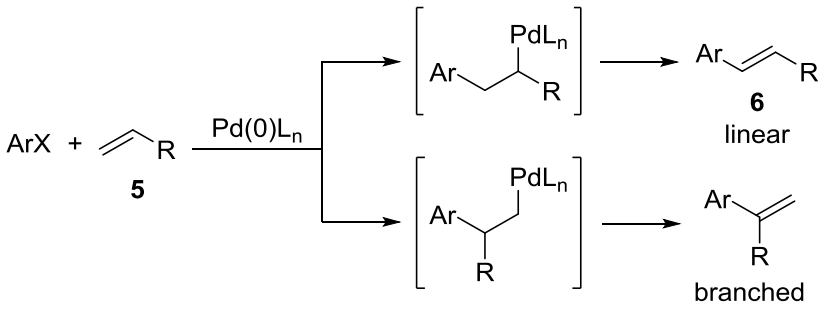
In 1973, Mizoroki extended the scope of the reaction to other organic halides and it was found that aryl bromides were more reactive than the chlorides, but less reactive than iodides: PhI > PhBr > PhCl.[19] Although this was the last communication made on the topic by the research group of Mizoroki, this was the first example where PPh_3 was reported as a palladium ligand in the reaction. At the same time, Dieck and Heck also investigated the role of phosphine ligands and reported the coupling of different aryl bromides with methyl acrylate in the presence of $Pd(OAc)_2$ (1 mol%) and PPh_3 (2 mol%) under neat conditions using organic bases (Scheme 6).[20]



Scheme 6: Heck's catalytic cross-coupling procedure with PPh_3

However, there were limitations of these reactions, such as the regioselectivity of the formed substituted alkene products. In 1974, Heck found that electron-deficient alkenes (acrylates or styrenes) favoured the coupling at the terminal position to give the linear products, while electron-rich vinyl ethers or vinyl amides favoured the coupling adjacent to the heteroatom to give the branched

products (Scheme 7).[20] Upon submitting neutral alkenes to the reaction, different regioisomers formed competitively, with low selectivity (typically favouring the linear regioisomers).

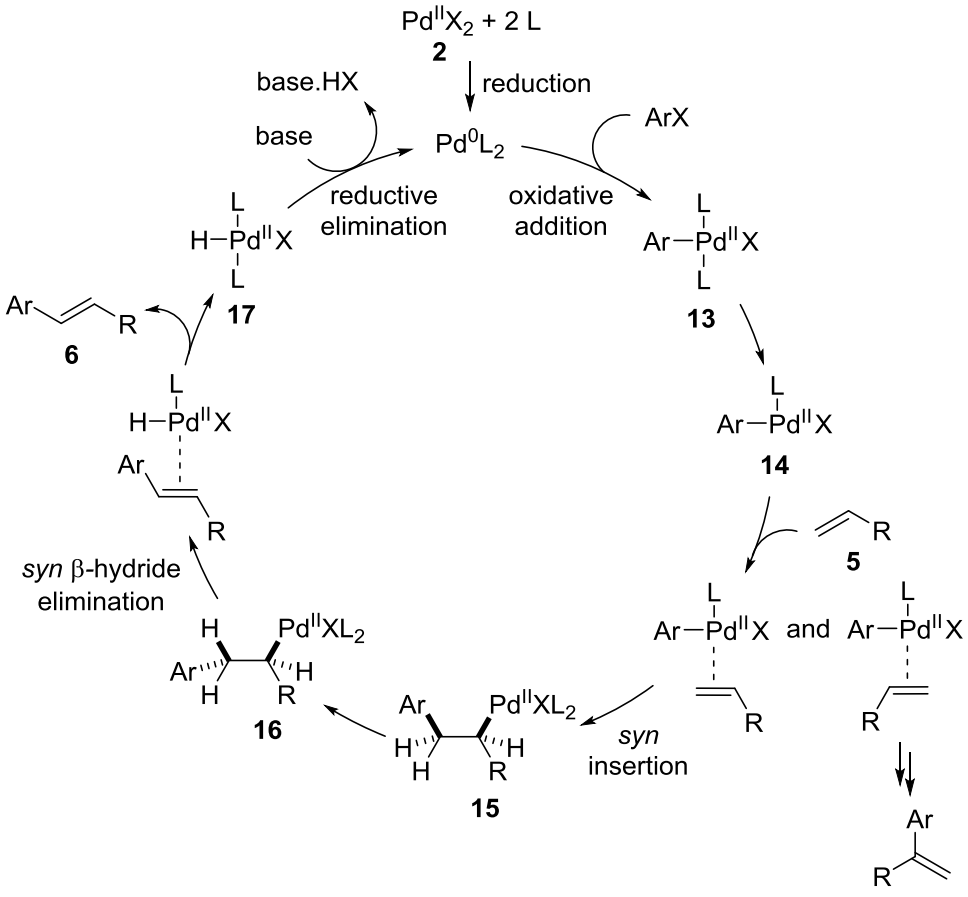


Scheme 7: Regioselectivity in the Mirozoki-Heck reaction

Heck and co-workers continued to develop the reaction with the introduction of phosphine ligands in the coupling of aryl bromides.[20–22] It was found that the reaction with $Pd(OAc)_2$ in the presence of the triarylphosphine, $P(o\text{-}Tol)_3$ was more efficient than PPh_3. Since then, a plethora of applications have been found for the reaction, all with different sets of conditions (palladium catalyst, ligand, base), which contributed to palladium being the most widely used in transition metal catalysis.[3] The Mizoroki-Heck reaction is a vinylic substitution reaction, whereby a vinylic hydrogen is substituted by an aryl, vinyl or alkyl group without β hydrogens on an sp^3 carbon atom, and thus affords highly substituted alkenes regioselectively. The organic halide can be an iodide or bromide and even triflates are suitable in the reaction. The alkene partner can be mono- or disubstituted and various electronic properties are allowed, with the reaction being most efficient for terminal alkenes containing an electron-withdrawing group (eg. CO_2R, CN, Ph). Both organic and inorganic bases can be utilised, such as NEt_3, NaOAc or K_2CO_3. All these general features lead to the powerful synthetic method the Heck-reaction represents in organic synthesis; its importance is unquestionable and highlighted in the many applications.

1.1.1 Mechanisms of the Mizoroki-Heck reaction

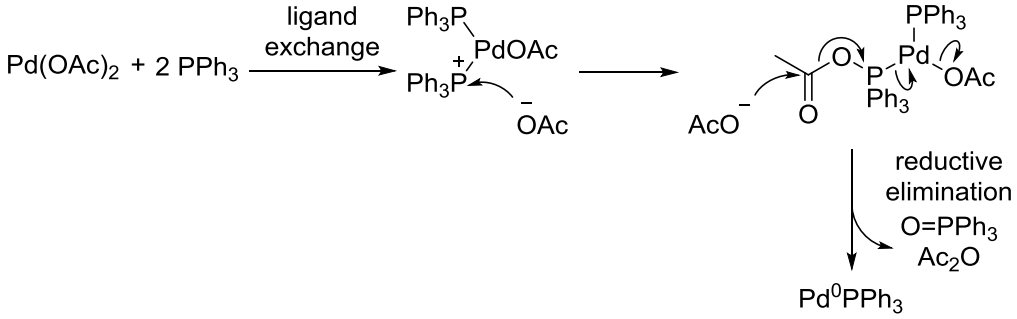
The first full catalytic cycle for the reaction was reported by Heck in 1972.[5] Initially, the formation of **13** *via* oxidative addition of aryl iodide to palladium was proposed, which occurred only after the $Pd(OAc)_2$ was reduced to Pd(0) by the alkene (Scheme 8). After reaction of **13** with the alkene coupling partner, the hydridopalladium species **17** regenerated the active Pd(0) catalyst by the addition of base to eliminate HI. This mechanism was later reviewed and became more detailed with the introduction of monophosphine ligands (L) associated with the $Pd(OAc)_2$ catalyst and is still generally accepted.[20] Therefore, the catalytic cycle follows a sequence of oxidative addition, migratory *syn* insertion, internal C-C bond rotation, *syn* β-hydride elimination and reductive elimination steps.



Scheme 8: General catalytic cycle of the Heck reaction, neutral pathway

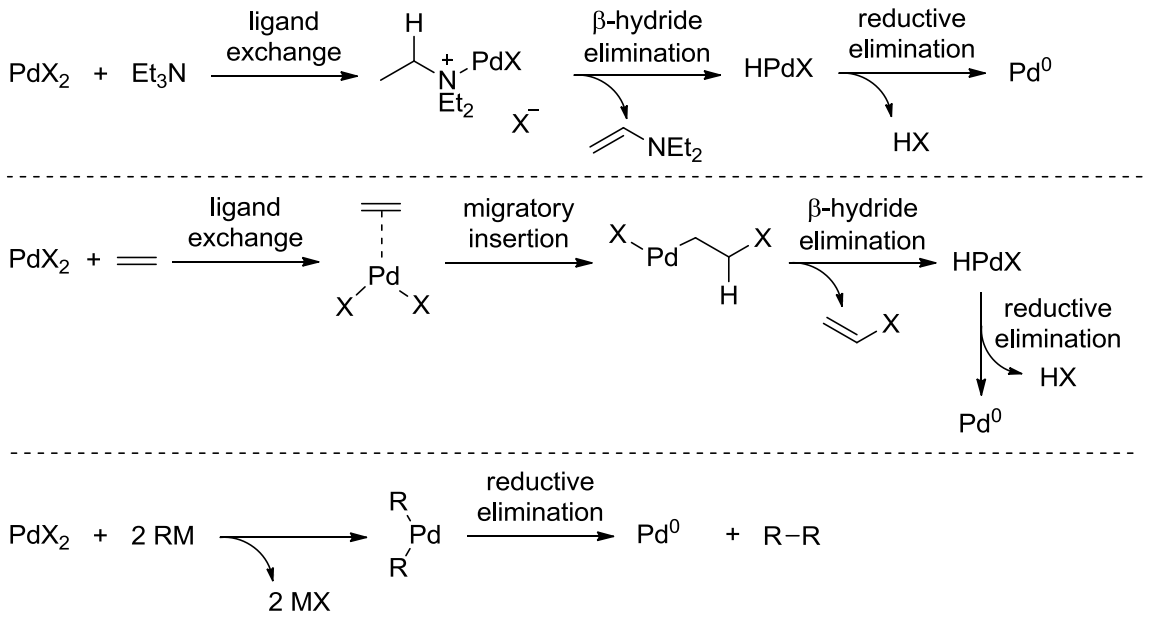
The first stage of the Heck reaction is the preactivation of the Pd(II) catalyst to afford a coordinatively unsaturated Pd(0) species in a reduction process. It is

crucial, as only Pd(0) with a vacant coordination site can initiate the oxidative addition. The formation of the active catalyst involves multiple ligand exchanges and most often occurs *via* phosphine-assisted reactions and the formation of phosphine oxide (Scheme 9).[3] A primary role of phosphine ligands bound to the palladium is to support the zero valent oxidation state of the metal centre. This can also occur in the forms of stable PdL_4 or PdL_3 complexes (L = PPh_3).



Scheme 9: *In situ* formation of Pd(0) with PPh_3

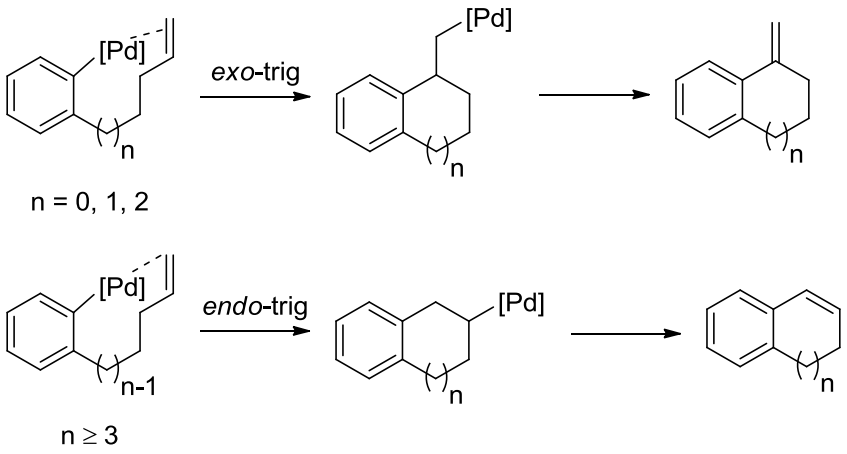
In the case of phosphine-free systems, the Pd(II) precatalyst can also be reduced by the reagents of the reaction. Thus, amines, olefins, or organometallics, such as butyllithium or trialkylaluminium were reported to be effective reducing agents (Scheme 10).[13,23] In all cases, only two strongly bound ligands are allowed on the active Pd(0) catalyst prior to oxidative addition. Moreover, ammonium salt additives (eg. tetrabutylammonium halide, R_4NX) can greatly improve the reaction in the absence of phosphine ligands.[24] In this case, the reduction of Pd(II) is initiated at elevated temperatures (100–130 °C), whereby the thermolytic decomposition of $Pd(OAc)_2$ leads to the formation of Pd(0) nanoparticles stabilised by R_4NX.[25]



Scheme 10: *In situ* formation of Pd(0) without phosphine ligands

After the formation of the palladium(0) species, the first step of the catalytic cycle is the oxidative addition of the aryl halide ArX to the Pd(0) complex. It proceeds *via* a concerted mechanism, in which the cleavage of the Ar-X bond is simultaneous with the formation of Pd-Ar and Pd-X bonds. The oxidative addition is sensitive to the nature of the nucleofuge and the strength of Ar-X and Pd-X bonds. Thus, under the same reaction conditions, it was previously observed by both Mizoroki and Heck that the aryl halide reactivity decreases in the following order: ArI > ArOTf > ArBr > ArCl.[18,19] This suggested the oxidative addition was the rate determining stage of the cycle (Scheme 8). As this step gives the σ-aryl-palladium(II) halide complex **13**, prior to the migratory insertion, it must undergo ligand dissociation to provide a coordination site around the metal centre. Thus, coordination of **14** to the alkene allows for *syn* insertion to form a σ-alkyl-palladium(II) halide intermediate **15**. This migratory insertion is the product forming step in the mechanism, as a new C-C bond forms (also known as carbopalladation, due to the concurrent formation of a Pd-C bond). As this is an irreversible step, it determines the regioselectivity of the reaction. The formation of two isomeric σ-alkyl-palladium(II) halide species could proceed *via* the arylation of the alkene in both α- or β-carbon atoms which results in branched or linear arylated alkenes, respectively. Regiochemistry in Mizoroki-Heck reactions was found to be similar to the Michael addition, whereby the new

C–C bond formed at the least hindered carbon of the alkene, resulting in a 1,2-disubstituted alkene.[26] However, due to the continuous fine-tuning of the reaction, there are now conditions which allow reactions to be performed in a way which leads to 1,1-disubstituted alkenes.[27,28] The formation of a mixture of regioisomers was observed for neutral and electron-rich alkenes (substituted with OR or NR_2). For intramolecular Heck reactions, however, there is another factor that determines the regioselectivity during migratory insertion. This step is governed by the length of the tether and the size of the ring which is being formed, thus, the mode of ring closure can be different. Depending on the length of the tether, conformational effects play a role in the formation of the favoured product. Therefore, formation of small rings (5-, 6- or 7-membered rings) proceeds predominantly *via* an *exo*-trig cyclisation (Scheme 11). In contrast to this, for the formation of macrocyclic compounds (≥8-membered rings), steric effects dominate and the *endo*-trig mode of cyclisation is preferred. However, the rules did not apply for Danishefsky's total synthesis of taxol, where an intramolecular Heck reaction resulted in a key intermediate containing an 8-membered ring with an *exo*-double bond.[29] This suggests that steric and electronic effects compete with conformational factors when forming medium–sized rings.



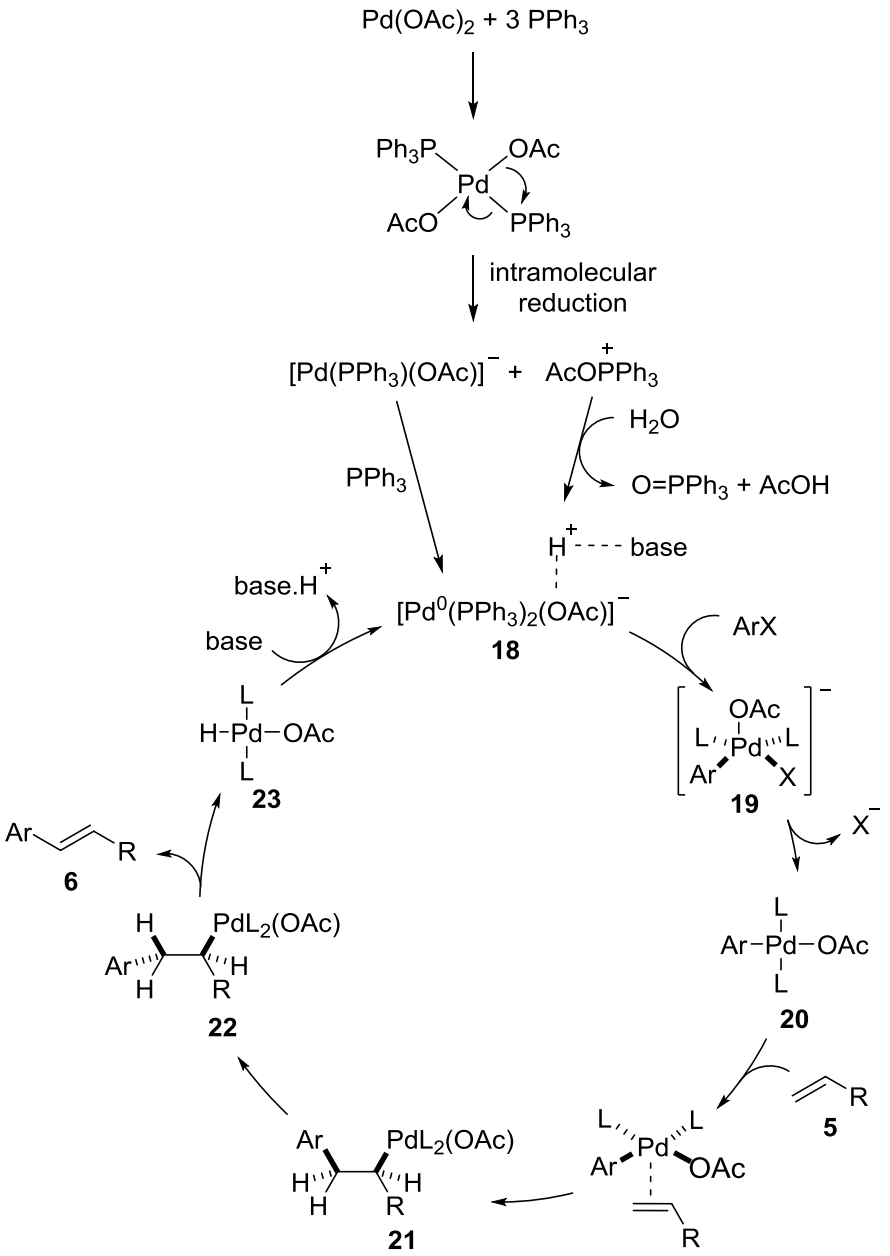
Scheme 11: Regioselectivity in intramolecular Mizoroki-Heck reactions

The next step of the catalytic cycle is an internal C-C bond rotation, which allows for the sp^3 β-hydrogen to be *syn* relative to the palladium in intermediate **16** and subsequent *syn* β-hydride elimination results in the formation of the product as well as the hydridopalladium(II) halide complex **17** (Scheme 8).

Product dissociation usually delivers a *trans* 1,2-disubstituted alkene and the catalytically inactive **17**. The β-hydride elimination step is potentially reversible and can lead to the formation of alkene isomerisation products *via* consecutive reinsertion-elimination processes, unless the next base-induced reductive elimination step occurs faster. A stoichiometric amount of base is necessary, as it reacts with HX to shift the equilibrium of this last step towards regeneration of the active catalyst $Pd(0)L_2$, which then enters the next catalytic cycle.

The overall cycle always follows the four elemental steps proposed by Heck (oxidative addition, alkene insertion, β-hydride elimination and reductive elimination). However, the general catalytic cycle on Scheme 8 has been modified due to extensive mechanistic investigations. As a consequence, a lot of factors play a role in the mechanism of the Heck reaction, as a great variety of intermediate palladium complexes can form. This largely depends on the reaction conditions, namely the starting material aryl derivatives (halides or triflates), the alkenes (electron-rich or electron-deficient), the Pd(0) precursor (Pd(0) complexes, $Pd(OAc)_2$, palladacycles), the ligand (mono- or bisphosphines, NHCs), the base and the additives. For example, if the conditions involve palladium(II) acetate and excess monophosphine ligands (eg. PPh_3) the mechanism proceeds *via* an anionic pathway, which was shown in recent studies by Amatore and Jutand (Scheme 12).[30] The name refers to the formal charge of the first palladium(II) complex in the cycle. It was found that the acetate ligand on the precatalyst had an influence on the mechanism. In the preactivation stage, the Pd(II) catalyst is reduced to Pd(0) by PPh_3 in an intramolecular reaction and the phosphine ligand is oxidised to phosphine oxide. The active form of the catalyst is the 16-electron anionic **18** stabilised by the base *via* hydrogen bonding. The oxidative addition generates another anionic palladium complex **19** which is a pentacoordinate palladium(II) complex, whereby both halide and acetate ions remain coordinated to the metal centre. However, due to its short-life, it instantly loses the halide to become neutral complex **20**. The increased reactivity of $[PhPd(OAc)(PPh_3)_2]$ (compared to $[PhPdI(PPh_3)_2]$) has been attributed to the acetate ligand, which may assist in the dissociation of a phosphine ligand to make available a coordination site around the metal centre.[31] The rest of the cycle follows the same route as in the neutral pathway. This mechanism highlights the important role of acetate anions which are

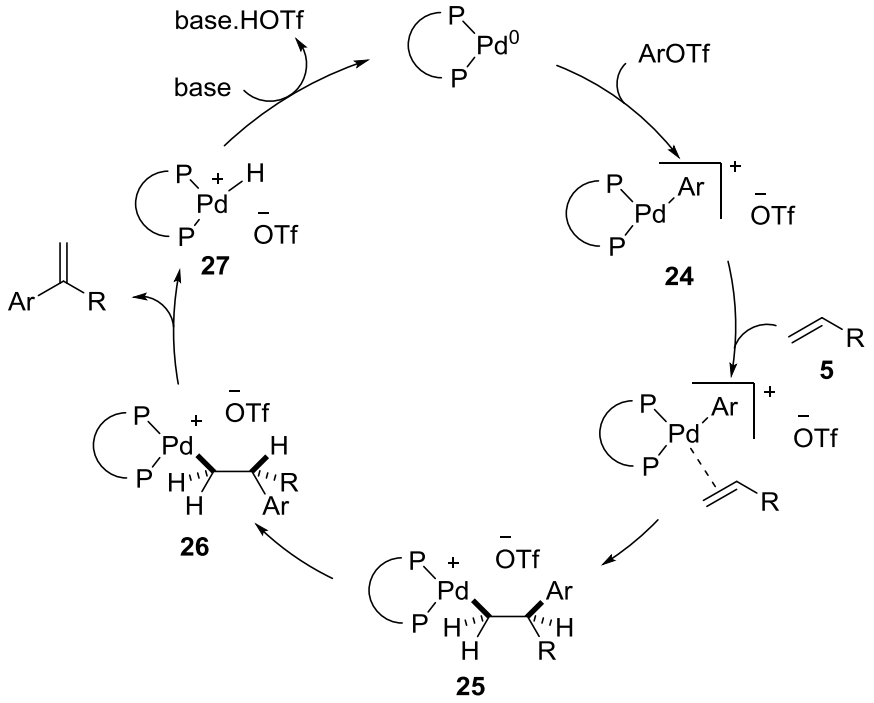
delivered by the precatalyst $Pd(OAc)_2$ and are ligands in both Pd(0) and Pd(II) complexes throughout the catalytic cycle. A similar anionic pathway is also proposed for reactions involving bulky tri(*tert*-butyl)phosphine complexes.[32]



Scheme 12: Anionic pathway

In a halide-free system, where aryl or vinyl triflates are subjected to the Heck reaction, a third mechanism can be described (Scheme 13).[33] Cabri and Hayashi independently proposed a cationic pathway to describe the Heck reaction of aryl triflates in the presence of bidentate phosphine ligands *via* 16-electron, cationic palladium(II) intermediates.[34,35] Oxidative addition of the aryl triflate to the

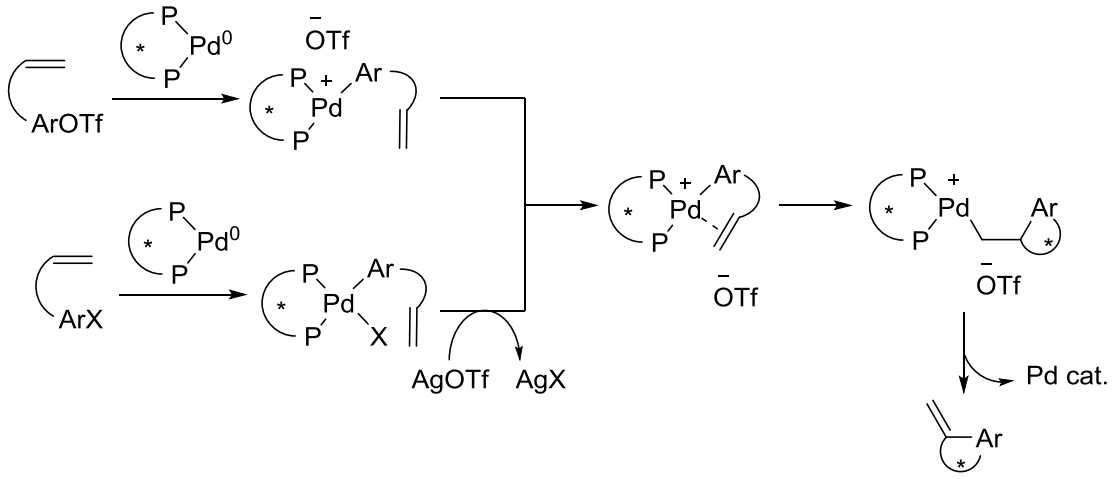
Pd(0) catalyst generates a cationic palladium(II) aryl complex **24** as the triflate dissociates. This mechanism is different from the neutral catalytic cycle in that the palladium contains an extra vacant site due to the weakly coordinating triflate counterion, thus being coordinatively unsaturated throughout the process. This allows for the coordination to the alkene directly, without ligand dissociation. Thus, the bidentate diphosphine ligand is chelated to the metal centre throughout the alkene coordination and migratory insertion steps. A stoichiometric amount of base is still required to reduce **27** to Pd(0).



Scheme 13: Cationic pathway

For example, the coupling of electron-rich alkenes (poor π-acceptors but good σ-donors) with aryl triflates in the presence of chelating phosphines proceeds *via* this mechanism to give branched 1,1-disubstituted alkenes.[36] This is due to the strong interaction between the cationic Pd(II) intermediates and electron-rich alkenes. It is possible to switch between cationic and neutral Pd(II) manifolds: addition of a soluble halide to reactions involving aryl or vinyl triflates follow a neutral pathway,[37] whereas the addition of a halide scavanger (such as AgOTf or Ag_2CO_3) results in the cationic pathway being favoured (Scheme 14). Indeed, silver(I) salts may be used to initiate the cationic pathway in reactions of aryl halides.[38] Thallium(I) salts have also been reported for abstracting halides in

Heck reactions, but the high toxicity associated with these reagents led to the preferred use of silver(I) salts. The asymmetric intramolecular Heck reaction of aryl triflates or halides mediated by a Ag(I) additive, in the presence of a chiral diphosphine ligand is also believed to follow the cationic pathway. In both cases, the cationic Pd(II) intermediate occupies a vacant coordination site for permitting the pendant alkene coordination. Partial dissociation of the chiral diphosphine was believed to lead to modest enantioselectivities due to diminished rigidity of the ligand.



Scheme 14: Asymmetric intramolecular Heck reaction *via* the cationic pathway

Unlike in the neutral pathway, the regioselectivity is not governed by steric factors. Cationic intermediates favour C-C bond formation at the more electron-poor terminus of the alkene, as this can better stabilise a developing positive charge (Figure 1).[39]

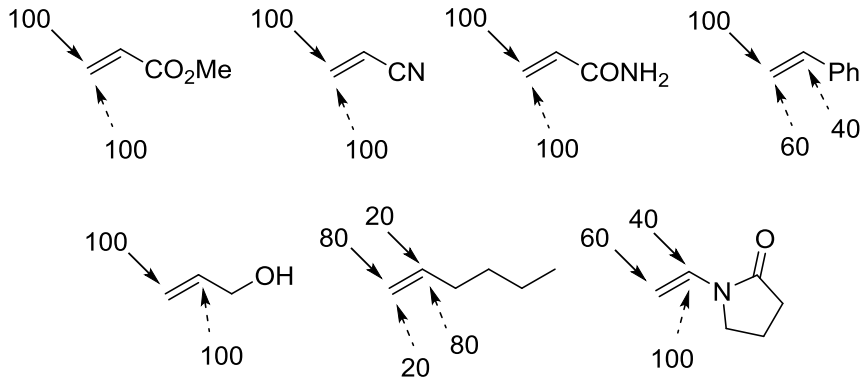
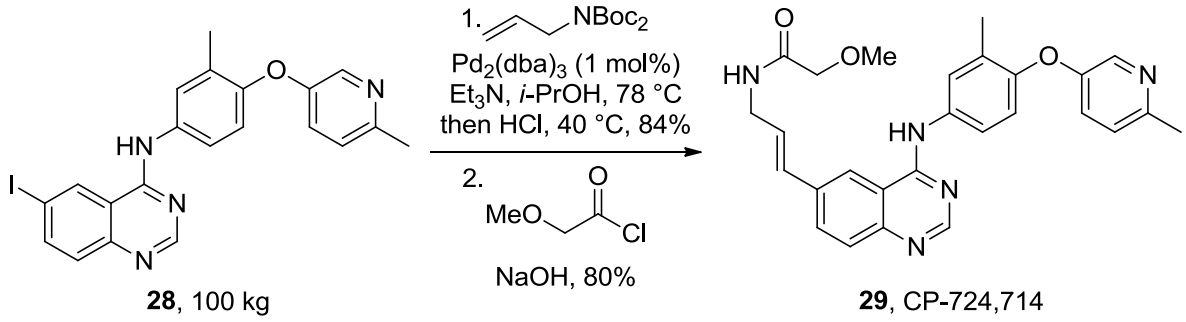


Figure 1: Regioselectivity in neutral (plain arrow) vs cationic (dashed arrow) pathway

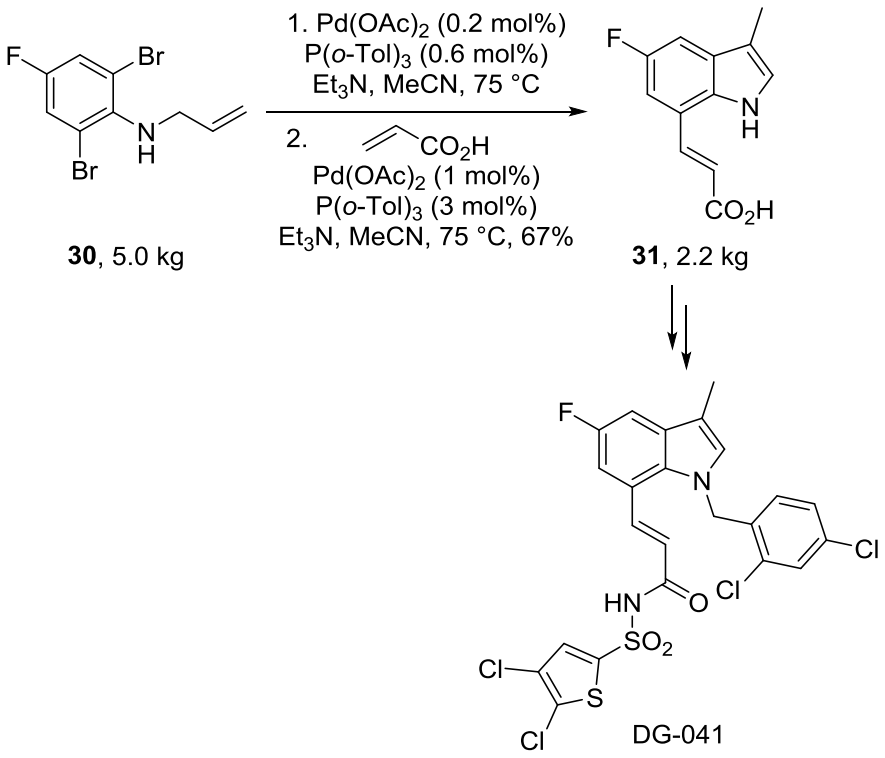
1.1.2 Applications of the Mizoroki-Heck reaction

The Mizoroki-Heck reaction has proved to be an incredibly powerful method for the coupling of aryl halides (or triflates) with alkenes, and has shown high functional group tolerance.[40–43] Heck reactions are widely utilised even for sensitive substrates, although sometimes screening of the reaction conditions is required to develop optimised conditions for new substrates. Still, not surprisingly, it is one of the most widely used methods for C-C bond formation in academia and industry. For example, the synthesis of the anti-cancer compound CP-724,714 was evaluated for a multikilogram scale process and among the different synthetic routes investigated, the most efficient route utilised a Heck coupling as the key alkene insertion step (Scheme 15).[40] Thus, Boc-protected allylamine underwent an intermolecular Heck reaction with the iodo quinazoline **28** to afford the coupled product, and acidic treatment resulted in the hydrochloride salt of the primary amine in 84% yield. The synthesis of the pharmaceutically active compound **29** was complete after reaction with methoxyacetyl chloride under basic conditions.



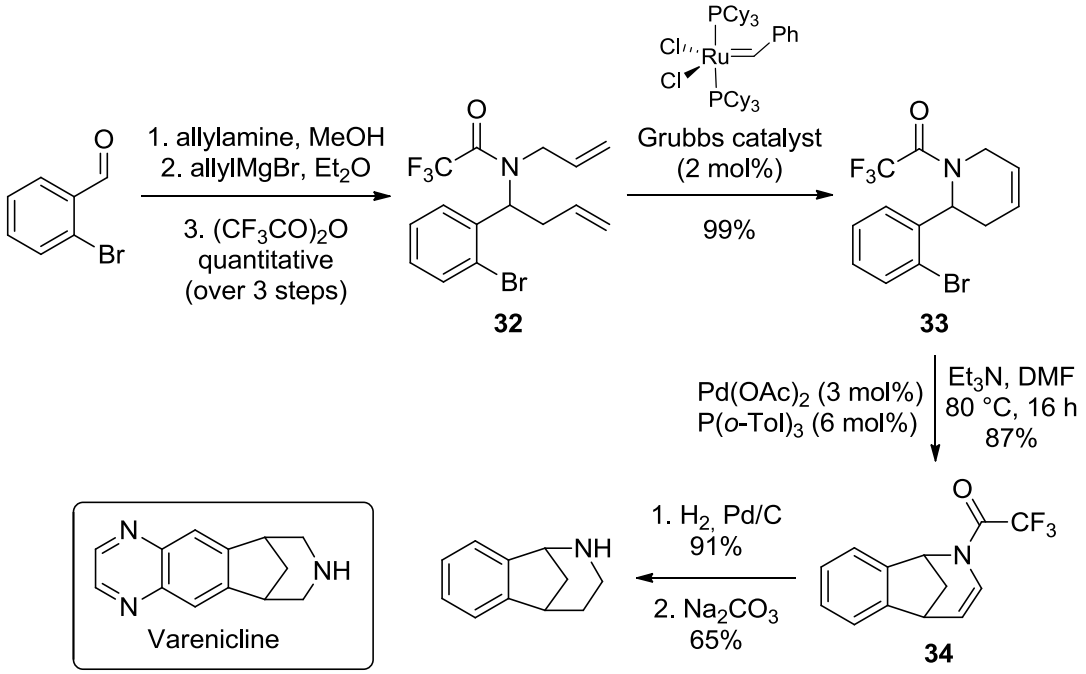
Scheme 15: Synthesis of CP-724,714[40]

In another large-scale example, a double Mizoroki-Heck reaction was performed for the synthesis of an EP_3 receptor antagonist DG-041 (Scheme 16).[41] The key steps in the optimised route contained two sequential Heck reactions, involving an intramolecular Heck cyclisation of allylamine **30** followed by an intermolecular Heck coupling. This afforded key intermediate **31** with a highly substituted indole core in 67% yield over the two steps.



Scheme 16: Synthesis of DG-041[41]

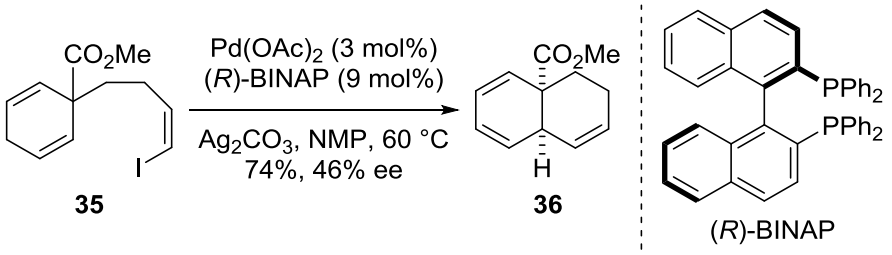
Also, key intermediate **34** in the total synthesis of a structural analogue of Chantix® (or varenicline, treatment of nicotine addiction) was synthesised by a route which involved a Heck reaction (Scheme 17).[42,43] Ring-closing metathesis (RCM) and intramolecular Heck cyclisation were the key steps for the formation of the bridged benzazepine core. The RCM precursor **32** was achieved in a quantitative yield in a three-step procedure from 2-bromobenzaldehyde and the ruthenium-catalysed cyclisation afforded a tetrahydropyridine derivative **33**. The subsequent intramolecular Heck reaction generated the [3.2.1]-bicyclic benzazepine **34** in 87% yield.



Scheme 17: Synthesis of varenicline analogue[42,43]

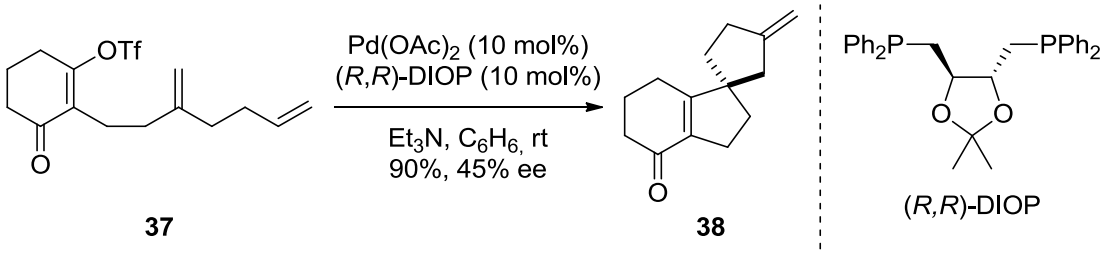
1.1.3 Asymmetric Mizoroki-Heck reaction

The discovery and development of the asymmetric variant of the Mizoroki-Heck reaction was inspired by the need for the preparation of tertiary and quaternary stereocentres by C-C bond formation in natural product total synthesis.[44] During the past 30 years, the catalytic asymmetric Heck reaction has become a reliable method for enantioselective synthesis.[45] In 1989, Shibasaki and Overman independently reported the first significant examples in the development of the asymmetric Mirozoki-Heck reaction catalysed by chiral palladium complexes.[46,47] Shibasaki described the synthesis of a tertiary carbon stereocentre in the formation of *cis*-decalin **36** *via* an intramolecular Heck cyclisation (Scheme 18).[46] The optimised conditions involved the use of $Pd(OAc)_2$ (3 mol%), (*R*)-BINAP as the chiral ligand and silver carbonate. Although the product was obtained in 74% yield, the enantioselectivity was modest at 46% enantiomeric excess (ee). In their study, various chiral diphosphine ligands were examined, and BINAP provided the best result. This reaction was important, as it demonstrated for the first time that an intramolecular Heck reaction could be employed for the asymmetric preparation of tertiary stereocentres.



Scheme 18: Shibasaki's asymmetric Heck reaction[46]

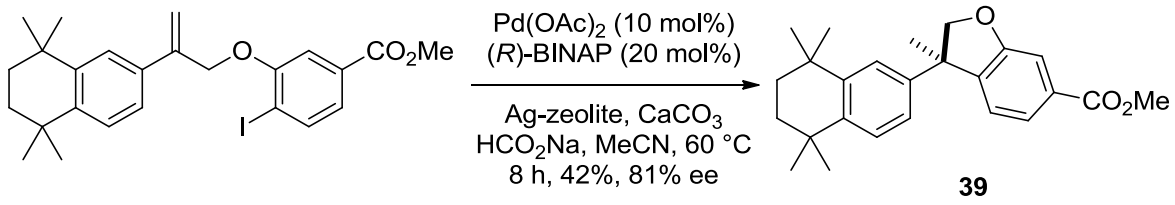
In the same year, Overman published the first asymmetric Heck cyclisation for the direct formation of a quaternary carbon stereocentre (Scheme 19).[47] The formation of spirocycle **38** was shown, which formed *via* two sequential Heck cyclisations from trienyl triflate **37** at room temperature. The optimised conditions involved the use of $Pd(OAc)_2$ (10 mol%), (*R*,*R*)-DIOP as the chiral ligand and triethylamine. This afforded the spirocyclic product **38** in 90% yield and 45% ee.



Scheme 19: Overman's asymmetric Heck reaction[47]

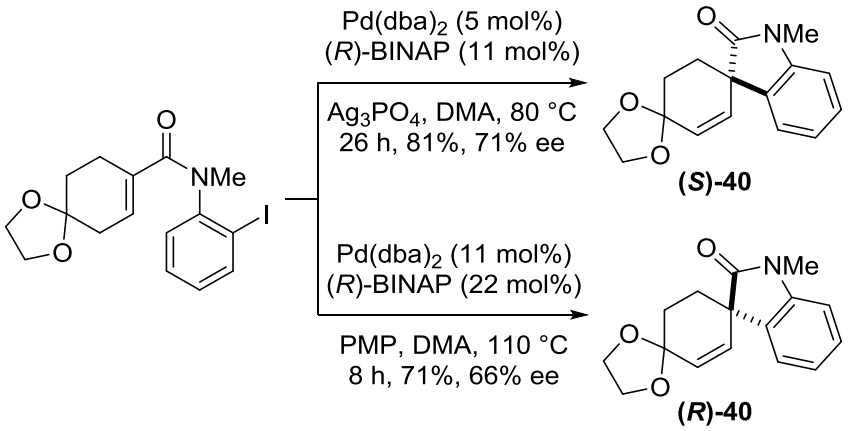
Since then, the catalytic asymmetric Heck reaction has become an area of extensive research worldwide, and it has been developed into a powerful tool for the enantioselective cyclisation of complex substrates. For example, Diaz and co-workers reported the asymmetric synthesis of a conformationally restricted retinoid **39** containing a benzylic quaternary stereocentre (Scheme 20).[48] The optimised conditions involved the use of $Pd(OAc)_2$, (*R*)-BINAP, Ag-exchanged zeolite to induce the cationic pathway and $CaCO_3$ as base. After completion of the 5-*exo*-trig cyclisation, the intermediate could not undergo elimination in the absence of a β-hydrogen, thus sodium formate was added as a hydride source to induce the release of the product and regeneration of the Pd(0) catalyst. This gave the retinoid **39** in 42% yield and 81% ee. The authors also noted that poorer enantioselectivity was observed when the Heck reaction

proceeded in the absence of silver (neutral pathway). Thus, when the aryl iodide was subjected to the neutral reaction pathway, a strong Pd-I bond in the square planar neutral intermediate allowed for the alkene coordination-insertion steps to proceed *via* the dissociation of one of the weaker Pd-phosphine ligands. Therefore, if the ligand was a chiral diphosphine, the chiral information was lost. In order to achieve higher enantioselectivities, the addition of silver-exchanged zeolite was required. This induced the formation of a cationic intermediate whereby palladium remained coordinated to the chiral diphosphine ligand and ultimately resulted in an enantioselective process.



Scheme 20: Asymmetric synthesis of retinoid 39 by Diaz[48]

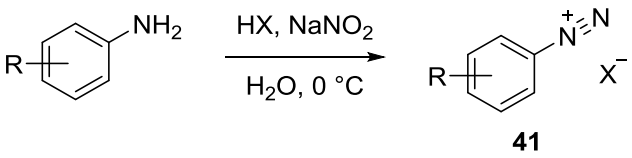
In a study for the asymmetric synthesis of oxindole derivatives, Overman and co-workers investigated the intramolecular Heck reactions of (*E*)-α,β-unsaturated 2-iodoanilides, and found that both enantiomers of the spirooxindole product could be synthesised using a single enantiomer of the chiral BINAP diphosphine ligand (Scheme 21).[49] Depending on the reaction conditions the stereochemistry was reversed in the cyclisation (silver vs amine-promoted conditions). Thus, the use of Ag(I) salts in the intramolecular Heck cyclisation resulted in **(*S*)-40** in 71% ee, while use of the hindered amine base 1,2,2,6,6-pentamethylpiperidine (PMP) produced the **(*R*)-40** in 66% ee.



Scheme 21: Overman's asymmetric oxindole synthesis[49]

1.2 The Heck-Matsuda reaction

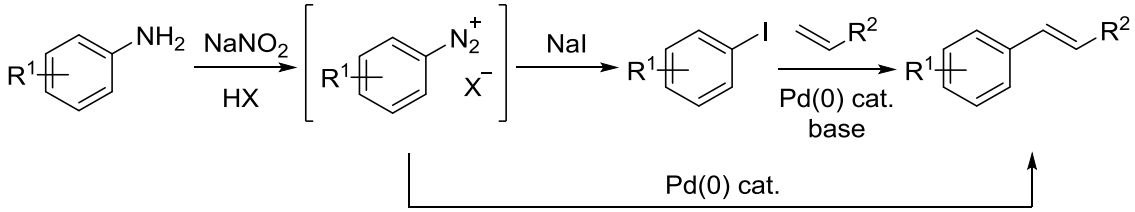
Diazonium salts **41** were first prepared in the 19th century by Johann Peter Grieß from anilines under harsh conditions of sodium nitrite in the presence of strong acids (Scheme 22). These traditional conditions led to unstable aryl diazonium salts which had the tendency to be highly explosive, especially with chloride or acetate counterions.[50,51] Also, strong acidic conditions were not always tolerated by some anilines and hence, the substrate scope could be limited with the exclusion of acid-sensitive functional group containing starting materials. This restricted the widespread synthetic utility of such intermediates, and the development of novel, safe methods employing mild conditions for diazotisation only started to increase more recently.[51,52]



Scheme 22: Traditional formation of diazonium salts from anilines

Initially, diazonium salts were utilised in nucleophilic substitution reactions, such as the Sandmeyer reaction, for the synthesis of aryl halides, which could then be applied in transition metal-catalysed transformations (Scheme 23).[53,54] However, diazonium salts are highly reactive aryl halide surrogates, which can be used in palladium-catalysed cross-coupling reactions involving sensitive

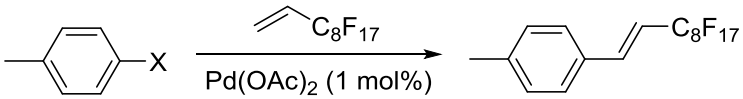
substrates, and indeed, their application in organic synthesis is increasing.[51,52] This is due to their tolerant nature towards a wide range of reaction conditions as well as the enhanced reactivity over aryl halides which enables the cross-coupling reactions to proceed at low temperatures, without the presence of a base and ligands.



Scheme 23: Diazonium salts as aryl halide surrogates

In 1977, Kikukawa and Matsuda reported the first application of aryl diazonium salts as coupling partners in the Mizoroki-Heck arylation of alkenes under Pd(0) catalysis.[55–57] Since then, it is known as the Heck-Matsuda reaction, acknowledging the pioneering discovery of Matsuda *et al.*, who reported the replacement of aryl halides with aryl diazonium salts in the Heck reaction for C-C bond formation.[55] The reaction proceeded under mild conditions due to the increased electrophilic nature of the diazonium salts, in hydrophilic solvents at room temperature and could be monitored by the production of nitrogen gas. As this process did not require the use of ligands or a base, it was considered highly efficient and sustainable.[51] Also, safety hazards associated with aryl diazonium salts have been overcome by using the more thermally stable tetrafluoroborate salts.[57] The superior reactivity of aryl diazonium salts over aryl halides in C-C bond formation was proved by Genêt *et al.*, who carried out a comparative study (Scheme 24).[58] Thus, an electron-poor alkene with a perfluoroalkyl chain was subjected to the Heck-Matsuda reaction with *p*-toluenediazonium tetrafluoroborate, 4-iodotoluene and 4-bromotoluene, respectively. It was found that, in the presence of $Pd(OAc)_2$ (1 mol%), the coupled products were afforded cleanly and exclusively as *E*-alkenes. Importantly, the aryl diazonium tetrafluoroborate substrate allowed for the application of milder Heck conditions and displayed higher turnover number (TON) and turnover frequency (TOF) values than the aryl halides to highlight the more efficient coupling

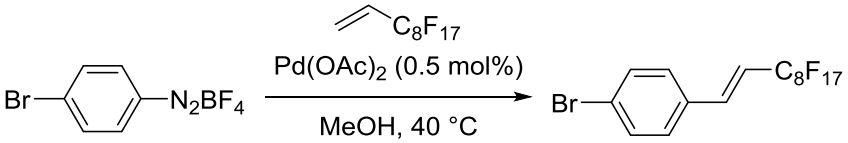
process. It was concluded, that for the Heck-Matsuda reaction, the reactivity of the electrophilic coupling partner decreases in the following order N_2^+> I >> Br.



		TON	TOF
X = N_2BF_4	MeOH, 40 °C	100	200
X = I	$NaHCO_3$, *n*-Bu_4NHSO_4, DMF, 90 °C	80	7
X = Br	$NaHCO_3$, *n*-Bu_4NHSO_4, DMF, 90 °C	18	0.4

Scheme 24: Superior reactivity of diazonium salts in the Heck-Matsuda reaction[56]

The advantage of aryl diazonium salts containing halide groups as electrophilic coupling partners in the Heck-Matsuda reaction is that they allow for chemoselective control, hence their different electrophilic nature.[51] In addition to the studies involving the synthesis of perfluoroalkylated aryl compounds, the Genêt research group also reported the chemoselective substitution of the diazonium N_2 group, which occurred in the presence of other nucleofuge groups, such as bromine and iodine (Scheme 25).[58] The results indicated, that no background competing Heck reaction took place in the Heck-Matsuda reaction of bromo-substituted aryl diazonium salt **42** and the coupled product **43** formed quantitatively in methanol. As a consequence, the exceptional chemoselectivity shown by halide-substituted aryl diazonium salts in cross-coupling reactions has the potential to be further utilised in other cross-coupling reactions for the synthesis of more complex compounds.

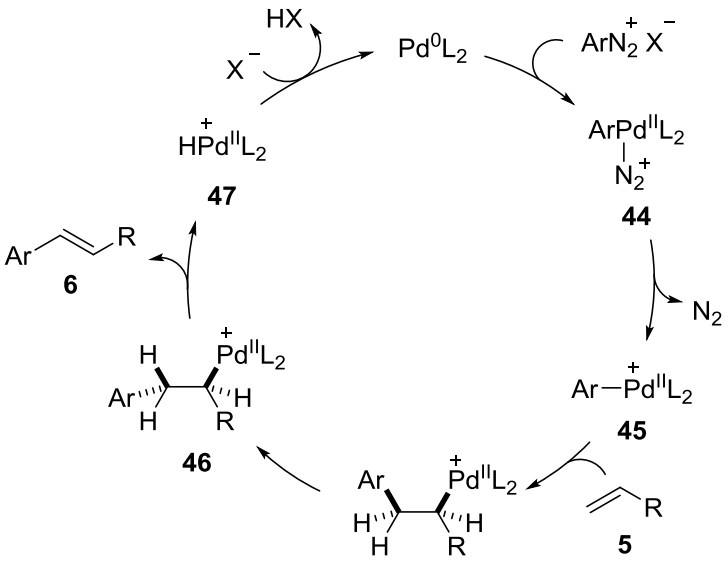


42 **43**

Scheme 25: Chemoselectivity in Heck-Matsuda reactions

The catalytic cycle of the Heck-Matsuda reaction is very similar to the Mizoroki-Heck mechanism and typically described by the cationic pathway (Scheme 26).[52] After catalyst preactivation, oxidative addition of the Pd(0) complex proceeds very quickly *via* insertion into the C-N bond of the diazonium species. Due to the

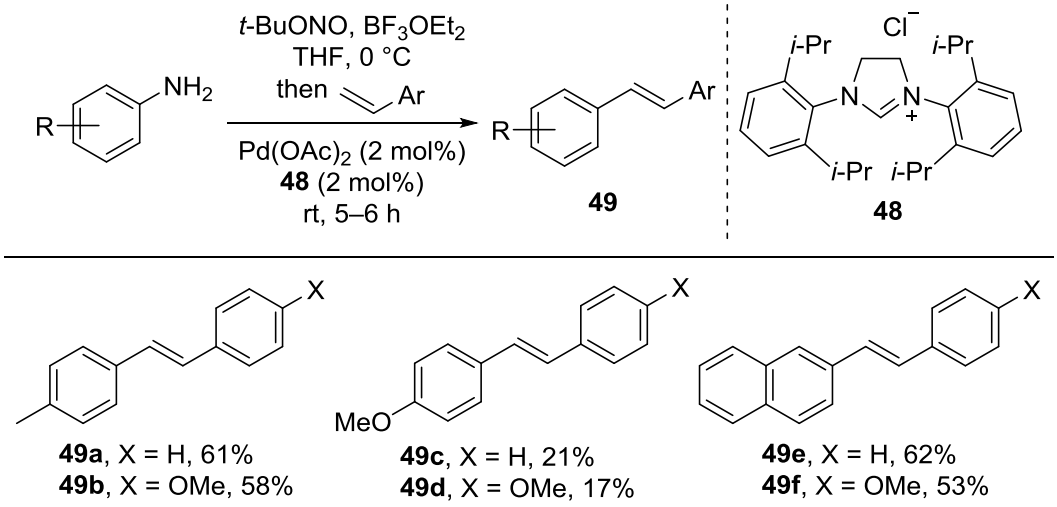
reactive nature of the aryl diazonium cation, the catalytic cycle can be carried out at low temperatures.[52] The resulting intermediate **44** containing the Pd(II)-N_2 bond is prone to ionisation, thus spontaneously eliminates N_2 gas and generates a cationic palladium(II) species **45**. Unlike the Mizoroki-Heck reaction, where the rate determining step is the oxidative addition, in the Heck-Matsuda reaction, the ease of this step suggests that the rate-limiting step occurs further along the cycle.[51] Indeed, as Roglans *et al.*, found through the application of electrospray ionisation mass spectrometry, the rate determining step for the Heck-Matsuda reaction is the migratory insertion.[59] The rest of the catalytic cycle follows the same elemental steps as in the Mizoroki-Heck cationic pathway: after internal C-C bond rotation, **46** undergoes a *syn* β-hydride elimination to release the coupled product and upon reductive elimination, the active catalyst is regenerated from **47**.



Scheme 26: Catalytic cycle of the Heck-Matsuda reaction

As aryl diazonium salts are highly reactive, the Heck-Matsuda reaction conditions require fine-tuning in order to prevent side reactions and degradation products. Consequently, recent studies in this research area have focused on the development of improved catalytic systems to increase the economic viability and efficiency of the reaction.[60–65] For example, in 2002, Andrus and co-workers reported the application of imidazolium carbene **48** as a palladium ligand that allowed for the efficient coupling of styrenes and arenediazonium salts under base-free conditions in one-pot (Scheme 27).[60] The aryl diazonium salts were

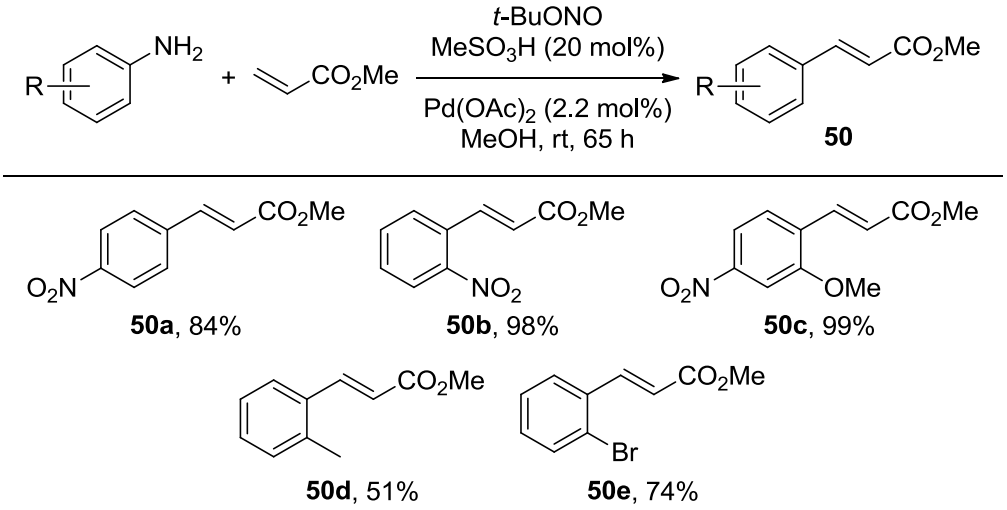
prepared *in situ* by using *tert*-butyl nitrite and boron trifluoride etherate at 0 °C. Following this, the palladium-catalysed reaction proceeded at room temperature. The *in situ* formed Pd(0) complex expressed high catalytic activity and thus could be employed in low catalyst loadings (2 mol%). The corresponding coupled products were achieved in 17–62% yield, whereby generally modest yields were obtained for the 4-methyl and 2-naphthyl derivatives. Electron-rich compounds **49c** and **49d** resulted in lower yield.



Scheme 27: Heck-Matsuda reaction by Andrus and co-workers[58]

More recently, the Felpin research group have made a major contribution in understanding the Heck-Matsuda reaction as well as developing new applications.[61–65] In 2011, the Felpin group developed a one-pot tandem diazotisation-Heck-Matsuda process starting from anilines and using catalytic amounts of diazonium salts *via* a double catalytic cycle (Scheme 28).[64] The aryldiazonium salts, prepared *in situ* by using *t*ert-butyl nitrite and catalytic amounts of methanesulfonic acid (20 mol%), were reacted with methyl acrylate in the presence of $Pd(OAc)_2$ (2.2 mol%). The procedure gave the cross-coupled products in generally high yields over a reaction time of 65 h. Aniline starting materials with different substitution patterns were screened and found that although the highest yielding substrate was **50c**, an electron-withdrawing group in the *ortho*-position was also beneficial for the coupling to give **50b**. It was also shown, that the bromo-substituted aniline underwent the Heck-Matsuda reaction chemoselectively to give **50e**. This one-pot tandem process was highly advantageous, as the reactive aryl diazonium salt was generated *in situ*, and any

potential hazards regarding handling and storage were avoided. The highly reactive nature of the diazonium salt also allowed for the reaction to take place under mild conditions without the need for bulky phosphine ligands or base to drive the reaction.

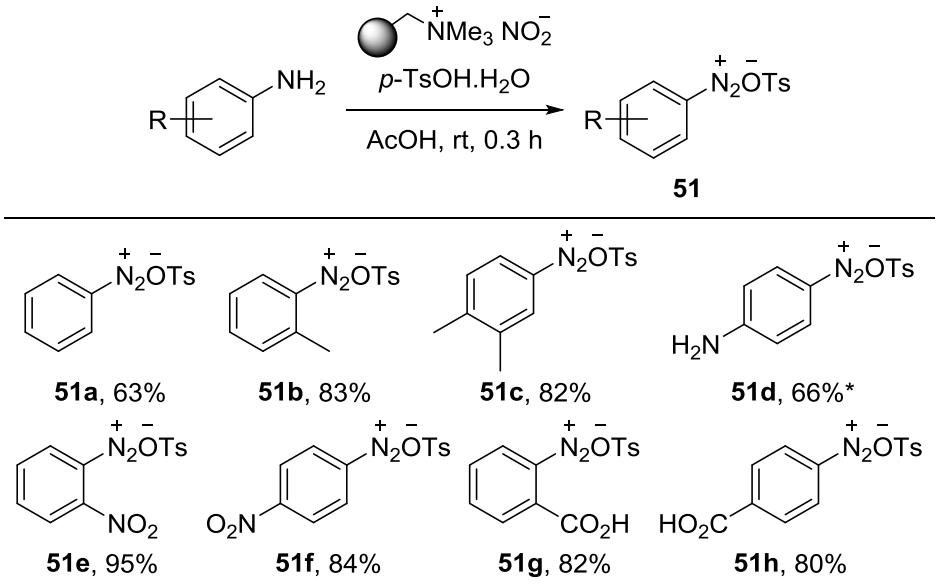


Scheme 28: One-pot tandem process by Felpin and co-workers[64]

Since then, further improvement of the reaction conditions has led to more efficient, sustainable processes. For example, Gholinejad developed the Heck-Matsuda reaction in aqueous media using an agarose supported palladium nanoparticle catalyst.[66] The polysaccharide solid support facilitated catalytic recovery *via* gel formation upon cooling. Therefore, the palladium catalyst could be re-used for up to three catalytic cycles, with comparable yields each time (87–90%). Also, Singh reported an environmentally benign catalytic system which utilised supermagnetic zinc-ferrite nanoparticles coated in palladium as a catalyst for the coupling.[67,68] The reaction occurred in water, affording the products in 80–86% yield. Moreover, the catalyst could be recycled *via* magnetic separation and re-used.

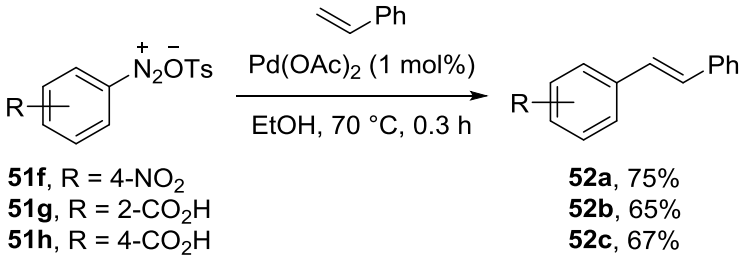
An important milestone in the evolution of the Heck-Matsuda reaction was the synthesis and characterisation of aryl diazonium tosylate salts. Their synthesis was first reported by Filimonov and was conducted by a polymer-supported diazotisation reagent under mild conditions from anilines (Scheme 29).[69] The polymer-supported nitrite reagent was prepared by ion exchange of the tetramethylammonium hydroxide resin, Amberlyst® A26 with aqueous sodium

nitrite. It was shown that the highly stable aryl diazonium tosylate salts could be stored at room temperature for months and were thermally stable up to 600 °C according to DSC studies. This was due to the strong affinity between the tosylate counterion and diazonium salt, proved by X-ray crystallographic analysis. The ease of use and recyclability of the polymer supported nitrite reagent made it a safe alternative. The simple diazotisation method allowed for the rapid synthesis and safe isolation of aryl diazonium tosylate salts **51a–h** in good yields. Although unsubstituted aniline gave a modest 63% yield for **51a**, various substituents were tolerated in the diazotisation reaction. It was also noted, that *p*-phenylenediamine did not undergo double diazonium salt formation and only gave **51d** in 66%. Excellent isolated yield of 95% was obtained for **51e** containing an *ortho*-nitro group; free carbocylic acid containing analogues **51g** and **51h** were also prepared using this method.



Scheme 29: Synthesis of aryl diazonium tosylate salts; * reaction was carried out in MeOH

In addition to this, the application of aryl diazonium tosylate salts in palladium-catalysed cross-coupling reactions such as the Heck-Matsuda was also carried out.[69–71] The previously synthesised aryl diazonium tosylate salts **51f–h** were submitted to the Heck-Matsuda reaction with styrene in the presence of $Pd(OAc)_2$ (1 mol%) and the corresponding *E*-stilbenes **52a–c** were achieved in 65–75% yield (Scheme 30).[69]



51f, R = 4-NO_2
51g, R = 2-CO_2H
51h, R = 4-CO_2H

52a, 75%
52b, 65%
52c, 67%

Scheme 30: Heck-Matsuda reaction of aryl diazonium tosylate salts

1.3 One-pot processes

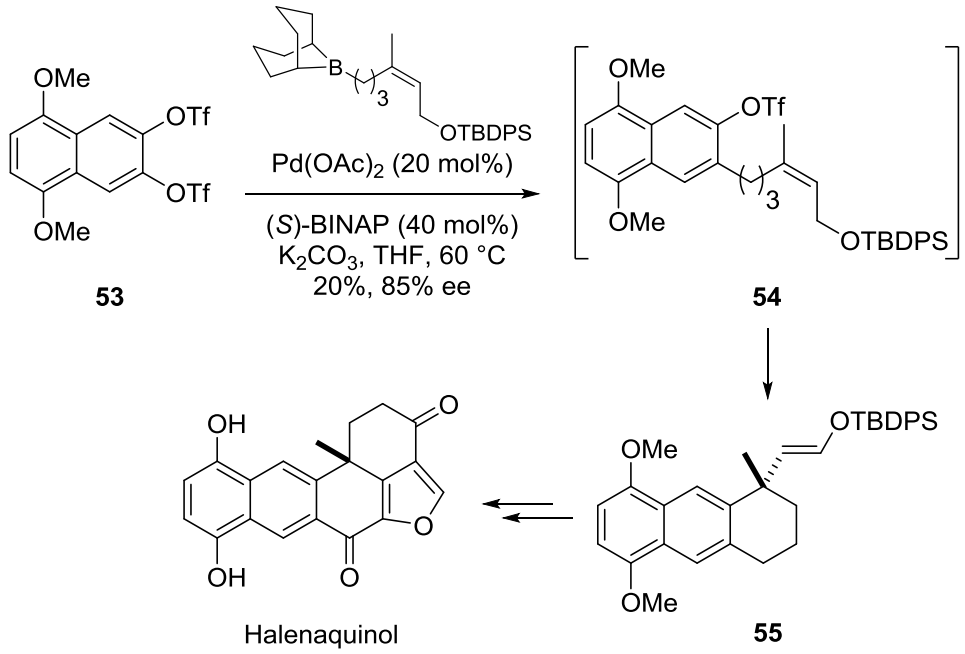
Modern synthetic organic chemistry is facing the important objective of maximising reaction efficiency while decreasing environmental footprint.[72] As a consequence, progressive scientific efforts have focused on the design and development of new sustainable synthetic methodologies.[73] Creating minimal environmental impact can be challenging, and for better understanding, four categories have been proposed by organic chemists to describe the new methods: step-, pot-, atom-, and redox economy.[74–77] Step economy refers to minimising the number of synthetic steps to prepare the target compound,[74] and is closely related with redox economy, which is a decrease of undesired changes in oxidation states of intermediates to reduce the number of steps. Atom economy is the incorporation of all atoms of each reagent into the final product during the reaction.[75,76] Lastly, pot economy means avoiding the isolation and purification of intermediates by carrying out several sequential reactions in the same vessel.[77] With the development of one-pot multistep processes all these economic advantages are addressed.

The one-pot multi-bond forming strategy is a powerful approach for the synthesis of complex molecules that has been used in a wide variety of transformations.[72,73,78] Its broad applicability in the field of organic synthesis relies on the simple fact that this process provides several reaction steps in just one operation, which saves considerable time and money on the separation, isolation and purification of intermediates while ultimately increasing the chemical yield. Moreover, it avoids the handling of unstable and sensitive intermediates. It also meets the standards of greener chemistry with reduction in the amount of solvents and reagents required as well as generated waste.

There are three main classes of one-pot processes: tandem, domino/cascade, or sequential one-pot multistep process (also known as telescoping synthesis).[79]

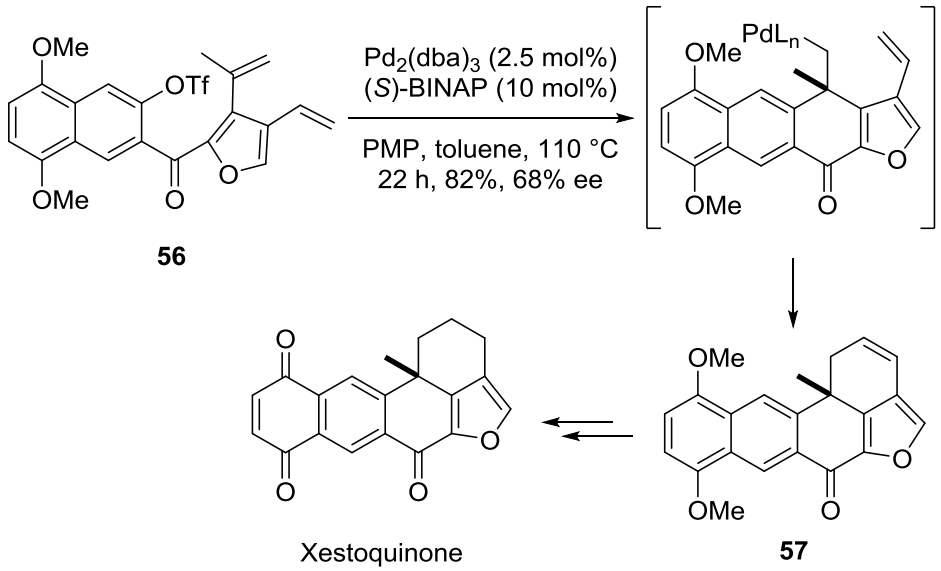
1.3.1 One-pot process initiated by the Mizoroki-Heck reaction

The Mizoroki-Heck reaction is a significant tool in C–C bond formation, and has been extensively used as a single step in the total synthesis of natural products and other synthetically important compounds. Moreover, this reaction can be combined with other transformations in one-pot processes for more efficient and sustainable methodologies. For example, Shibasaki and co-workers extended their studies in the field of intramolecular Heck reactions and reported the cyclisation of bistriflate **53** for the synthesis of polyketides (Scheme 31).[80] The key intermediate **55** was prepared in a one-pot procedure involving a cascade Suzuki-Miyaura cross-coupling and asymmetric Mizoroki-Heck reaction. Suzuki-Miyaura coupling of the symmetric bistriflate **53** with the 9-BBN derived alkyl borane was mediated by $Pd(OAc)_2$. The same catalyst was then used for the intramolecular cyclisation of **54** with the trisubstituted alkene. The one-pot reaction gave tetrahydroanthracene **55** with a quaternary benzylic stereocentre in 20% yield and 86% ee.



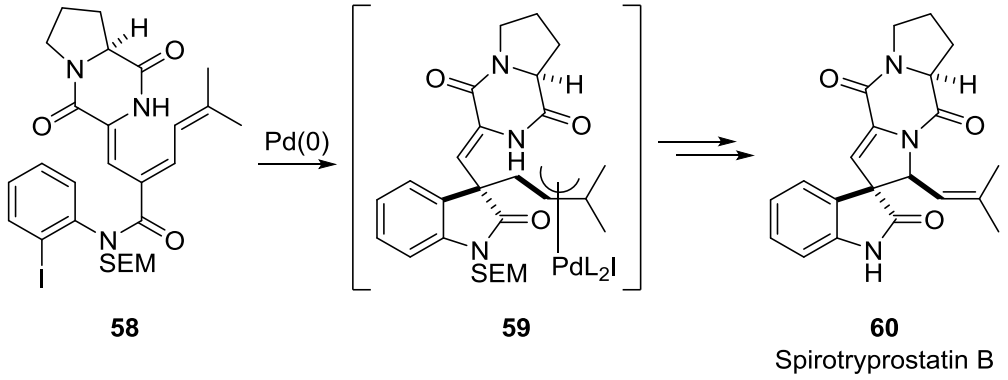
Scheme 31: One-pot cascade process by Shibasaki and co-workers[80]

Keay and co-workers have also studied the asymmetric total synthesis of polyketides (Scheme 32).[81] They reported a one-pot cascade double Heck cyclisation as the key step in the first enantioselective synthesis of xestoquinone. The transformation proceeded *via* an intramolecular asymmetric 6-*exo* cyclisation of **56** to install the benzylic quaternary stereocentre, and in the absence of a β-hydrogen, was followed by a second cyclisation to form the pentacyclic product **57**. Due to the developing ring strain, the typically favoured *exo* cyclisation was not viable, thus the second cyclisation followed a 6-*endo* pattern and resulted in the polyene compound **57** in 82% yield and 68% ee.



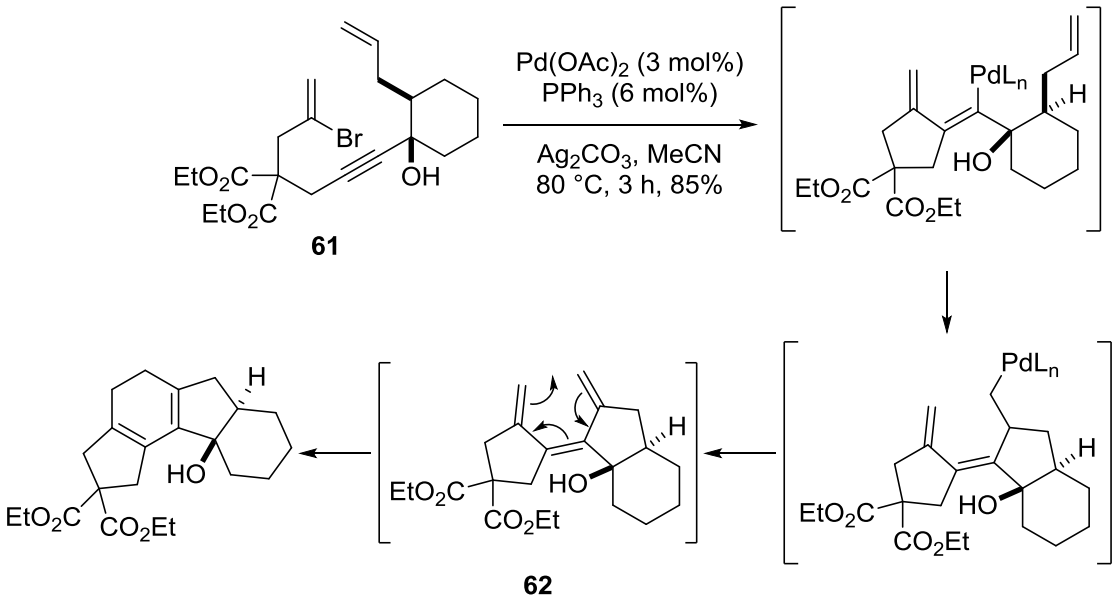
Scheme 32: One-pot cascade process by Keay and co-workers[81]

In another example by the Overman group, a one-pot tandem asymmetric Heck cyclisation was developed for the synthesis of the alkaloid spirotryprostatin B (Scheme 33).[82] The strategy involved the favoured 5-*exo* intramolecular Heck cyclisation of the enantiopure triene precursor **58**. This afforded an η^3-allylpalladium intermediate **59**, which was spontaneously trapped by the proximal nitrogen of the tethered diketopiperazine. Cleavage of the SEM protecting group produced natural product **60**.



Scheme 33: One-pot tandem process by Overman and co-workers[82]

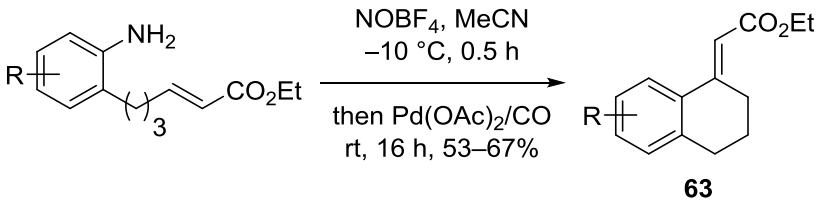
The research group of de Meijere reported the one-pot cascade cyclisation in the synthesis of polycyclic scaffolds from alkyne precursor **61** (Scheme 34).[83] In their work, the sequential transformations involved the formation of two 5-membered rings by intramolecular Heck reactions (both 5-*exo*), followed by the 6π-electrocyclisation of the triene intermediate **62** for the construction of the final 6-membered ring.



Scheme 34: One-pot cascade process by de Meijere and co-workers[83]

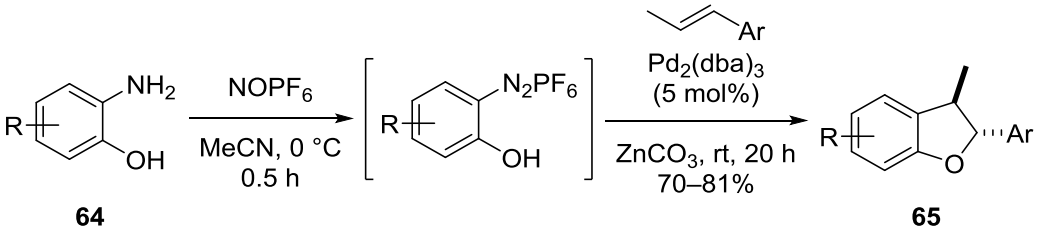
1.3.2 One-pot process initiated by the Heck-Matsuda reaction

Although the number of publications that apply the Heck-Matsuda reaction for the arylation of acrylates,[63] styrenes,[84] vinylphosphonates,[85] allylic alcohols,[85] cyclic enol ethers,[87] and even alkynes[88,89] with stable aryl diazonium salts is increasing, the literature of one-pot processes involving this type of cross-coupling is still fairly limited. This is possibly due to the highly reactive nature of the aryl diazonium salts and continuous fine-tuning of the experimental conditions needed to gain control over the reaction. However, to further minimise the safety issues involving the handling and storage of aryl diazonium salts, one-pot diazotisation-Heck-Matsuda reactions have been developed. For example, Correia and co-workers reported the one-pot tandem diazotisation followed by intramolecular Heck-Matsuda cyclisation of α,β-unsaturated esters which provided tetrahydronaphthalenes **63** in 53–67% yield (Scheme 35).[90] This was achieved by using nitrosonium tetrafluoroborate as the nitrite source for the formation of the aryl diazonium salt intermediate at low temperature, followed by the cyclisation step at room temperature in the presence of $Pd(OAc)_2$ which was reduced *in situ* by carbon monoxide.



Scheme 35: One-pot tandem process by Correia and co-workers[90]

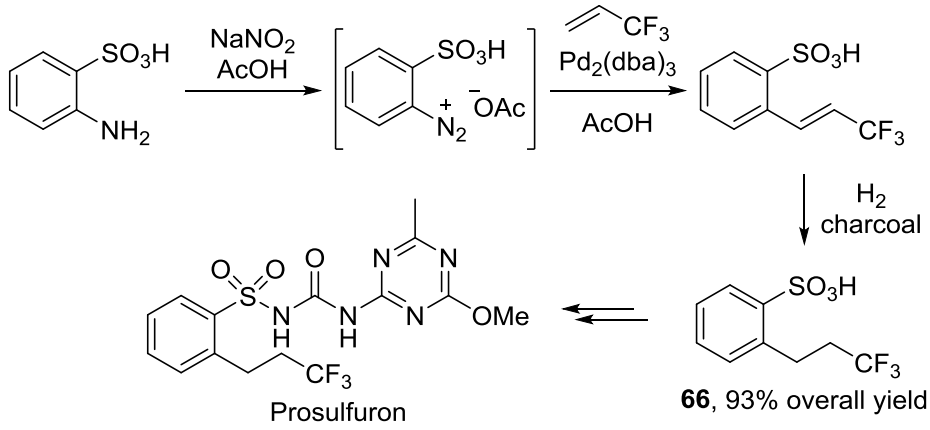
In another example, *trans*-dihydrobenzofurans **65** were synthesised in a one-pot tandem diazotisation-Heck-Matsuda process (Scheme 36).[91] The diastereoselective construction of such heterocycles was achieved by using substituted aminophenols **64** as starting materials. *In situ* diazotisation afforded the aryl diazonium hexafluorophosphate salts and these were submitted to the oxyarylation reaction with $Pd_2(dba)_3$ (5 mol%) which gave dihydrobenzofurans **65** in 70–81% yield.



64 **65**

Scheme 36: One-pot tandem process by Sefkow and co-workers[91]

Heck-Matsuda reactions have also been applied in the formal and total syntheses of natural products and pharmaceutically active compounds. This was demonstrated by the synthesis of the potent psychoactive agent indatraline,[92] the antidepressant paroxetine,[93] and natural product reservatrol.[94] Moreover, a one-pot diazotisation-Heck-Matsuda process was developed for the industrial synthesis of the herbicide prosulfuron (Scheme 37).[95,96] The key steps in the route involved the *in situ* formation of aryl diazonium sulfonate salt (isolable) followed by arylation of 3,3,3-trifluoropropene under $Pd_2(dba)_3$ catalysis and subsequent reduction of the *E*-alkene with the addition of hydrogen and charcoal. This sequence afforded the key intermediate **66** in 93% yield over the three steps.



Scheme 37: Industrial one-pot process for the preparation of prosulfuron[95,96]

1.4 Conclusions

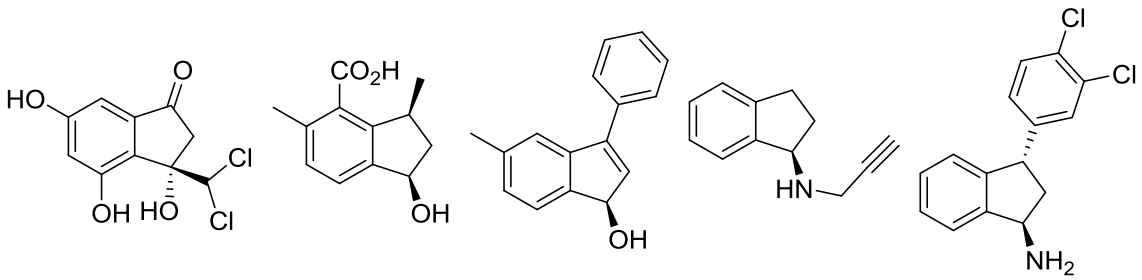
In summary, the Mizoroki-Heck reaction has been widely studied and expanded to include various substrates and thus has become a powerful method for the highly efficient synthesis of quaternary carbon stereocentres as well as polycyclic structures. This is mainly due to its incredible functional group tolerance, which has enabled it to become an important tool for the formation of C–C bonds. Despite its robustness, the Heck reaction involving aryl halides and triflates still has some limitations, such as the use of air sensitive phosphine ligands or high temperatures which can lead to the formation of byproducts and/or catalyst deactivation. To overcome these limitations, the Heck-Matsuda reaction can be a suitable alternative for cross-coupling reactions. The readily available aniline starting materials allow for the aryl diazonium salts to be prepared *in situ*, and usually enable the use of much milder reaction conditions, which often exclude a base or ligands. These features of the Heck-Matsuda reaction can potentially solve various problems encountered with aryl halides in the traditional Heck protocol.

2.0 Results and Discussion

2.1 One-pot Multistep Asymmetric Synthesis of Alkylidene 1-Alkylindane-1-ols

2.1.1 Introduction

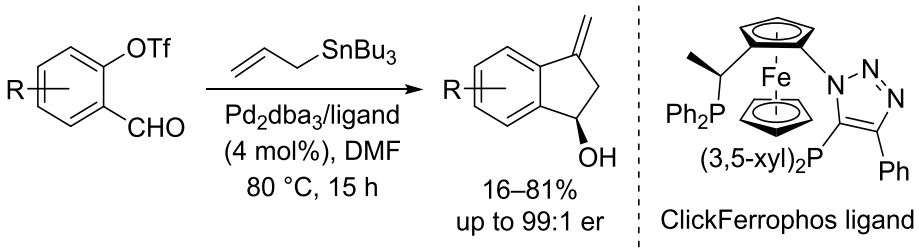
Chiral indane-1-ol derivatives have been widely used as valuable key intermediates in the total synthesis of biologically relevant complex molecules and many pharmaceutically active agents.[97] The importance of this 5,6-fused carbocyclic building block is highlighted in its many derivatives that possess various biological activities, including antiallergic, antitumor, anticonvulsant, fungicidal and herbicidal activities.[98] For example, the natural product tripartin (**67**) was isolated from a bacterium associated with the larva of the dung beetle *Copris tripartitus* and has shown to display specific activity as a histone demethylase inhibitor (Figure 2).[99] Also, indane **68** served as a valuable key intermediate in the formal total synthesis of the neurotoxin sesquiterpenoid anisatin, native to the Japanese star anise (*Illicium anisatum*).[100] More importantly, indane scaffolds are also frequently found in drug molecules, such as **69**, which was used as a key intermediate in the synthesis of the muscarinic receptor antagonist (*R*)-tolterodine.[101] Indane derivatives with C-1 amino substitution are also of significance such as rasagiline (**70**),[102] used in the treatment for early symptoms of Parkinson's disease. Moreover, (+)-indatraline (**71**),[103] a non-selective monoamine transporter inhibitor has been shown to block the reuptake of neurotransmitters such as dopamine, serotonin, and norepinephrine with similar effects as cocaine and thus, could be used to treat cocaine, methamphetamine and MDMA addiction.



67 **68** **69** **70** **71**

Figure 2: Indane scaffold in natural products and pharmaceuticals

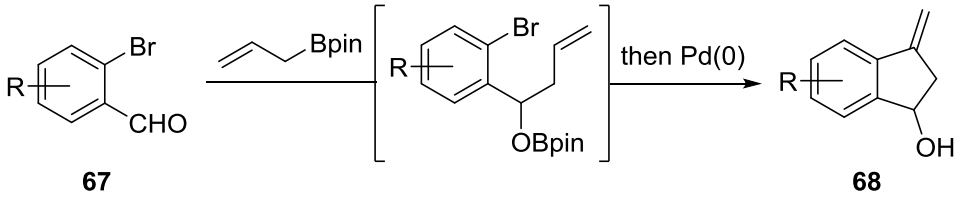
Due to their importance, a number of synthetic strategies have been developed for the preparation of chiral indan-1-ol building blocks.[97,98] Recent efforts focused on the synthesis of such scaffolds bearing a 3-methylene moiety and a secondary alcohol centre at the C-1 position.[104–109] For this, benzaldehyde derivatives were used as starting materials in asymmetric allylation reactions with allylzinc and allyllithium reagents,[104] and a subsequent metal-catalysed C-C bond forming reaction completed the synthesis of the fused carbocycle.[105] In addition to this, one-pot asymmetric methods were also reported by the research groups of Schmalz and Fukuwaza, which operated *via* electrophilic activation of benzaldehydes through *ortho*-palladation (Lewis acid activation of the carbonyl group).[107,108] The one-pot two-step asymmetric synthesis of 3-(methylene)indan-1-ols was described by using *o*-formylaryl iodides or triflates in an allylstannylation followed by palladium-catalysed Mizoroki-Heck reaction in the presence of chiral phosphine ligands (Taniaphos[107] or ClickFerrophos[108]) for the intramolecular 5-*exo*-trig cyclisation (Scheme 38). There are, however, limitations to this process, such as the highly air sensitive nature of *ortho*-formylaryl triflates, the excessive amounts of allyltributylstannane (2.0 equiv.) and narrow scope.



Scheme 38: Asymmetric domino allylstannylation-Heck reaction reported by Fukuzawa and co-workers[108]

2.1.2 Previous work in the Sutherland group

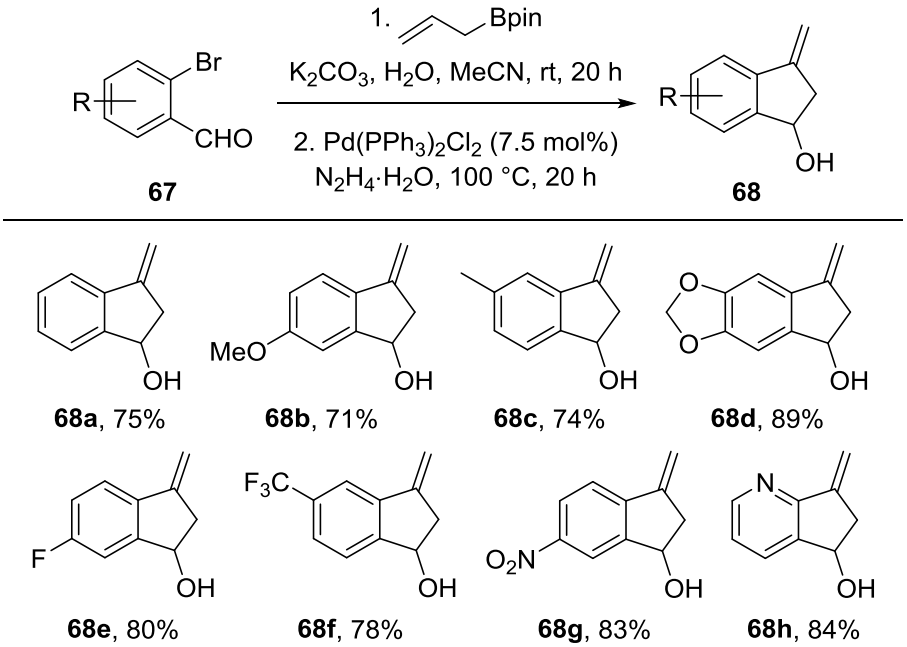
In 2015, the Sutherland research group published a novel, operationally simple, high-yielding one-pot asymmetric synthesis of 3-(methylene)indan-1-ols **68**.[109] This one-pot, two-step procedure involved allylboration of 2-bromobenzaldehydes **67** with the air- and water-stable, nontoxic allylboronic acid pinacol ester followed by palladium-catalysed intramolecular Heck reaction (Scheme 39).



67 **68**

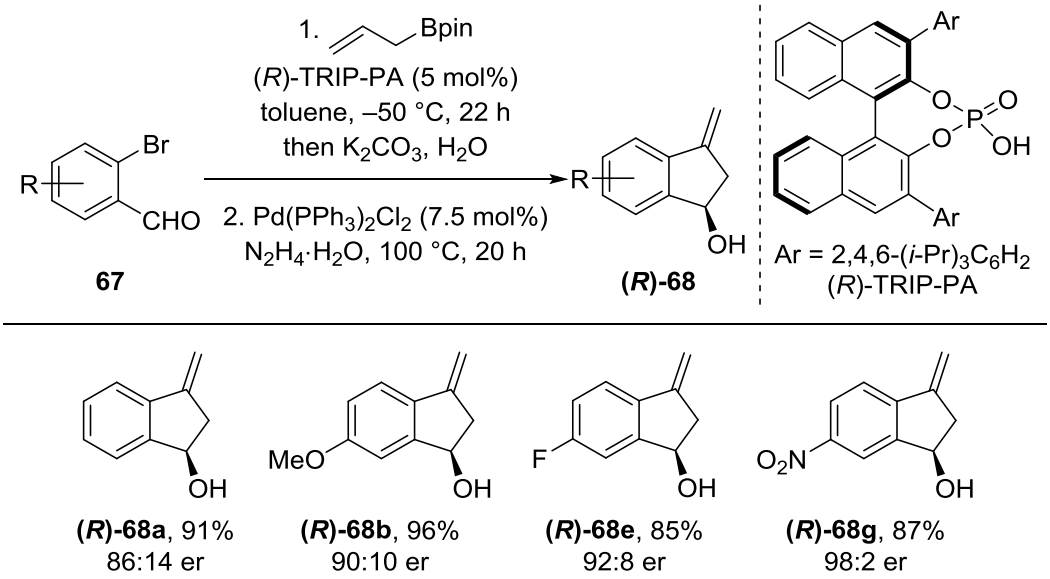
Scheme 39: One-pot allylboration-Heck reaction

Initially, the racemic version of this procedure was developed and the study began with optimisation of the reaction conditions from 2-bromobenzaldehyde (**67a**). Originally, it was planned as a tandem reaction, and when all the reagents were added at once no cyclisation product was observed and only the homoallylic alcohol product was achieved. This highlighted the necessity of stepwise addition of reagents for each stage. Upon investigating the one-pot, two-step reaction, the Heck reaction step needed to be optimised and this meant screening the appropriate catalyst, catalyst loading and reaction temperature. Thus, the optimised reaction conditions involved allylboronic acid pinacol ester as the allylating agent in acetonitrile and water in the first stage of the process. Potassium carbonate was added as base in order to promote the hydrolysis of the borate ester intermediate and liberate the homoallylic alcohol before the cyclisation step. Once the allylboration was complete, using bis(triphenylphosphine)palladium(II) dichloride (7.5 mol%), which was reduced *in situ* with hydrazine monohydrate[105] in the Heck reaction, allowed for the efficient synthesis of 3-(methylene)indan-1-ol (**68a**) in 75% yield (Scheme 40). The same conditions were applied for a broad range of 2-bromobenzaldehydes to show the generality of the one-pot process. This was demonstrated with an extensive substrate scope containing both electron-rich and electron-deficient 3-(methylene)indan-1-ols **68b–h** in 71–89% yield.



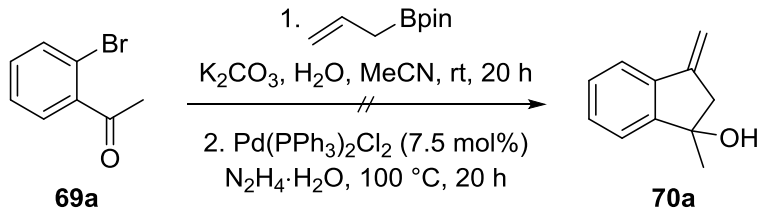
Scheme 40: Substrate scope of the racemic one-pot process

In addition to the racemic process, modification of the one-pot reaction to incorporate the chiral Brønsted acid catalysed allylboration allowed for the synthesis of optically active 3-(methylene)indan-1-ol derivatives (Scheme 41). This was achieved by introducing a catalytic amount of the sterically congested chiral binaphthyl derived phosphoric acid (*R*)-TRIP-PA in the allylboration step and also some alterations in the reaction conditions (solvent and temperature). Incorporating these new conditions to the one-pot, two-step process, a number of optically pure 3-(methylene)indan-1-ols **(*R*)-68a**, **b**, **e**, **g** were prepared in 85–96% yield and evaluation by chiral HPLC confirmed enantiomeric ratios (er) up to 98:2. To confirm that the Heck reaction had no effect on the stereochemical outcome, the homoallylic alcohol intermediate was isolated and compared to the indanol product of the one-pot process. As expected, the same level of enantioselectivity was observed.



Scheme 41: Substrate scope of the asymmetric one-pot procedure

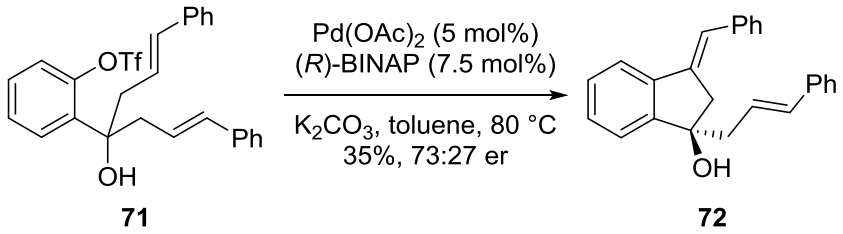
Upon investigating the extension of the substrate scope, 2'-bromoacetophenone (**69a**) was also applied in the one-pot reaction for the synthesis of indanol **70a** with a tertiary alcohol at the C-1 position (Scheme 42).[110] This substrate, however, did not undergo the allylation with allylboronic acid pinacol ester, indicating the more challenging synthesis of 1-methyl-3-(methylene)indan-1-ols.



Scheme 42: 2'-Bromoacetophenone in the one-pot process

While there are a number of methods for the synthesis of 3-(methylene)indan-1-ols from benzaldehydes, preparation of such scaffolds bearing a tertiary alcohol centre is not straightforward and less well-known in the literature. In 2000, Grigg and co-workers described a strategy that utilised 2'-bromoaryl alkyl ketones in palladium-catalysed reactions with allene.[111] More recently, Mahendar and Satyanarayana reported a multistep route *via ortho*-bromobenzyl tertiary alcohol intermediates.[104] Their study also showed the versatility of such intermediates. Depending on the substitution pattern on the tertiary alcohol, chromenes also could be synthesised. For the asymmetric synthesis of 1-alkyl-3-

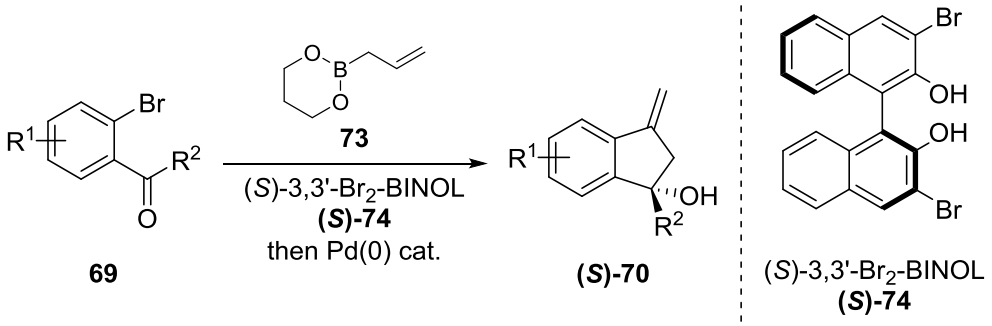
(methylene)indan-1-ols, only one reaction is known, a catalytic desymmetrising intramolecular Heck reaction of a bishomoallylic alcohol **71** by Oestreich and co-workers (Scheme 43).[112] The yield of **72** was 35% and the enantioselectivity was moderate. As a reason for this, the authors suggest that the hydroxy-directed migratory insertion is not favoured when constructing a 5-membered ring as this proceeds *via* a virtually planar and strained 5-membered Pd-O chelate.[113]



Scheme 43: Desymmetrising intramolecular Heck reaction

2.1.3 Proposed research

The main objective of this project was to develop a novel one-pot asymmetric procedure for the synthesis of optically active 1-alkyl-3-(methylene)indan-1-ols **70** (Scheme 44). This would expand the scope of the successful one-pot process previously discovered in the group.[109] Crucially, new conditions were required for the asymmetric allylation of ketones, which would be compatible with the intramolecular Heck reaction. To achieve this goal, the difficulty of the asymmetric allylation of aryl ketones to install the tertiary alcohol stereocentre would be overcome by utilising the work of Schaus and co-workers.[114] They reported the asymmetric allylboration of ketones with *B*-allyl-1,3,2-dioxaborinane (**73**) as allylating agent in the presence of (*S*)-3,3'-Br_2-BINOL [**(*S*)-74**] catalyst. This reaction resulted in the corresponding enantiopure homoallylic alcohols bearing a quaternary stereocentre. More importantly, the asymmetric formation of the homoallylic alcohol from 2'-bromoacetophenone (95% yield and 98:2 er) was also described. It has been previously shown that the intramolecular Heck cyclisation step had no effect on the stereochemical outcome of the one-pot process,[109] thus, incorporating the Schaus allylation process with a Heck cyclisation would allow the one-pot, two-step asymmetric synthesis of 1-alkyl-3-(methylene)indan-1-ols.



Scheme 44: Proposed one-pot asymmetric synthesis of 1-methyl-3-(methylene)indan-1-ols

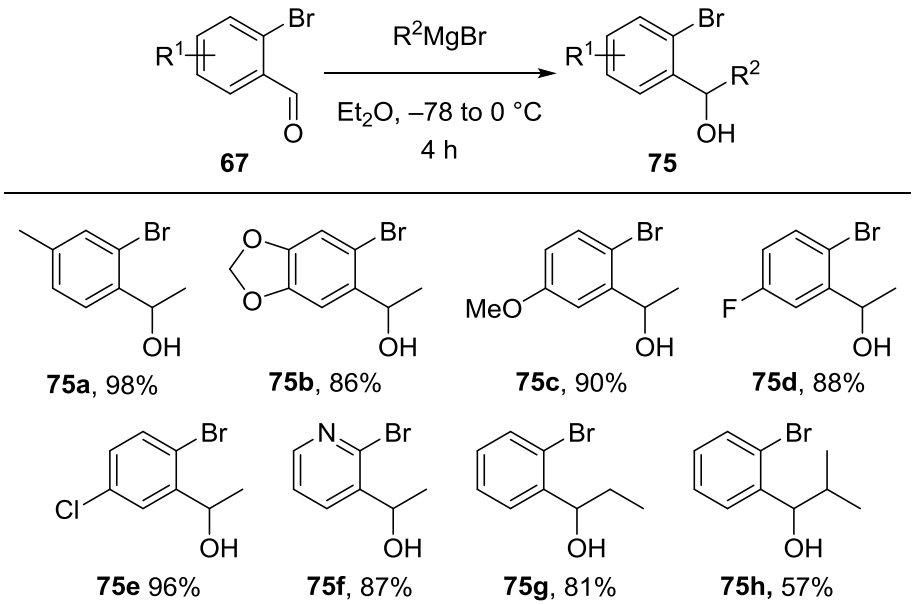
The next objective would be to evaluate the scope of this asymmetric one-pot process in order to show the effect of the different electronic and steric properties of the aryl ketones. As only 2'-bromoacetophenone (**69a**) was commercially available, the other functionalised 2'-bromoaryl alkyl ketones would require synthesis.

Finally, the enantioselectivity of the process would be determined by chiral HPLC analysis. For this investigation, the 1-alkyl-3-(methylene)indan-1-ols would also be synthesised as racemic mixtures for use as standards.

2.1.4 Synthesis of the 2'-bromoaryl alkyl ketone starting materials

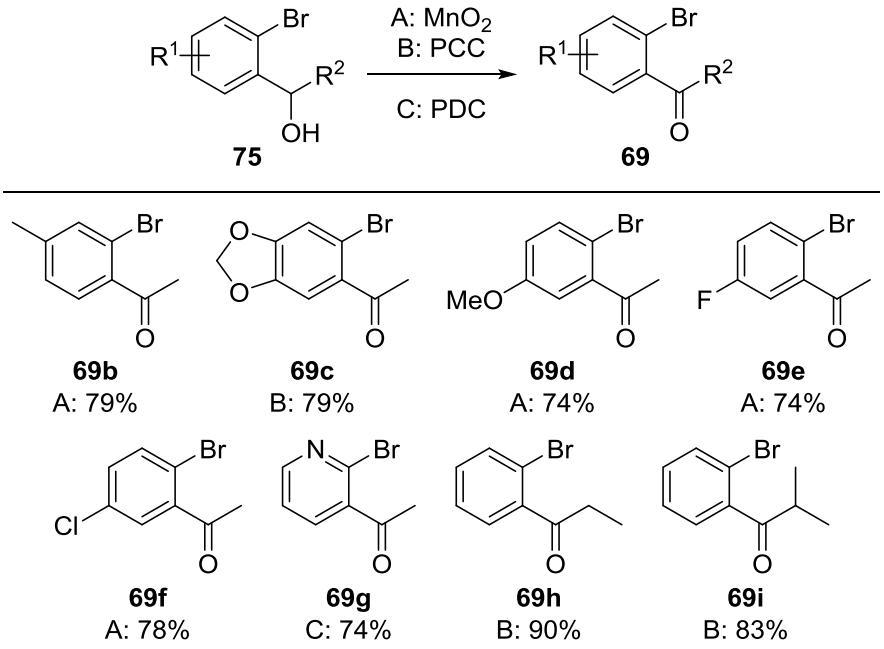
As only 2'-bromoacetophenone (**69a**) was commercially available, the targeted 2'-bromoaryl ketone compounds that would serve as starting materials for the allylboration-Heck reaction were all synthesised.[115] The main approach for the preparation of the ketone compounds was the 1,2-addition/oxidation of substituted 2-bromobenzaldehydes (**67**, Scheme 45). The two-step strategy involved the use of methylmagnesium bromide in the first step. Use of the Grignard reagent was generally applicable for the preparation of both electron-rich **75a–c** and electron-deficient **75d–f** secondary alcohols. This reaction gave the secondary alcohols as the sole products in 86–98% yield. In order to expand the scope with various alkyl side-chain containing analogues, next the preparation of secondary alcohols with ethyl and isopropyl groups was considered. These were also synthesised using 1,2-addition. Upon reaction with ethyl- and isopropylmagnesium bromide in the 1,2-addition of 2-

bromobenzaldehyde, extended side-chain containing secondary alcohols **75g** and **75h** were prepared under the standard conditions. Only the isopropyl derivative **75h** was isolated in a somewhat lower yield. This is due to a more sterically hindered Grignard reagent.



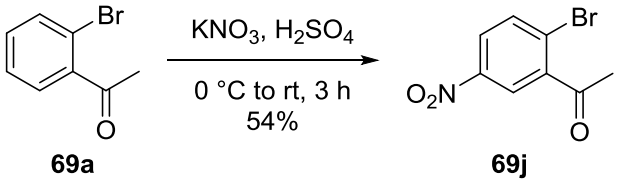
Scheme 45: Scope of the 1,2-addition

Next, oxidation of the secondary alcohols was carried out to give the aryl ketone compounds **69b–i** (Scheme 46). Oxidation with excess manganese(IV) dioxide was applicable for half of the secondary alcohols **75b**, **d**, **e**, **f**, and the corresponding ketones were isolated in 74–79% yield. For all of these substrates, the reaction proceeded cleanly. However, when using this procedure for the oxidation of the piperonal analogue **75c**, only a maximum yield of 19% was obtained after several attempts. In order to improve the yield, a stronger oxidising agent, pyridinium chlorochromate (PCC) was used. This resulted in a more efficient reaction and piperonal derived ketone **69c** was isolated in 79% yield. Based on a literature precedent, where a similar pyridine based secondary alcohol was oxidised, pyridinium dichromate (PDC) was used for the preparation of ketone **69g**.[116] Oxidation with PCC was also applied for the preparation of the ethyl and isopropyl side-chain containing ketones **69h** and **69i**, which were isolated in 90% and 83% yield, respectively.



Scheme 46: Scope of the oxidation. Conditions A: MnO_2, $CHCl_3$, Δ, 18 h; B: PCC, CH_2Cl_2, rt, 2 h; C: PDC, DMF, rt, 18 h

To complete the range of ketones with various electronic properties, 2'-bromoacetophenone with a nitro functionality was also synthesised (Scheme 47). 1-(2'-Bromo-5'-nitrophenyl)ethan-1-one (**69j**) was achieved in 54% yield *via* a nitration reaction based on a procedure by Hartley and co-workers.[117] It should be noted that nitration of **69a** only occurred in the *para* position according to the ^{1}H NMR spectrum of the reaction mixture.

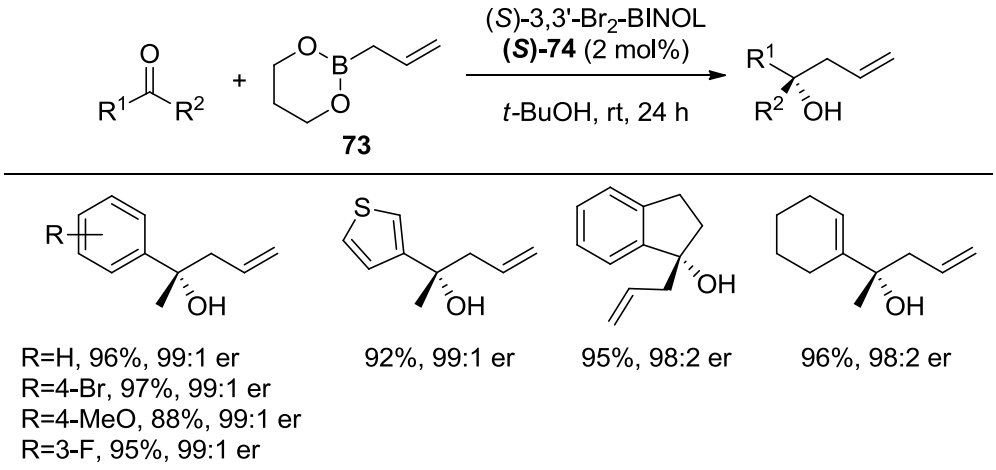


Scheme 47: Nitration of 2'-bromoacetophenone (69a)

2.1.5 One-pot asymmetric synthesis of 1-alkyl-3-(methylene)indan-1-ols

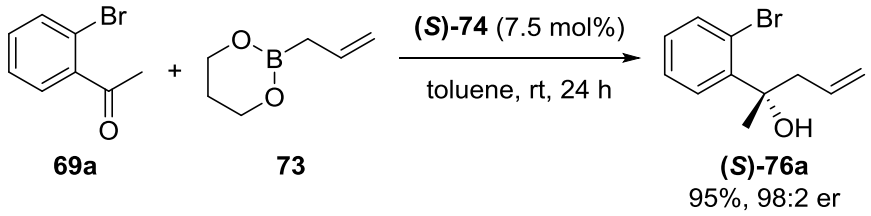
Having **69a** and the previously synthesised 2'-bromoaryl alkyl ketones **69b–j** in hand, the next stage of this project was to investigate their reactivity and selectivity in the preparation of 1-alkyl-3-(methylene)indan-1-ols. For this, the development of the one-pot two-step asymmetric allylboration/intramolecular

Heck reaction was required. There are several methods found in literature for the catalytic asymmetric allylation of aryl ketones.[114,118–122] After exploring the results of other research groups in this field, we based our approach on work conducted by Schaus and co-workers (Scheme 48).[114] They have successfully shown the efficient asymmetric allylation of a wide range of ketones using allyldioxaborinane **73** in the presence of the dibrominated BINOL catalyst **(*S*)-74** which together form a catalyst-associated boronate complex. The chiral diol catalyst acts as a suitable exchangeable ligand with Brønsted acidic characteristics, thus promoting the asymmetric reaction. The use of the cyclic allylating agent **73** allowed the synthesis of the homoallylic alcohols containing various aryl groups; both electron-withdrawing and electron-donating groups on the aromatic ring were tolerated. Moreover, it was shown that heteroaryl, bicyclic and cycloalkene derivatives were also suitable substrates for the reaction. Compared to their previous results obtained in *i*-PrOH, the use of the less coordinating *t*-BuOH resulted in nearly quantitative yields and high enantioselectivity (up to 99:1 er) in the case of a number of substrates.



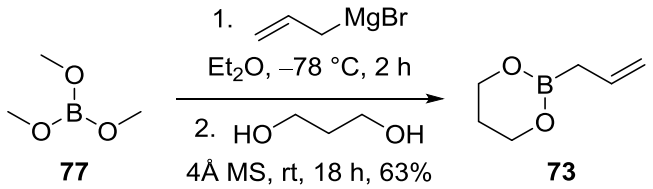
Scheme 48: Asymmetric allylation of ketones by Schaus and co-workers[114]

Challenging ketone substrates were also studied, such as the *ortho*-bromoaryl containing **69a**. The reaction conditions for this substrate had to be altered in order to achieve similar results (Scheme 49). Thus, changing the solvent to toluene and elevating the catalyst loading of **(*S*)-74** to 7.5 mol%, the corresponding homoallylic alcohol **76a** was synthesised in 95% yield and 98:2 er.



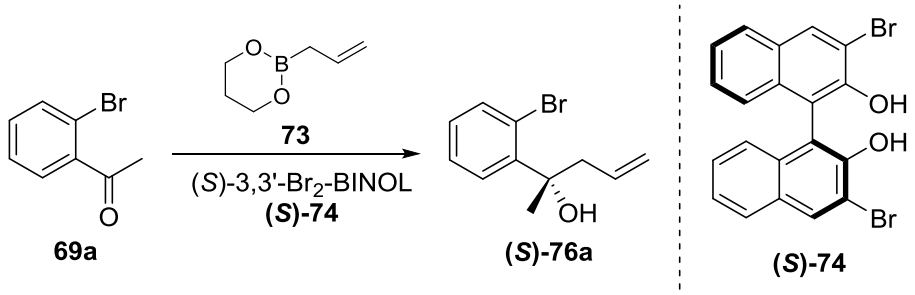
Scheme 49: Asymmetric allylation of 69a

Encouraged by the result of the literature example, the development of our one-pot asymmetric process including the allylboration of 2'-bromoaryl ketones in the first stage began by screening similar conditions.[115] For this, the two-step synthesis of allyldioxaborinane **73** was necessary from trimethylborate (**77**) as this was not commercially available (Scheme 50). Allylation by allylmagnesium bromide was followed by ligand exchange with 1,3-propanediol and the cyclic borinane compound **73** was achieved in 63% on a multigram scale. This allylating agent was then used for the optimisation process.



Scheme 50: Two-step synthesis of allylating agent 73

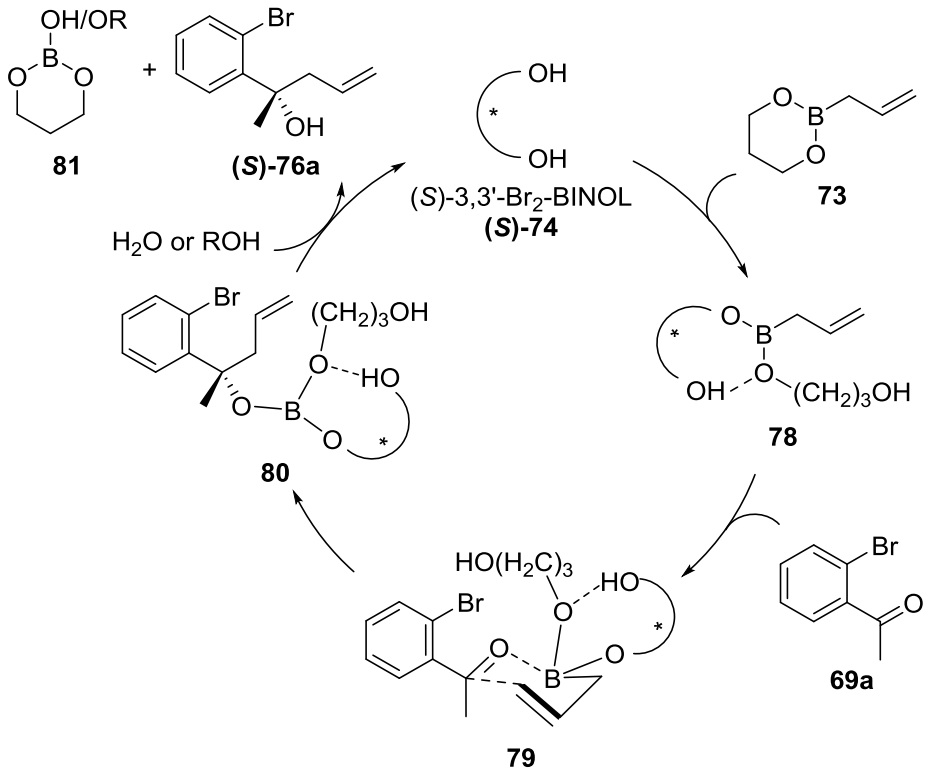
The asymmetric allylation of **69a** was attempted using similar conditions as described by the Schaus study and 21% yield of **(*S*)-76a** was obtained (Table 1, entry 1). As the Heck reaction for the cyclisation step required elevated temperatures and toluene as the solvent, the allylation was next investigated using this solvent. Elevating the catalyst loading of BINOL **(*S*)-74** to 7.5 mol%, a similar result of 25% yield was achieved for **(*S*)-76a** (entry 2). Further optimisation revealed the necessity of longer reaction times and also, increasing the temperature to 35 °C proved to be beneficial. Thus, homoallylic alcohol **(*S*)-76a** was synthesised in a quantitative yield (entry 4) and analysis by chiral HPLC showed 98:2 er. All chiral HPLC methods were calibrated with the corresponding racemic mixtures.



Entry	Catalyst loading of **(*S*)-74a** (mol%)	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)	er
1	5	*t*-BuOH	rt	24	21	-
2	7.5	toluene	rt	24	25	-
3	7.5	toluene	rt	72	67	-
4	**7.5**	**toluene**	**35 °C**	**120**	**100**	**98:2**

Table 1: Optimisation of the asymmetric allylation of 69a

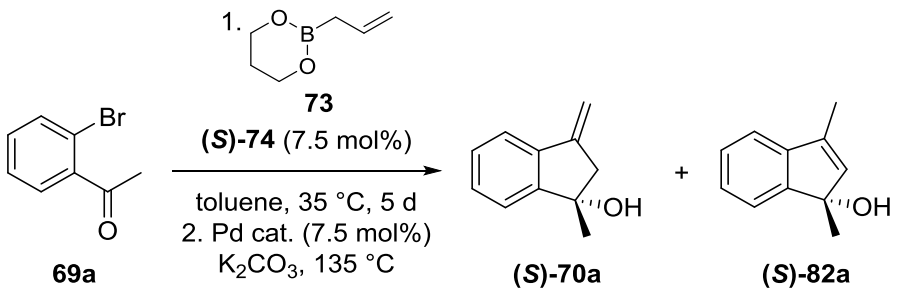
The outstanding selectivity of the allylating agent **73** in the presence of the (*S*)-3,3'-Br_2-BINOL catalyst (**74**) is due to the crucial ligand exchange processes. The catalytic cycle presented in Scheme 51 shows the coordinating effect of borinane **73** with the chiral diol catalyst. Thus, the cycle starts with ligand exchange on the boron centre which increases the nucleophilicity and is stabilised by hydrogen bonding. This allows for the coordination of the carbonyl oxygen of the substrate **69a** to the chiral biphenol-boronate complex **78**. The allylation of the ketone follows a concerted mechanism *via* the chair-like transition state **79** (s*i* facial attack on the ketone). After the enantioselective reaction is complete, the product **(*S*)-76a** is liberated in a final ligand exchange on the boron centre. Finally, the dissociation of the boronate-BINOL complex and hence regeneration of the active catalyst **(*S*)-74** is likely to be driven by the electron-withdrawing *ortho*-bromine atoms which make the O-B bond slightly weaker.



Scheme 51: Plausible catalytic cycle for the asymmetric allylation of ketones

Next, conditions for the one-pot, two-step synthesis of (1*S*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70a**] were investigated which involved the already optimised allylation procedure. Therefore, 2'-bromoacetophenone (**69a**) was submitted to the asymmetric allylation and once full conversion was achieved, the Heck reaction was performed with the addition of $Pd(PPh_3)_4$ (7.5 mol%) and potassium carbonate (Table 2, entry 1). This second step was conducted at 135 °C (which required the reaction to be performed in a sealed tube) and gave the target indanol **(*S*)-70a** as the major product after 24 h. While intramolecular Heck reactions for the construction of 5-, 6-, and 7-membered rings are highly *exo* selective, the presence of the palladium catalyst can induce the isomerisation of the *exo*-cyclic double bond to the more stable *endo* regioisomer. This isomerisation resulted in two products from the one-pot process, where the major compound was the *exo*-cyclic indanol **(*S*)-70a** and the minor compound was the *endo*-cyclic indenol **(*S*)-82a**. In order to improve on the overall yield and *exo*:*endo* alkene selectivity of the process, other palladium catalysts were investigated and the use of $PdCl_2$(dppf) indeed resulted in higher isolated yield (entry 2). As it gave a lower *exo*:*endo* alkene ratio of the products, this catalyst was abandoned. The most selective catalyst was $PdCl_2(PPh_3)_2$ and

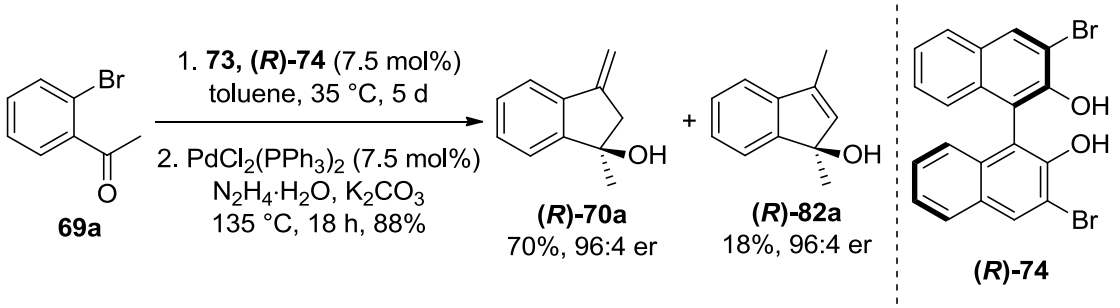
this gave the highest overall yield of both regioisomers in 90% (entry 3). This reaction led to a 5:1 ratio in favour of the indanol compound **(*S*)-70a** which was isolated in a 75% yield. Chiral HPLC analysis showed 96:4 er for both of the products **(*S*)-70a** and **(*S*)-82a**.



Entry	Pd catalyst	Reaction time (h)	Yield (%)	Ratio of **(*S*)-70a**:**(*S*)-82a**	er
1	$Pd(PPh_3)_4$	24	57	2:1	-
2	$PdCl_2$(dppf)	24	77	1.5:1	-
3*	**$PdCl_2(PPh_3)_2$**	**18**	**90**	**5:1**	**96:4**

Table 2: Optimisation of the one-pot process. *Hydrazine monohydrate was added as *in situ* Pd(II) reductant[105]

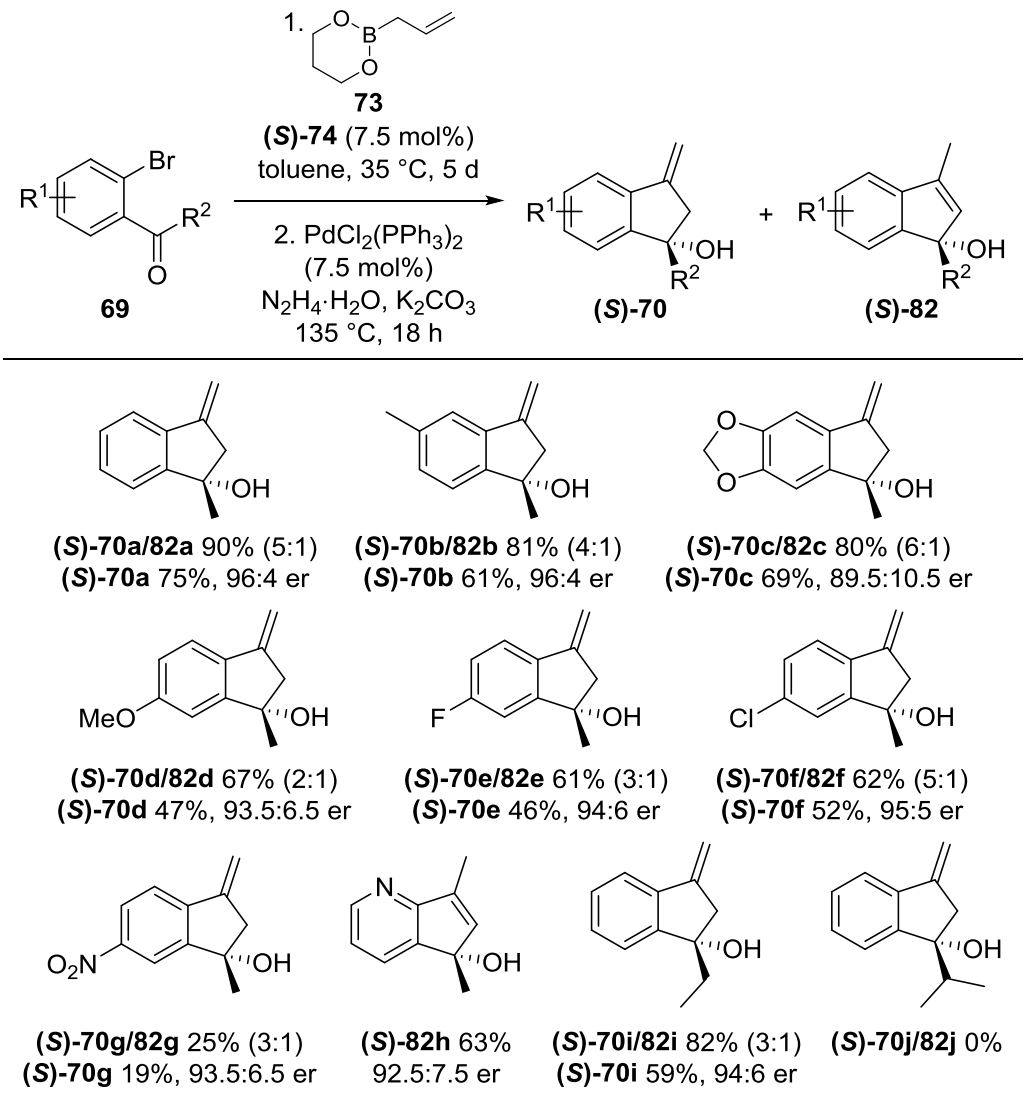
Following the successful optimisation of the one-pot synthesis of **(*S*)-70a**, the substrate scope was next explored with the range of 2'-bromoaryl alkyl ketones (**69b–j**). Initially, the ease of accessing both 1-alkyl-3-(methylene)indan-1-ol enantiomers using either (*S*)-3,3'-Br_2-BINOL [**(*S*)-74**] or (*R*)-3,3'-Br_2-BINOL [**(*R*)-74**] was examined. Thus, the one-pot process from **69a** was repeated, this time using **(*R*)-74**, and as expected, this resulted in similar yield and enantioselectivity (Scheme 52). Indanol **(*R*)-70a** was obtained in 70% yield and 96:4 er.



Scheme 52: One-pot reaction of 69a using (*R*)-74

For the rest of the substrate scope, **(*S*)-74** was used as catalyst and 2'-bromoaryl methyl ketones **69b–h** with a range of aryl substituents were submitted to the one-pot process (Scheme 53). Electron-rich substrates gave the highest overall yield of 80–90% over the two steps for **(*S*)-70a/82a**, **(*S*)-70b/82b** and **(*S*)-70c/82c** with high *exo* selectivity (4:1 to 6:1). Indanols **(*S*)-70a** and **(*S*)-70b** were isolated in 61–75% yield and showed a consistent er of 96:4. Only piperonal derivative **(*S*)-70c** showed somewhat lower enantioselectivity with 89.5:10.5 er. Methoxy-derived indanols **(*S*)-70d** and **(*S*)-82d** were isolated in a slightly lower overall yield of 67%. For this electron-rich system, a low alkene isomer ratio of 2:1 was observed and thus, the *exo*-alkene containing indanol **(*S*)-70d** was isolated in only 47% yield (93.5:6.5 er). It is believed that after the completion of the Heck cyclisation step, the methoxy group facilitated alkene isomerisation in the presence of the palladium catalyst. Other studies have previously shown that the synthesis of similar electron-rich racemic 1-alkyl-3-(methylene)indan-1-ols was complicated by the formation of the indene product which was generated *via* dehydration.[104] This only occurred in acidic media and this kind of side reaction was not observed in this asymmetric study. However, the electron-rich oxygen containing compounds were difficult to isolate as sole isomers and also, their spectroscopic characterisation in deuterated chloroform was not viable. This was due to equilibration between the *exo*-cyclic **(*S*)-70** and *endo*-cyclic **(*S*)-82** indanol forms in the slightly acidic chloroform. This kind of isomerisation by the $CDCl_3$ was also described in a study by Satyanarayana.[104] Even after 10 minutes, the sample of *exo*-cyclic indanol of **(*S*)-70c** and **(*S*)-70d** showed significant amounts of the indenol isomer **(*S*)-82** with *endo* double bond. For these systems, deuterated methanol was required as the NMR solvent for analysis which did not facilitate alkene isomerisation. Electron-deficient analogues were next

synthesised and halogen-containing **(*S*)-70e/82e** and **(*S*)-70f/82f** formed with good overall yields of 61–62% and showed high enantioselectivity (94:6 to 95:5 er). However, nitro-substituted indanol **(*S*)-70g** was isolated in only 19% yield. Upon submitting the pyridine derived ketone **69g** to the one-pot process, the outcome was different to previous reactions. Interestingly, indenol **(*S*)-82h** was the sole product formed during the reaction. The *endo*-alkene containing **(*S*)-82h** was isolated in 63% yield and showed high enantioselectivity (92.5:7.5 er). It is possible that coordination of the Pd(0) catalyst to the adjacent nitrogen atom facilitates the isomerisation of the *exo*-alkene after the Heck reaction is complete. In order to extend the scope of the one-pot asymmetric process, different alkyl side-chain containing ketones were next investigated. High overall yield and alkene isomer ratio of 3:1 was obtained upon using 2'-bromophenyl ethyl ketone **69h** in the one-pot reaction. Indanol compound **(*S*)-70i** was isolated in 59% yield and produced a 94:6 er. However, submitting the ketone analogue **69i** with an isopropyl side-chain gave no product at the allylation step. The combined steric hindrance of the bulky alkyl ketone and the large *ortho*-bromo substituent prevent this reaction from taking place.

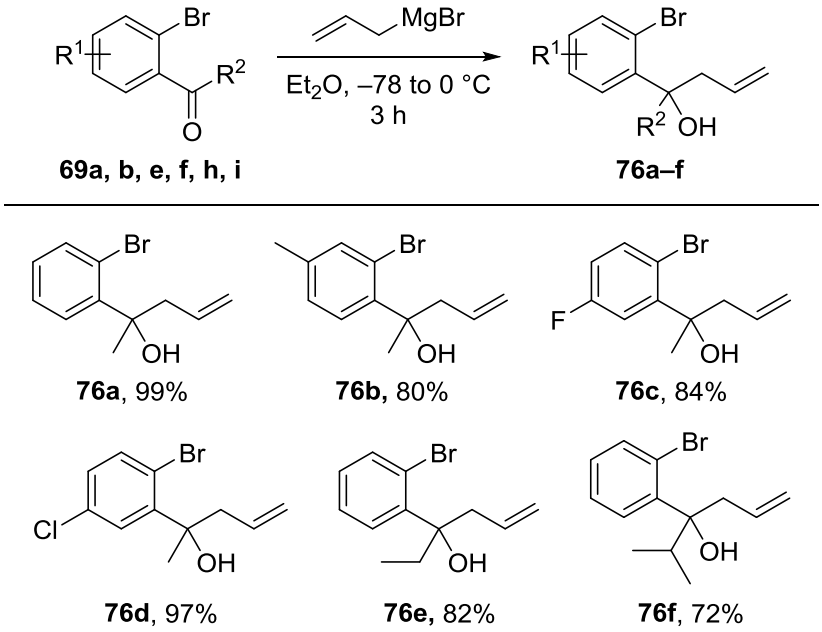


Scheme 53: Scope of the one-pot asymmetric allylboration/Heck reaction

2.1.6 Two-step racemic synthesis of 1-alkyl-3-(methylene)indan-1-ols

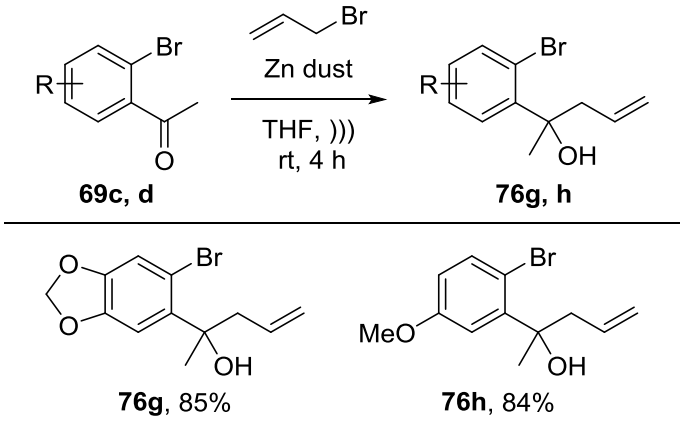
In order to investigate the enantioselectivity of the asymmetric one-pot process, preparation of the racemic analogues for evaluation was required. The synthesis of racemic 1-alkyl-3-(methylene)indan-1-ols **70a–j** was carried out *via* a two-step process which involved organometallic allylation followed by intramolecular Heck reaction for the construction of the 5,6-bicyclic core. First, racemic homoallylic alcohols **76a–j** were prepared. We aimed to develop a general allylation reaction using a boronate allylating agent, allylboronic acid pinacol ester. However, initial attempts for the allylation of 2'-bromoacetophenone (**69a**) with allylboronic acid pinacol ester gave only 39% yield, so instead the homoallylic alcohols were prepared by 1,2-addition with allylmagnesium bromide

(Scheme 54). This procedure gave a quantitative yield for **76a** after 3 h, and compounds **76b–f** were also synthesised using the same reaction. The standard allylation conditions gave electron-deficient **76c** and **76d** in 84% and 97% yield, respectively. Moreover, this reaction allowed for the preparation of homoallylic alcohols **76e** and **76f** with ethyl and isopropyl side-chains in good yield.



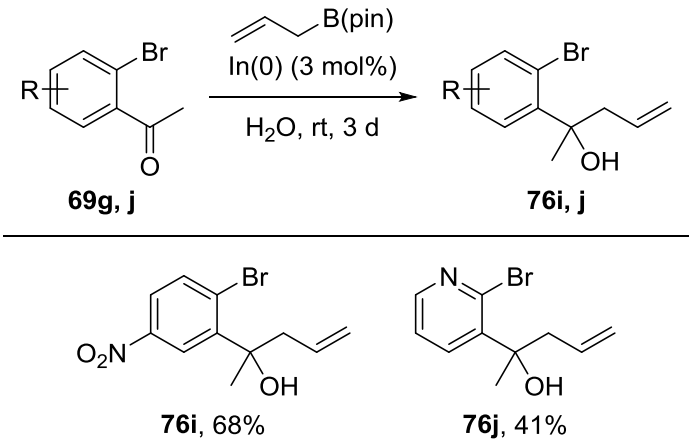
Scheme 54: Homoallylic alcohol synthesis with allylmagnesium bromide

Aryl ketones that gave rise to side reactions or no reaction with Grignard reagents were subjected to alternative addition reactions. For the synthesis of the oxygen containing electron rich compounds **76g** and **76h**, the *in situ* prepared allylzinc reagent was used and led to the target compounds in 84–85% yield (Scheme 55).



Scheme 55: Homoallylic alcohol synthesis with zinc and allyl bromide

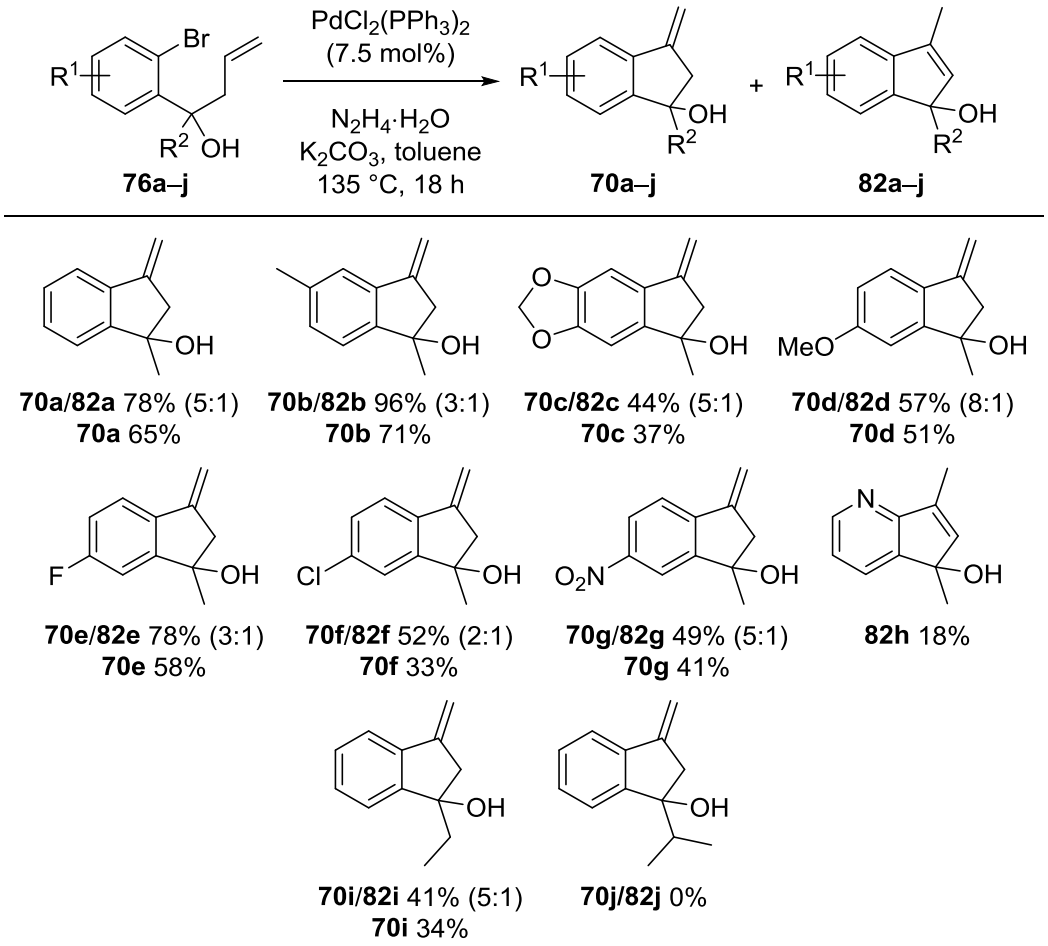
Finally, indium(0)-catalysed reaction with allylboronic acid pinacol ester was carried out for the allylation of ketones **69g** and **69j** and homoallylic alcohols **76i** and **76j** were achieved in 68% and 41% yield, respectively (Scheme 56).



Scheme 56: Homoallylic alcohol synthesis with indium and allylboronic acid pinacol ester

The racemic homoallylic alcohols **76a–j** were then submitted to the intramolecular Heck reaction to yield the corresponding racemic 1-alkyl-3-(methylene)indan-1-ols **70a–j** (Scheme 57). During this reaction, conditions were used from the previously optimised one-pot process. In comparison to the results obtained then, the regioselectivity of the crude reaction mixture analysed by ^{1}H NMR spectroscopy showed similar ratios of alkene isomers. Isolation of the compounds resulted in generally good to high overall yields for **70a/82a**, **70b/82b** and **70e/82e**. Halogenated indanols **70e** and **70f** were also synthesised in this reaction; the fluoro indanol **70e/82e** showed higher overall yield of 78%, but similar alkene isomer ratio as observed before (3:1). Although the chloroindanol **70f/82f** showed moderate overall yield, for some unknown reason the alkene isomer ratio was only 2:1. It is known that Heck reactions can proceed with aryl chlorides, but in this study side reaction arising from such a process was never observed. Interestingly, the nitro analogue **70g/82g** was achieved in a higher yield compared to the one-pot process: 41% vs 19%. The intramolecular Heck reaction of the pyridine derived homoallylic alcohol **76j** led to a 1:2 ratio in favour of the *endo*-cyclic indenol **82h** according to the ^{1}H NMR analysis of the crude reaction mixture. This was the first time this substrate yielded the indanol isomer **70h**, as it was never detected in the one-pot process. However, while peaks assigned to the *exo*-cyclic double bond were observed in

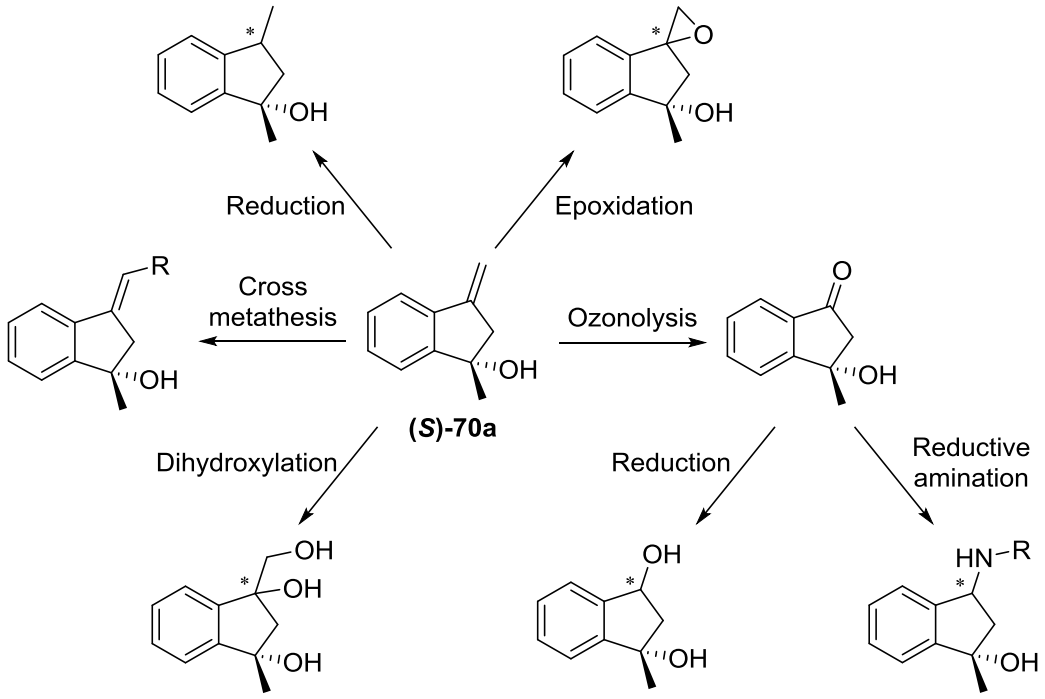
the ^{1}H NMR spectra at 5.23 and 6.05 ppm of the crude reaction mixture, only the *endo* isomer **82h** could be isolated in 18% yield. Finally, upon submitting the more bulky side-chain containing homoallylic alcohols **76e** and **76f** to the intramolecular Heck reaction, only the 1-ethyl indanol isomers **70i** and **82i** could be synthesised. As with the one-pot process, the isopropyl homoallylic alcohol **76f** gave no reaction under these conditions. The products prepared from this stage of the project were then used as standards to assess the enantioselectivity of the compounds isolated from the one-pot process.



Scheme 57: Scope of the intramolecular Heck reaction

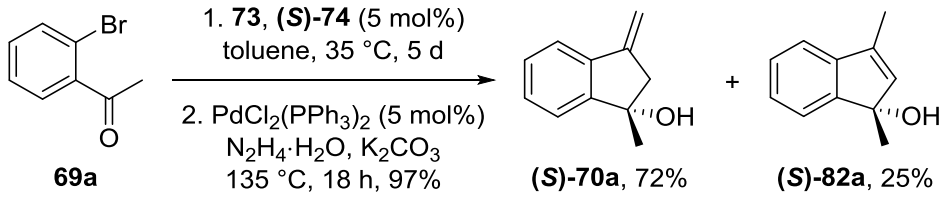
2.1.7 Functionalisation of (*S*)-70a

The final aim of this project was to demonstrate the synthetic utility of the 1-alkyl-3-(methylene)indan-1-ol products **(*S*)-70** formed in the one-pot asymmetric process. Thus, further functionalisation of the optically active scaffolds was next investigated. Alkenes are a common structural motif and the versatility and reactivity of these facilitate a large number of transformations to access a wide range of other functional groups. Thus, several alkene functionalisation reactions were considered from **(*S*)-70a**, such as cross metathesis, reduction and oxidation methods (Scheme 58).



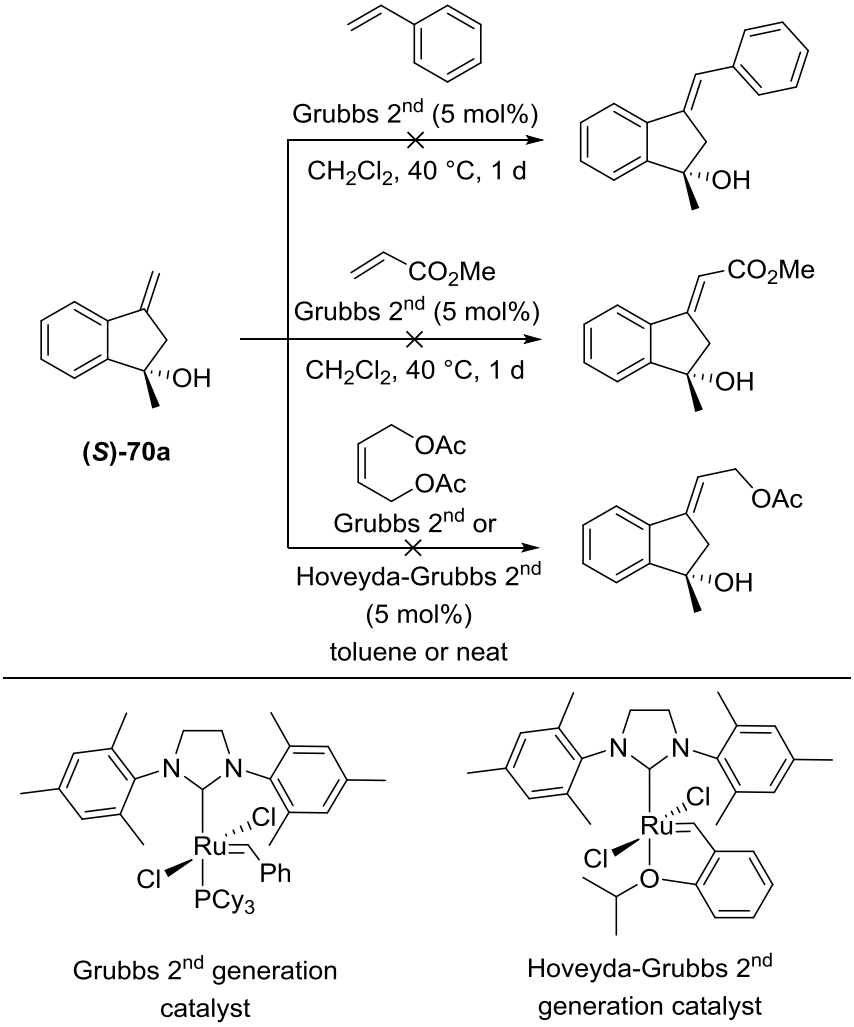
Scheme 58: Potential alkene transformations from (*S*)-70a

Prior to the use of **(*S*)-70a** in alkene transformations, its gram-scale synthesis was carried out (Scheme 59). It was found that by scaling-up the one-pot process, the amount of both **(*S*)-74** and the palladium(II) catalyst could be decreased to 5 mol%, which makes this procedure even more efficient. It should be noted that this still allowed for high overall (97%) and *exo*-indanol yield (72%) and enantioselectivity for **(*S*)-70a** was also maintained (96:4 er).



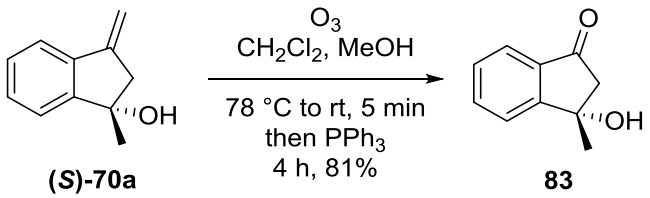
Scheme 59: Gram-scale synthesis of (*S*)-70a

With a large amount of **(*S*)-70a** in hand, the possible reactions of the *exo*-methylene group of the substrate were explored. In a brief study, the olefin cross metathesis of **(*S*)-70a** was investigated (Scheme 60). This compound was categorised as a type 3 alkene due to its 1,1-disubstituted nature and hence partners for the cross metathesis had to be from either type 1 or 2 alkenes.[123] For this reason, styrene (type 1) and methyl acrylate (type 2) were chosen as partners. With Grubbs 2nd generation catalyst (5 mol%), there was no reaction between **(*S*)-70a** and the alkene partners. ^{1}H NMR spectroscopy of the crude reaction mixture showed both starting materials and also the expected homodimers of the type 1 and 2 alkenes, which ruled out the possibility of loss of catalytic activity. To enhance the reactivity, an already homodimerised type 1 alkene as the cross metathesis partner was chosen for **(*S*)-70a**. The homodimer of allyl acetate as a *Z*-alkene (more reactive than the *E*-alkene) was then submitted to the reaction first with Grubbs 2nd generation catalyst at a higher temperature (110 °C), then using Hoveyda-Grubbs 2nd generation catalyst. In both cases no reaction was observed between the starting materials even under neat conditions, which is normally favourable in cross metathesis reactions.[123] The lack of cross metathesis activity could be due to the relative unreactivity of **(*S*)-70a** in this type of reaction, which means that this compound is a type 4 spectator alkene.[123] It is also possible that the free alcohol at C-1 could interfere with the ruthenium catalyst and deactivate it. However, in 2008 Grubbs reported the successful olefin cross metathesis of a free tertiary allylic alcohol (categorised as type 2 alkene) with the less bulky NHC containing 3rd generation catalyst.[124] As **(*S*)-70a** contains a different tertiary alcohol moiety, in order to overcome its possible limitations in cross metathesis reactions, protection of this homoallylic alcohol would be necessary.



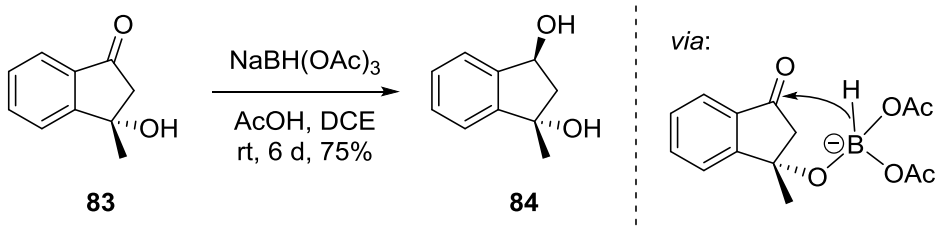
Scheme 60: Cross metathesis of (*S*)-70a

Next, another alkene functionalisation was explored and it was shown that indanone **83** could be easily generated *via* ozonolysis; compound **83** was obtained in 81% isolated yield (Scheme 61). Indanone core **83** is a structural analogue of tripartin (**67**, Figure 2), and an important intermediate towards more complex compounds.[125–127] Therefore, the synthetic utility of this as starting material in reduction and reductive amination reactions was investigated.



Scheme 61: Ozonolysis of (*S*)-70a

For the reduction of **83** to the diol compound **84**, sodium triacetoxyborohydride was the most selective. This is considered a mild reducing agent while exhibits remarkable selectivity, and its B-H bond is stabilised by the steric and electron-withdrawing effect of the acetoxy groups.[128] Reduction of **83** was performed in the presence of acetic acid and after a prolonged reaction time, **84** was isolated as a single diastereomer in 75% yield (Scheme 62). The structure of diol **84** was confirmed by X-ray crystallographic analysis and Figure 3 shows the result. It clearly demonstrates the *anti* relationship of the C-1 and C-3 hydroxyl groups. The mechanism involves the strong coordination of the borohydride species to the C-1 hydroxyl group which eventually leads to ligand exchange of one of the acetoxy groups with the C-1 hydroxyl group.[129] This then allows for the hydride delivery to take place on the same face.



83 **84**

Scheme 62: Reduction of indenone 83 to the *anti* diol compound 84

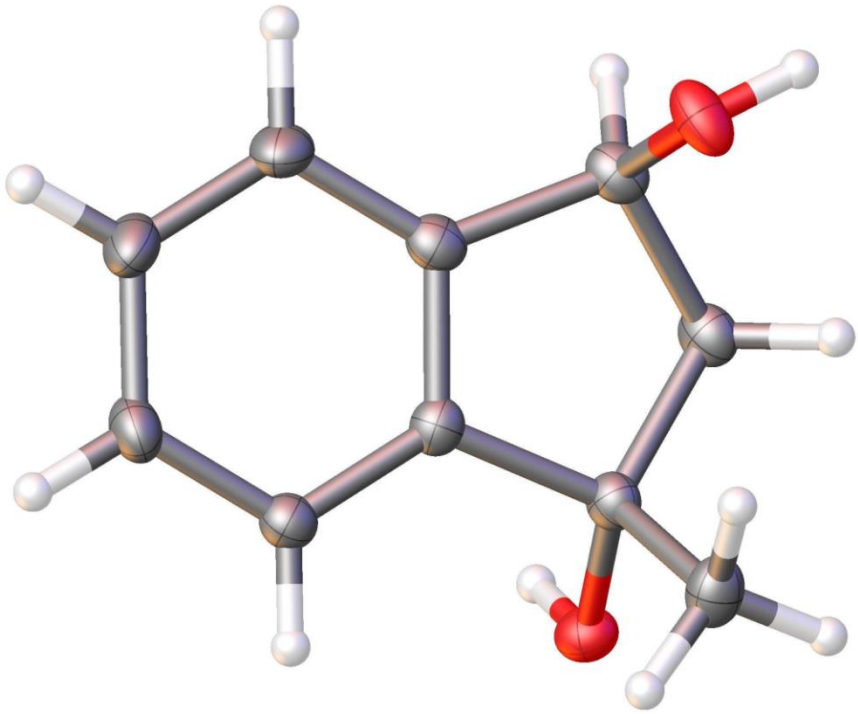
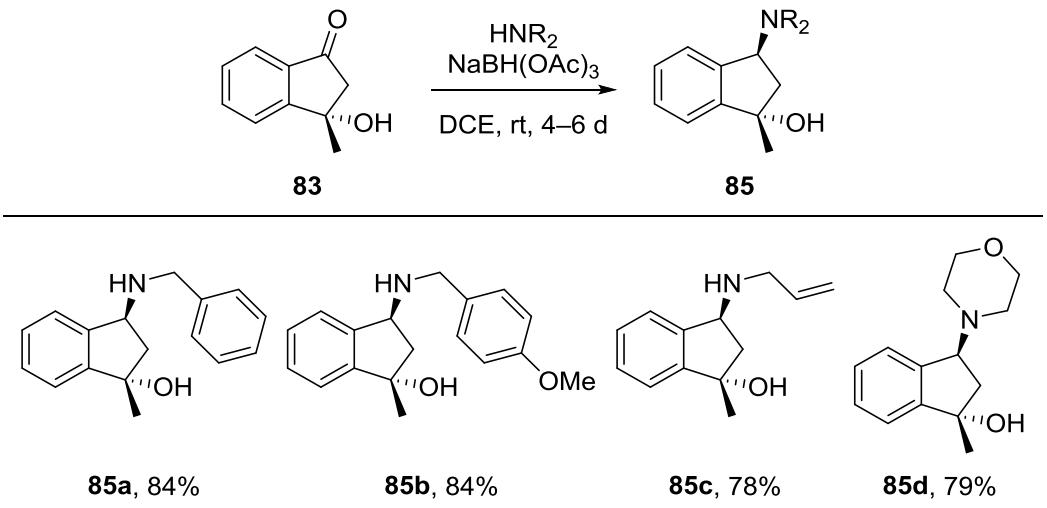


Figure 3: X-ray crystal structure of diol 84

Taking advantage of the highly selective reducing capability of sodium triacetoxyborohydride, it was also used for the reductive amination of indanone **83** in the presence of various amines (Scheme 63). As the reduction of iminium ions is faster than ketones, the reductive amination could be carried out as a one-pot process by introducing the borohydride reducing agent at the start. Benzylamines as well as alkyl and heterocyclic amines performed well in the reaction and gave the corresponding 3-aminoindan-1-ols **85a–d** as single diastereomers in 78–84% yield. As only the morpholine derivative **85d** formed crystals, its structure and relative stereochemistry could be determined by X-ray crystallography. Again, the same *anti* relationship between C-1 hydroxy and C-3 amine groups was observed (Figure 4). This indicated the same hydroxy-directed hydride delivery by sodium triacetoxyborohydride; a mechanism which operates with β-hydroxy ketones and ultimately results in *anti* diols and amino alcohols.[129]



Scheme 63: Diastereoselective reductive amination of 83

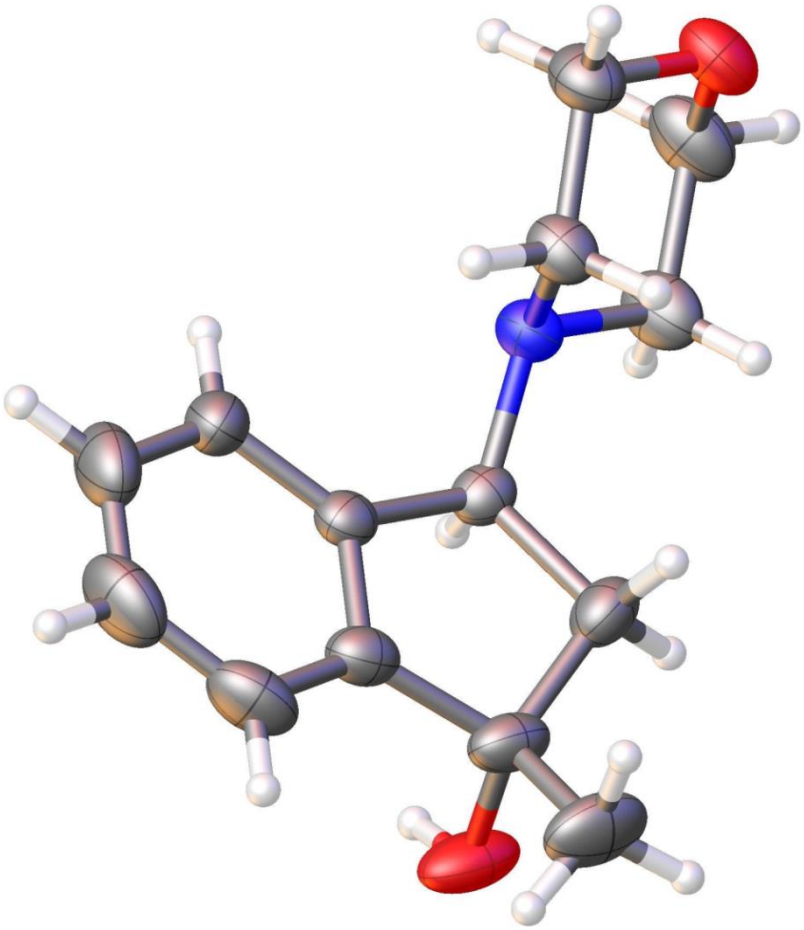


Figure 4: X-ray crystal structure of morpholine derivative 85d

2.1.8 Conclusions

In conclusion, a one-pot asymmetric allylboration/intramolecular Heck reaction process of 2'-bromoaryl alkyl ketones was successfully developed.[115] The one-pot procedure was shown to deliver a number of optically active 1-alkyl-3-(methylene)indan-1-ols with a tertiary alcohol stereocentre. The optimised conditions of the asymmetric approach provided an easy method for the synthesis of highly functionalised bicyclic scaffolds with high enantiomeric ratios (up to 96:4 er). It was also demonstrated that both indan-1-ol enantiomers could be accessed from the one-pot reaction by using either enantiomer of the 3,3'-Br_2-BINOL catalyst. Moreover, the efficient scale-up of the one-pot process was accomplished. Finally, it was shown that the 1,1-disubstituted alkene moiety could be easily converted into a ketone, which was then applied for the highly diastereoselective synthesis of a diol, as well as a series of novel 3-aminoindan-1-ols.

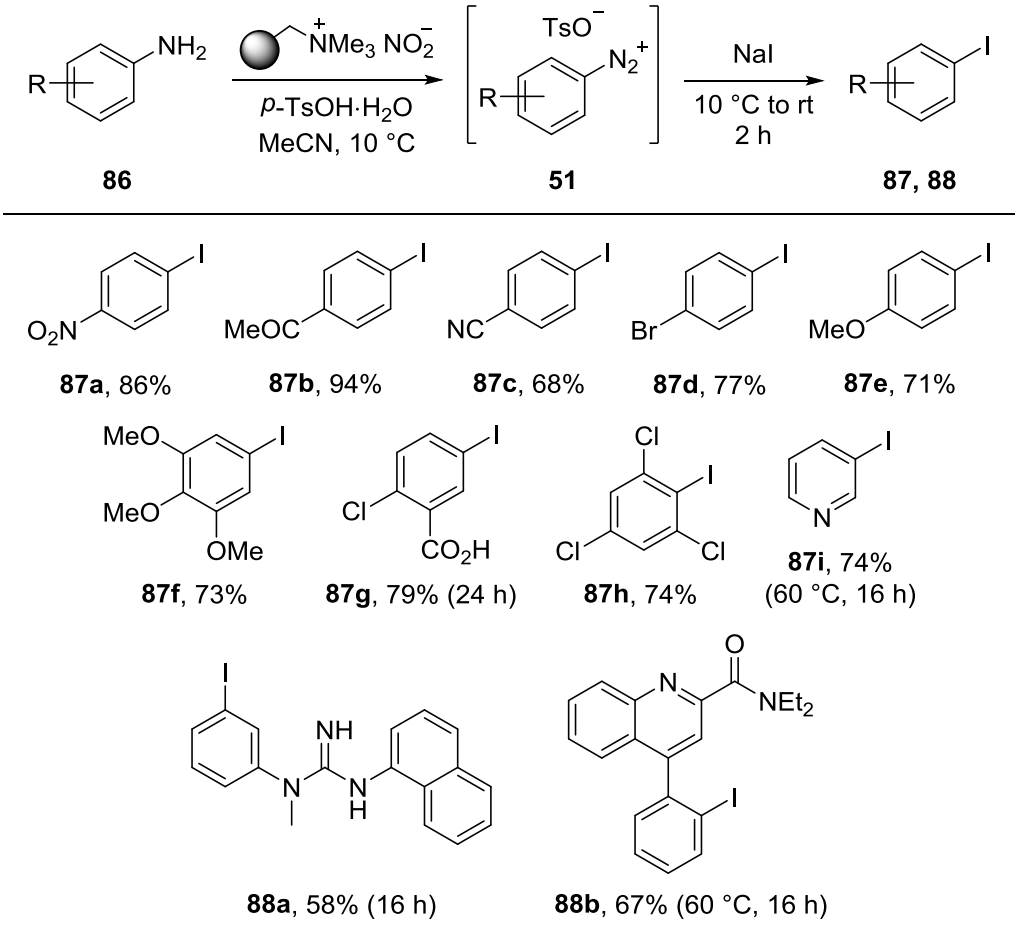
2.2 One-pot Tandem Reactions for the Synthesis of Methyl Cinnamates and 3,4-Dihydroquinolin-2-ones

2.2.1 Previous work in the Sutherland group

Extensive research has focused on the efficient synthesis of aryl iodides in the past few years within the Sutherland research group in order to easily access SPECT imaging agents for their biological evaluation.[130–139] While aryl iodides could be prepared in a number of synthetic ways, for example by halogen exchange from aryl bromides,[132] or by using pseudo halide-type leaving groups such as boronates[135,138,139] or sulfonates in aromatic substitution reactions, more recently research effort has been directed to the utilisation of aryl diazonium salt intermediates in the iodination process.[136,137] The diazonium salts formed from readily available anilines are undoubtedly powerful organic intermediates and upon submitting them to a Sandmeyer-type reaction, aryl iodides can be synthesised. Traditionally, diazotisation of anilines involved the use of sodium nitrite and a strong acid, such as hydrochloric acid or sulfuric acid.[140] The stability of the resulting reactive species depends on the acid present as this serves as the anionic counterion for the diazonium cation. Inorganic counterions can make these salts labile and they could potentially be harmful, leading to explosions and casualties.[51] For safety reasons, employing mild conditions for diazotisation of anilines is highly desirable and beneficial.

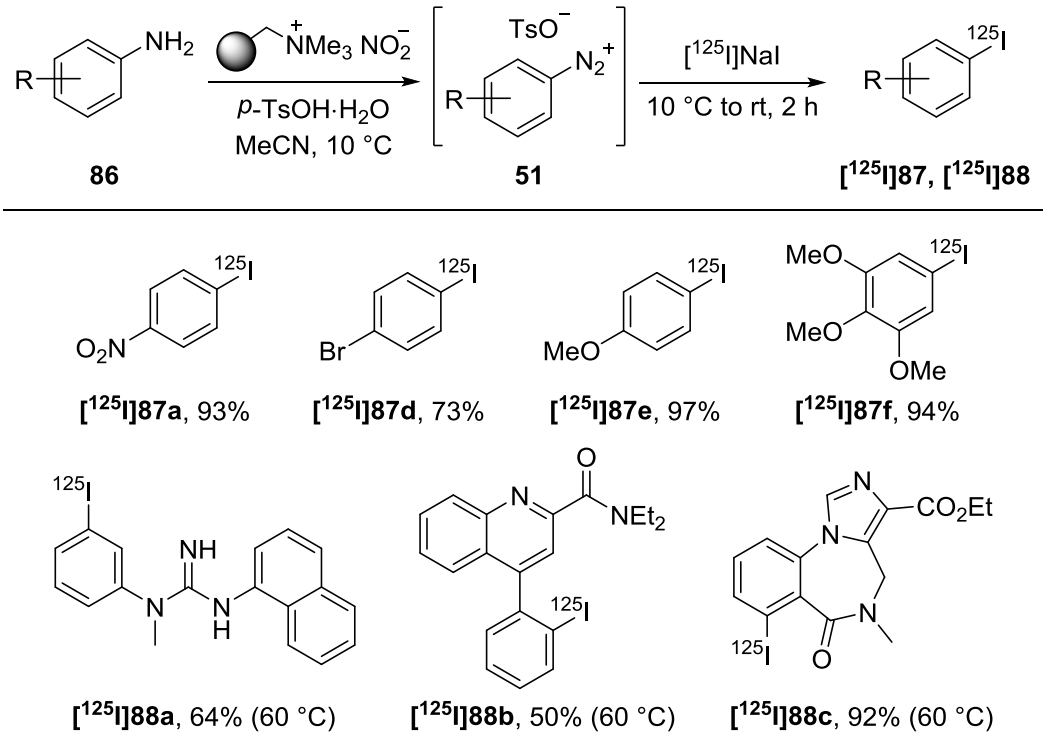
Previously in the group, it was shown that super-electrophilic diazonium salts allow the reaction to take place using mild conditions and deliver a number of aryl iodide products **87** in one-pot (Scheme 64).[136] Based on the research of Filimonov *et al.*,[69,141] and upon further optimisation, the best conditions for the one-pot process were found. This included the polymer-supported nitrite reagent, which was prepared by an ion exchange of tetraalkylammonium functionalised resin (Amberlyst® A26) with an aqueous solution of sodium nitrite.[69,135,136] The use of the polymer support allowed for an easy work-up by filtration and it could also be recycled. The proton source for the transformation was the cheap and readily available *p*-tosic acid. Previously, Filimonov *et al.*, reported that the optimal molar ratio for the rapid generation of the aryl diazonium salts was 3:3 resin-NO_2/*p*-TsOH with respective to the aniline starting

material and this was also the ratio of reagents used in the study by the Sutherland research group.[69] The highly efficient process involved the safe *in situ* formation of thermally stable aryl diazonium tosylate salts under mildly acidic reaction conditions, and their utilisation in a Sandmeyer-type iodination, leading to a wide range of aryl iodide compounds **87**. Electron-deficient *para*-substituted aryl iodides **87a** and **87b** were achieved in excellent yields. The scope also showed the good-yielding synthesis of electron-rich systems **87e** and **87f**. Preparation of the multi-substituted benzoic acid derivative **87g** required longer reaction time, as well as the highly electron-deficient 3-iodopyridine (**87i**), which was achieved using higher temperatures. Furthermore, the standard one-pot diazotisation-iodination procedure was also extended to the late stage iodination of aniline precursors for medicinally important compounds **88a** and **88b**.



Scheme 64: One-pot diazotisation-iodination procedure

Following this, several simple iodine-125-containing aryl compounds as well as currently used and potential SPECT imaging agents were also prepared using the one-pot process in high radiochemical yields (Scheme 65).[137] Optimisation led to the new conditions, which involved the radioactive sodium [^{125}I]iodide being the limiting reagent. For simple radioarenes radioiodination occurred at room temperature; however, heating was required for the late stage iodine-125 incorporation of the more complex structures **88a–c**. Overall, radiosynthesis of all the compounds took place within 2 hours, which was highly desirable as maintaining the specific activity of SPECT imaging agents containing isotopes with shorter half-life is important.

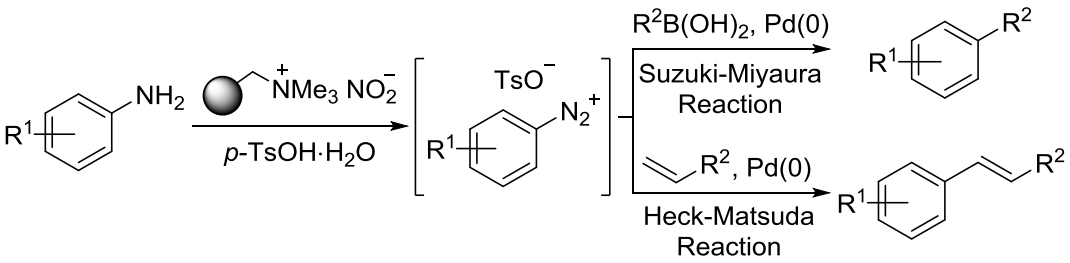


Scheme 65: One-pot diazotisation-radioiodination procedure

The development of this one-pot diazotisation and radioiodination protocol was very important as previously the preparation of radioarenes involved using toxic and unstable organotin intermediates for oxidative iododestannylation reaction with electrophilic iodine.[142] Another method for radioiodination is the nucleophilic halogen exchange reactions of aryl bromides which requires the application of high temperatures.[143]

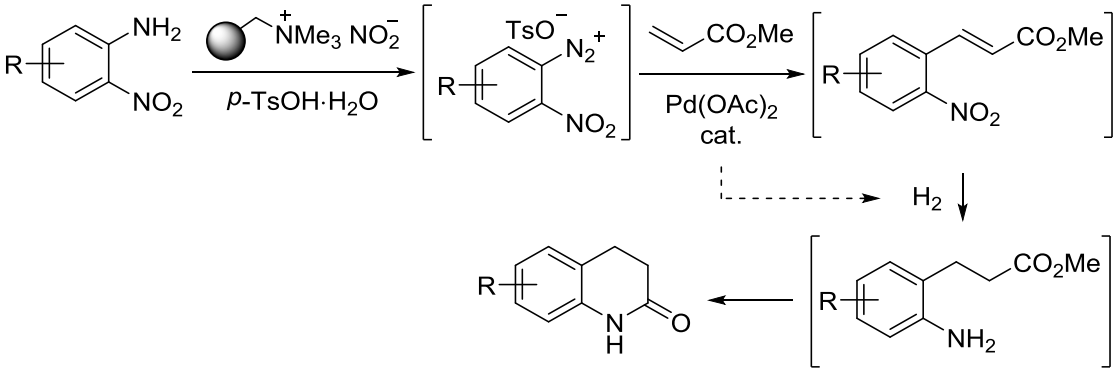
2.2.2 Proposed research

The main aim of this project was to extend the synthetic utility of this mild approach for the preparation of stable aryl diazonium salts for the development of a novel one-pot carbon-carbon bond-forming procedure. The reaction would start from readily available anilines and *via* diazotisation, the stable aryl diazonium tosylate salts would be achieved using the polymer-supported nitrite reagent in combination with *p*-tosic acid. These stable but reactive species would then be employed in transition metal-catalysed cross-coupling reactions to deliver the coupled products in one-pot. For this, boronic acids and alkenes would serve as coupling partners for the *in situ* formed pseudo-halide diazonium tosylate salts. This one-pot procedure would allow for the facile preparation of a range of coupled products using mild conditions (Scheme 66).



Scheme 66: Cross-coupling reactions of stable diazonium salt intermediates

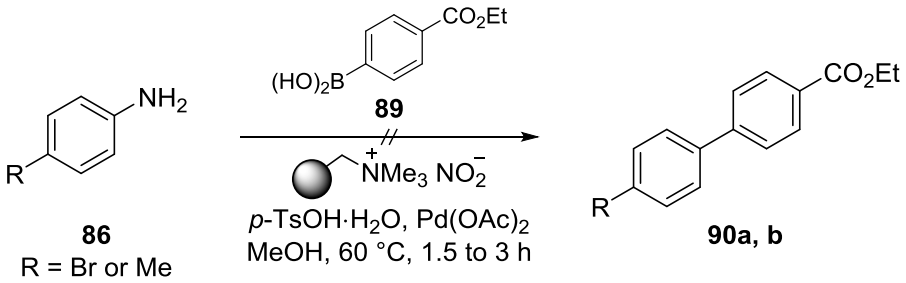
Another key objective of this research was to develop a one-pot tandem synthetic methodology for the construction of 3,4-dihydroquinolin-2-ones (Scheme 67). The multistep procedure would involve the rapid synthesis of methyl cinnamates bearing an *ortho*-nitro group in the palladium-catalysed Heck-Matsuda reaction. Without isolation, these intermediates would serve as important precursors for the formation of 3,4-dihydroquinolin-2-ones. With the use of hydrogen atmosphere, the alkene hydrogenation and nitro reduction processes in the presence of the reutilised palladium catalyst would be performed, and this would allow for the spontaneous intramolecular cyclisation to afford the final products.



Scheme 67: Synthetic route for the one-pot multistep preparation of 3,4-dihydroquinolin-2-ones

2.2.3 Attempted Suzuki-Miyaura reaction with aryl diazonium tosylate salts

The investigation of aryl diazonium tosylate salt application in cross-coupling reactions started with a brief study involving a one-pot tandem diazotisation-Suzuki reaction (Scheme 68). A few aniline staring materials were investigated in the one-pot process for the synthesis of biaryl compounds **90**. Neither 4-bromoaniline (**86**, R = Br) nor *p*-toluidine (**86**, R = Me) resulted in any of the coupled product, although all starting material was consumed. It is very possible that the reaction stopped after the fast aryl diazonium tosylate salt formation, with this relatively stable intermediate not able to react further under these conditions.

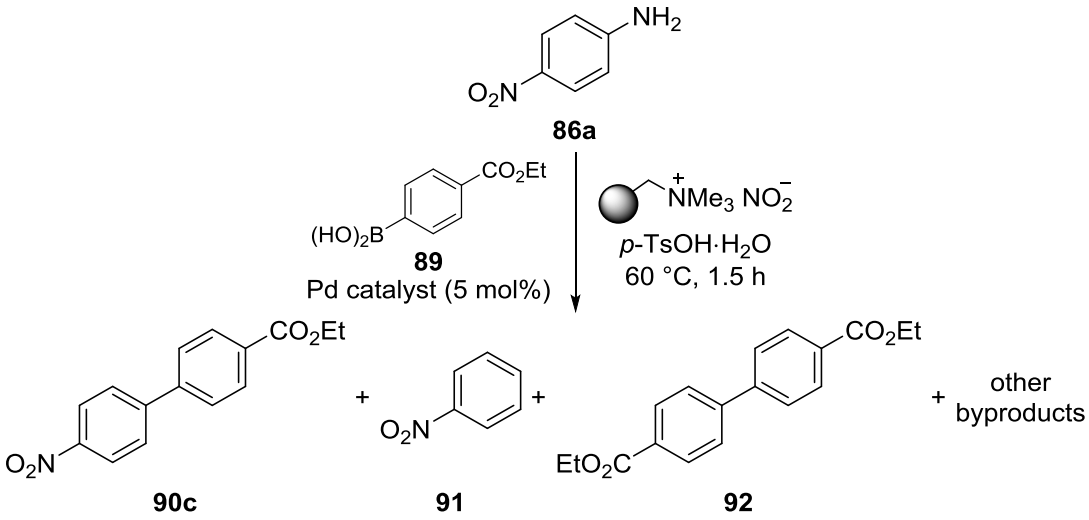


Scheme 68: Attempted one-pot tandem diazotisation-Suzuki reaction

However, when starting the process from 4-nitroaniline (**86a**) a complex mixture was obtained, whereby none of the aniline starting material was observed and only traces of coupled product **90c** formed (Table 3, entry 1). As this was the first time that the unsymmetrical biaryl product was detected, screening of the conditions for the one-pot process in order to find the optimal system was

carried out. By partial separation of the complex reaction mixtures the aim was to gain as much information about the process as possible in order to discover the optimal procedure.

Firstly, changing the palladium catalyst was studied but both tetrakis(triphenylphosphine)palladium(0) and palladium on carbon led to the dediazotisation product nitrobenzene **91** and the homocoupled boronic acid **92** (entries 2 and 3). The results suggested that along with the successful diazonium salt formation and fast dinitrogen elimination, a palladium-catalysed background reaction also took place.

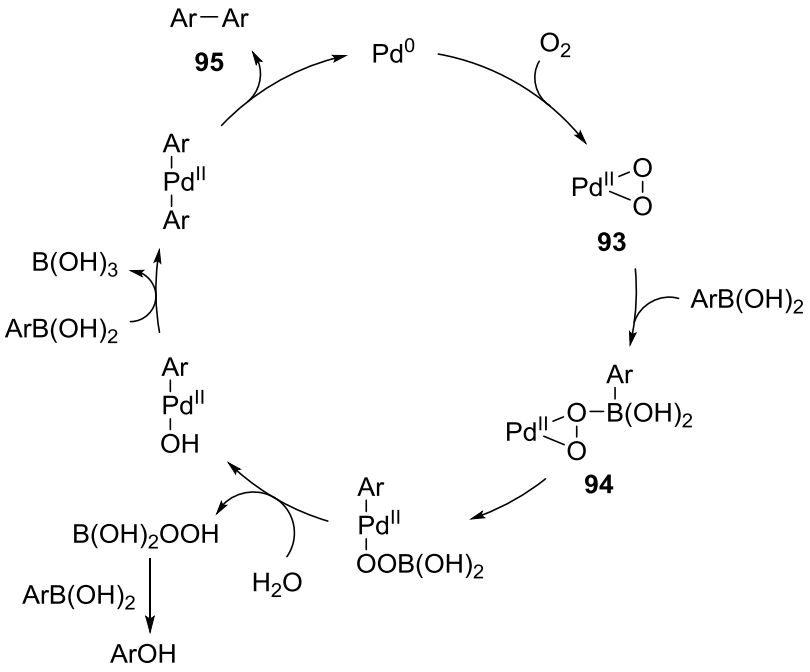


Entry	Catalyst	Solvent	Yield (%)
1	$Pd(OAc)_2$	MeOH	**90c**, 2
2	$Pd(PPh_3)_4$	MeOH	**91**, 56
3	10 wt% Pd/C	MeOH	**91**, 44 and **92**, 21
4[a]	$PdCl_2(dppf)$	1,4-dioxane/H_2O	**92**, 40
5[a]	$Pd(OAc)_2$	MeOH	**90c**, 9

Table 3: Optimisation of the one-pot diazotisation-Suzuki reaction of 4-nitroaniline (86a); [a]reaction was carried out stepwise.

As the reaction was not performed with the complete exclusion of air, the oxygen-mediated, palladium(0)-catalysed boronic acid homocoupling process could proceed *via* the generation of palladium(II) peroxo complexes **93** and **94**.

This was based on a collaborative work of Amatore and Jutand reported in 2006, where they have shown a plausible catalytic cycle for the formation of symmetric biaryls **95** *via* boronic acid homocoupling (Scheme 69).[144]

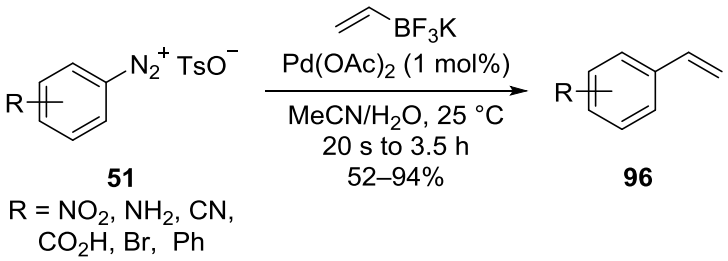


Scheme 69: Oxygen-mediated palladium(0)-catalysed boronic acid homocoupling; ligands on palladium are omitted for clarity

The idea of a stepwise two-step procedure led to the final attempts, and it was shown that by applying $PdCl_2$(dppf) in the presence of cesium carbonate as a base to activate the boronic acid reagent **89**, still no product formation occurred (entry 4). Instead, the homocoupled product **92** was detected again. Upon switching back the catalyst to $Pd(OAc)_2$, formation of the product **90c** was observed during ^{1}H NMR analysis of the reaction mixture, but was not separable from the multiple byproducts (entry 5).

The formation of the multiple byproducts made the optimisation of this process often difficult and led to crowded aromatic region of the ^{1}H NMR spectra due to the unreacted aryl diazonium salt and boronic acid coupling partner as well as the possible generation of ethyl benzoate after protodeboronation. The arising of multiple byproducts of this one-pot reaction and the failure of optimisation of product formation even in a stepwise method led to the abandonment of the diazotisation-Suzuki reaction process. While Suzuki coupling of aryl diazonium

salts has usually been described with the use of tetrafluoroborate salts, in a very recent collaborative work by Felpin and Postnikov, a process involving aryl diazonium tosylate salts **51** was developed (Scheme 70).[71] They reported the ultra-fast synthesis of a wide range of styrenes **96** from **51** with potassium vinyltrifluoroborate as coupling partner.

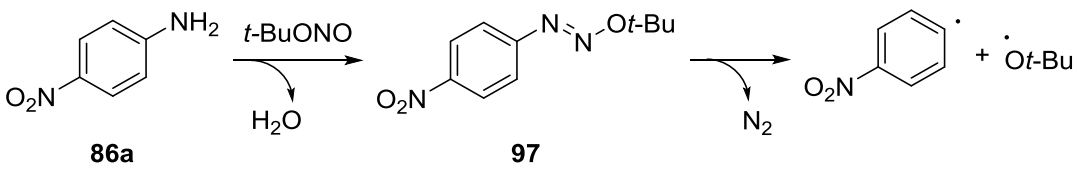


Scheme 70: Styrene synthesis from aryl diazonium tosylate salts with potassium vinyltrifluoroborate

2.2.4 Heck-Matsuda reaction of anilines

After obtaining the above results, the utilisation of diazonium tosylate salts in the Heck-Matsuda reaction with activated alkene coupling partners was next investigated.

Early research of the Heck-Matsuda reaction revealed that nitro-substituted aryl diazonium salts readily undergo a favourable homolytic dediazonisation pathway to result in a complex mixture.[57,145] Later, in 2017, Patil and co-workers predicted by DFT calculations, that this was due to the role of diazotisation reagent *tert*-butyl nitrite as it could form a covalent phenyl diazene adduct **97** with the diazonium cation instead of generating the salt as an ionpair. This could then allow inner sphere electron transfer to occur and homolytic dissociation of the adduct (Scheme 71).[146]

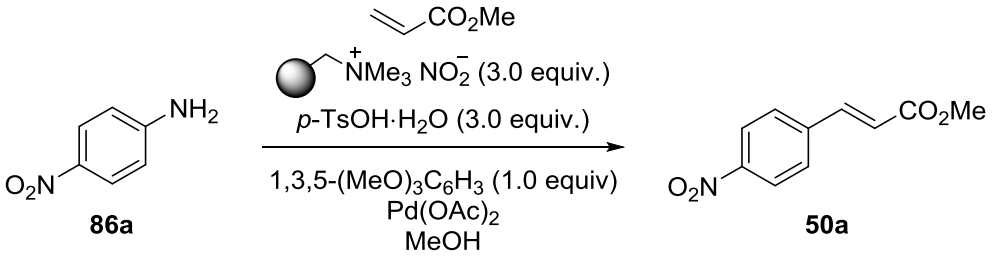


Scheme 71: Homolytic dediazonisation pathway of the diazene adduct from 4-nitroaniline (86a) *via* 97

However, as it has been already described earlier, Felpin and co-workers showed a one-pot diazotisation and Heck-Matsuda reaction that could overcome this issue, and allowed the generation of a range of coupled products **50a–e** including several nitro-substituted substrates (Scheme 28).[64] This was achieved by using the same nitrite source, *tert*-butyl nitrite in combination with methanesulfonic acid for the *in situ* diazonium salt formation and this was followed by the palladium catalysed Heck-Matsuda reaction with methyl acrylate. They were also able to show that, at the end of the Heck catalytic cycle, as one equivalent of acid was released, methanesulfonic acid could be used in substoichiometric amounts. The scope showed the formation of methyl cinnamates in good to high yields over the course of 65 hours.

We aimed to perform the Heck-Matsuda cross coupling reactions of anilines *via* stable aryl diazonium tosylate salts **51** with shorter reaction times as shown by the Felpin study. Also, in order to prove that issues associated with nitro analogues could be overcome (prone to homolytic dediazotisation), our investigation started with the optimisation of the *in situ* formation of the aryl diazonium tosylate salt from 4-nitroaniline (**86a**) followed by the Heck-Matsuda coupling with methyl acrylate to allow the formation of methyl cinnamate **50a** in one-pot (Table 4).[147] During optimisation of the one-pot tandem process the proton source, the catalyst loading, temperature and reaction time were screened. Notably, all reagents were added together at the start. The singlet aromatic peak of the internal standard 1,3,5-trimethoxybenzene at 6.09 ppm was used for reaction monitoring, which allowed all conversions to be calculated by ^{1}H NMR analysis of the crude reaction mixtures. These calculations were based on the calibrated aromatic peak of the internal standard measured against the more upfield α proton of methyl (*E*)-cinnamate **50a** at 6.56 ppm, which appears as a doublet with a 16.1 Hz *trans* coupling constant. Initial experiments revealed that the use of *p*-tosic acid as a proton source resulted in a higher conversion than with tetrafluoroboric acid (entries 1 and 2). While diazonium tetrafluoroborate salts have been widely used in palladium-catalysed coupling reactions, the use of the more stable diazonium tosylate salts is more beneficial, because these display higher stability and do not lead to the formation of the harmful HF byproduct.[148] Taking this into consideration, *p*-tosic acid was used for further optimisation. An increase in reaction temperature first to 40 °C then

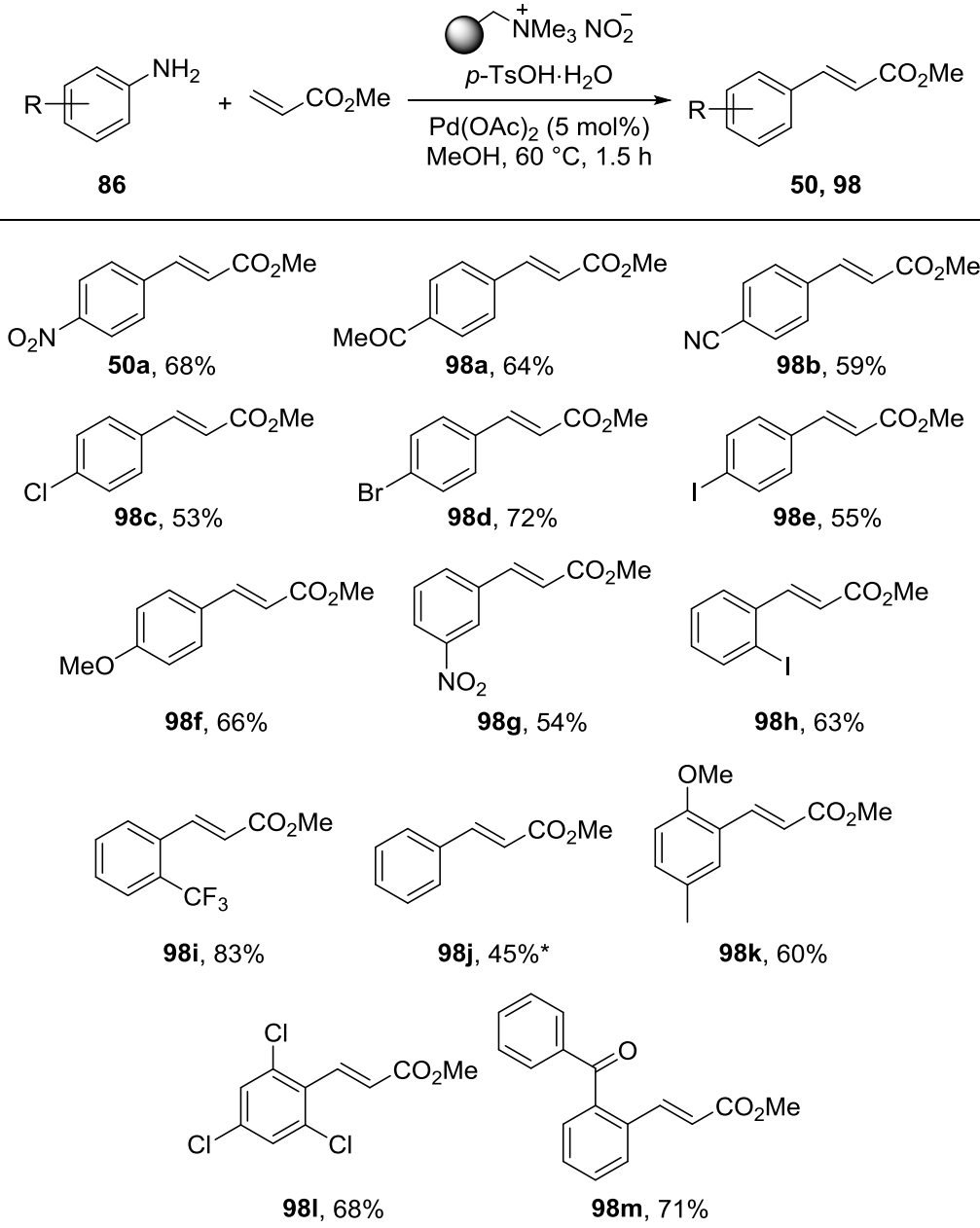
to 60 °C, resulted in higher conversions, 52% and 62%, respectively (entries 3 and 4). Heating also benefitted the process with much shorter reaction times (0.75 to 1 h). Therefore, full conversion was observed when both the $Pd(OAc)_2$ catalyst loading and the reaction time was increased (entry 5). As this meant that $Pd(OAc)_2$ (15 mol%) was needed, next a lower loading was tested for improved sustainability of the reaction. Using 5 mol%, the optimised conditions successfully gave complete conversion to methyl cinnamate **50a** and an isolated yield of 68% after 1.5 hours. As diazonium salts undergo azo coupling with electron-rich compounds (eg. anilines, phenols) to form azo dyes and pigments, the consumption of the diazonium salt intermediate could be monitored with the β-naphthol test. A co-spot of the reaction mixture and β-naphthol gave no colour on the TLC plate, indicating the negative result of the test, when the diazonium salt fully reacted. It has to be noted, that throughout the optimisation study no issues of dediazotisation was observed.



Entry	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Conversion (%)[a]
1[b]	10	20	24	38
2	10	20	24	48
3	10	40	1	52
4	10	60	0.75	62
5	15	60	1.5	100 (75)
6	**5**	**60**	**1.5**	**100 (68)**

Table 4: Optimisation of the one-pot tandem process; [a]isolated yields are shown in parentheses; [b]HBF_4 was used as the proton source.

Having the optimised conditions of a rapid and mild one-pot tandem process in hand, the scope of this transformation was next explored using various aniline substrates **86** and methyl acrylate (Scheme 72). It was found that irrespective of the electronic nature or the substitution pattern of the starting material anilines, all examples showed full conversion under the standard one-pot conditions and the corresponding coupled products **50a** and **98a–m** were furnished in moderate to good yields within 1.5 hours. Also, as it was already shown during optimisation of **50a**, exclusively *E*-alkene containing coupled products were achieved in this process based on the standard *trans* coupling constants. Both electron-rich and electron-deficient *para*-substituted anilines performed well in the process. Multi-substituted anilines were also tolerated in the one-pot process leading to compounds **98k** and **98l** in 60% and 68% yield, respectively. Upon using an *ortho*-substituted electron-deficient aniline, the best result was obtained and **98i** was isolated in 83% yield. This was important, as later we also aimed to extend the one-pot process to the synthesis of 3,4-dihydroquinolin-2-ones from 2-nitroanilines. More importantly, complete chemoselectivity was observed in the one-pot diazotisation and Heck-Matsuda coupling of halogenated anilines. This gave compounds **98c–e**, **98h** and **98l** as the sole products of the reaction in 53–72% yield and with no evidence for a competing background coupling reaction. The displayed high degree of chemoselectivity when synthesising bromo and iodo analogues exemplify the superior electrophilic nature of diazonium salts compared to halides. Moreover, this allows for further orthogonal functionalisation of methyl cinnamate products **98d** and **98e** in sequential Mizoroki-Heck and Suzuki-Miyaura couplings. Finally, sterically demanding aniline was also successfully incorporated in the scope and the highly conjugated benzophenone-derived **98m** was synthesised in 71% yield.



Scheme 72: Scope of the one-pot tandem diazotisation and Heck-Matsuda reaction; *10 mol% of $Pd(OAc)_2$ was used

During reaction scope evaluation, some aniline substrates gave only trace amount of the coupled product or did not give any product at all (Figure 5). Reaction of 3,4,5-trimethoxyaniline (**99**) under the standard conditions led to low mass recovery which was then found to be a 1:4 mixture of the product and 1,3,4,5-tetramethoxybenzene according to the peaks observed in ^1H NMR spectroscopy. The byproduct formation possibly occurred in the reaction of the electron-rich diazonium tosylate salt with the solvent methanol. 3-Aminopyridine (**100**) gave no product formation at all. Reaction of 1-

aminoanthraquinone (**101**) only led to trace amount of 9,10-anthraquinone, the product of dediazotisation.

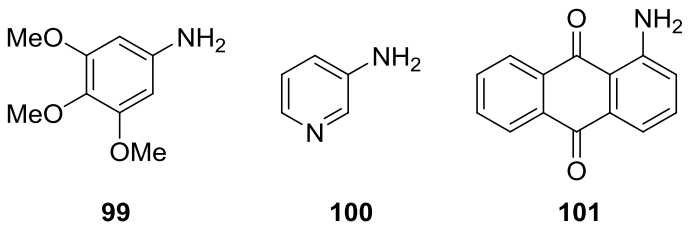
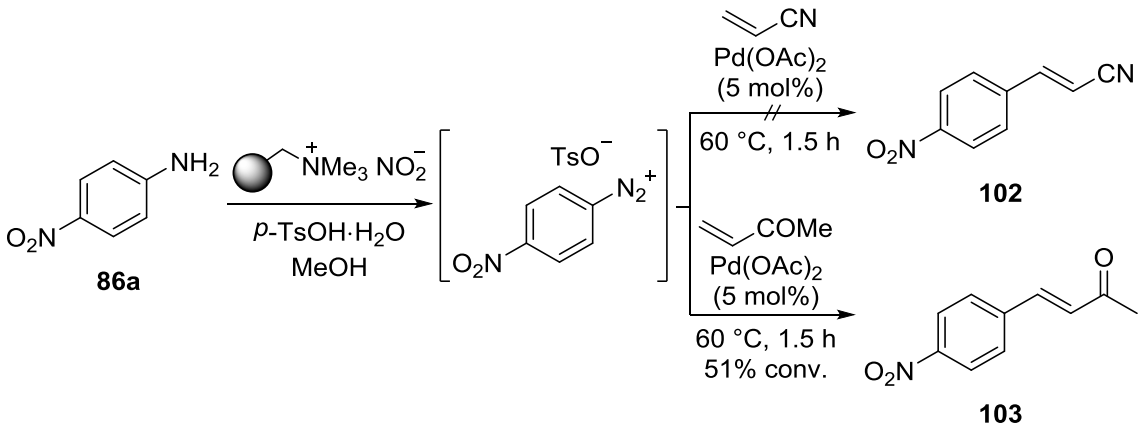


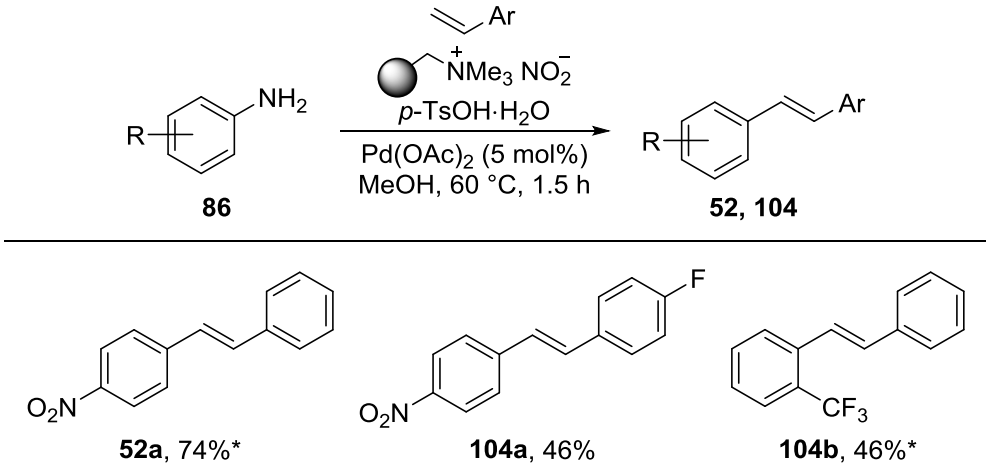
Figure 5: Unsuccessful substrates in the one-pot reaction

As the Heck-Matsuda reaction was successfully able to deliver a number of methyl cinnamate products **50a** and **98a–m**, other alkene coupling partners were also considered in this process. Acrylonitrile was also applied in the one-pot reaction with 4-nitroaniline (**86a**); however, this did not afford the coupled product **102** (Scheme 73). Upon using methanol as the solvent, the generation of 4-nitroanisole was detected from a reaction of **86a** with acrylonitrile. Other solvents, such as the aprotic THF or acetonitrile were also screened, but resulted in no tandem reaction. Product formation occurred when methyl vinyl ketone was the coupling partner and conversions up to 51% were observed according to ^{1}H NMR spectroscopy. However, separation and isolation of product **103** was problematic due to the multiple byproduct formation, and this one-pot process was not pursued any further.



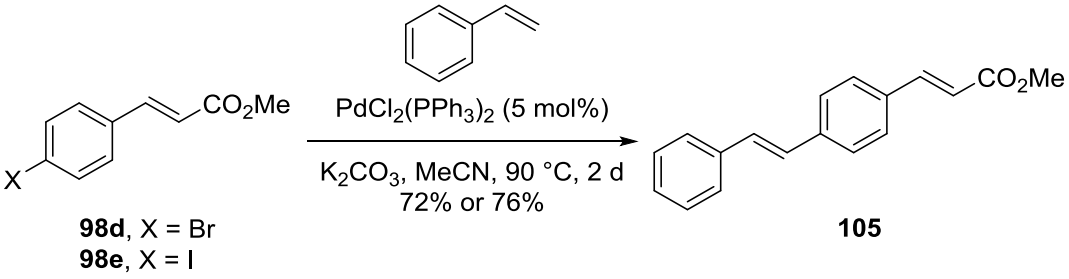
Scheme 73: Acrylonitrile and methyl vinyl ketone in the one-pot process with 86a

A new class of alkenes was also applied in the one-pot tandem process. This led to the extension of the one-pot procedure with the facile preparation of *E*-stilbenes using styrenes as coupling partners. Thus, reaction of 4-nitroaniline or 2-(trifluoromethyl)aniline with styrene or 4-fluorostyrene gave stilbenes **52a**, **104a** and **104b** exclusively as *E*-alkenes in moderate to good yields (Scheme 74). Evidence for alkene *E*-selectivity was observed in ^{1}H NMR spectroscopy, with large *trans* coupling constants of 16.4 Hz for **52a** and 16.0 Hz for fluorine-containing **104a** and **104b**.



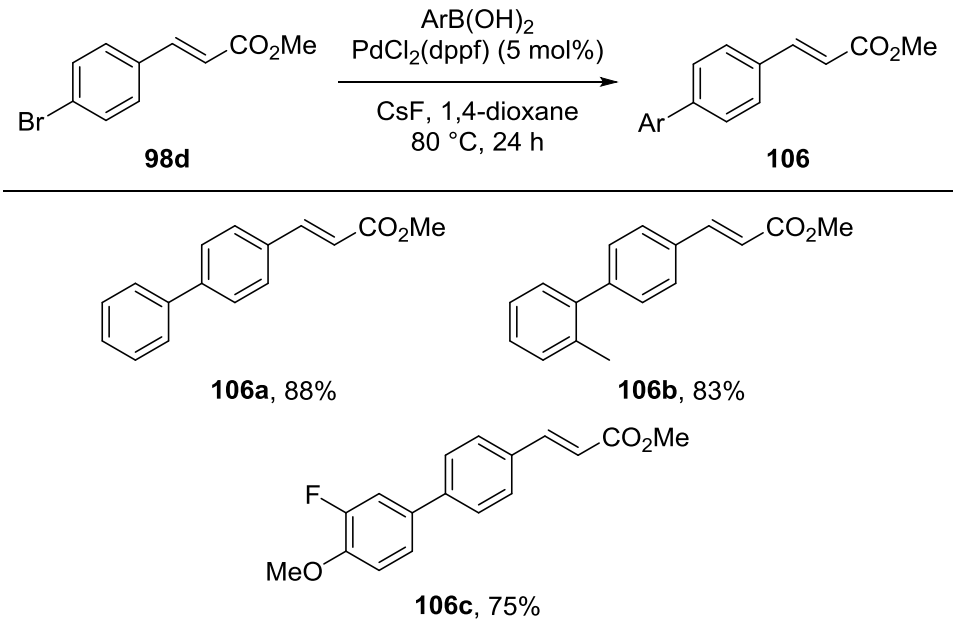
Scheme 74: Stilbene formation *via* the one-pot process; *10 mol% of $Pd(OAc)_2$ was used

We also wanted to demonstrate the multifunctional nature of 4-bromoaniline, as it can be applied in two consecutive coupling reactions. It was envisioned that both aryl amine and aryl bromide moieties could be employed in orthogonal chemoselective functionalisation. Therefore, the one-pot diazotisation and Heck-Matsuda reaction of 4-bromoaniline with methyl acrylate led to the formation of methyl (*E*)-3-(4-bromophenyl)acrylate (**98d**) in 72% yield under the standard conditions. The resulting methyl cinnamate derivative **98d** formed in a chemoselective way, still contained a bromide group which could be used for further functionalisation using palladium catalysis. For example, Heck and Suzuki couplings were possible which both utilise the bromide part of the compound. Submitting the 4-bromo analogue **98d** to the Heck reaction with styrene led to the construction of *E*-stilbene **105** in 72% yield (Scheme 75). It has to be noted, that the same compound was also synthesised in a similar two-step route from 4-iodoaniline, *via* methyl 4-iodocinnamate **98e**. In this case, using the same Heck reaction conditions, *E*-stilbene **105** was obtained in 76% yield.



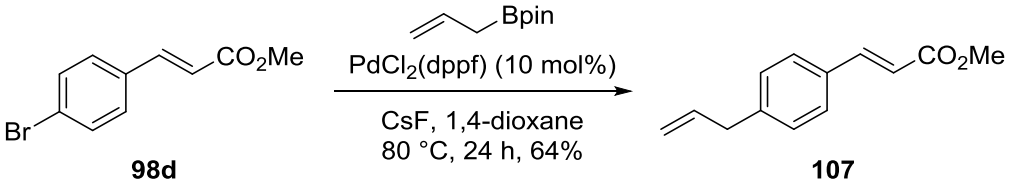
Scheme 75: Heck reaction of 98d/98e with styrene

Next, Suzuki couplings of **98d** were carried out using several boronic acids for the formation of unsymmetrical biaryl compounds **106a–c** (Scheme 76). Using phenylboronic acid as the coupling partner in the presence of $PdCl_2$(dppf) (5 mol%) and cesium fluoride gave **106a** in 88% yield. Substituted phenylboronic acids were also employed in the coupling reaction and under the same conditions **106b** and **106c** were achieved in 83% and 75% yield, respectively.



Scheme 76: Suzuki coupling of 98d with aryl boronic acids

Upon using allylboronic acid pinacol ester in the Suzuki coupling, **107** was prepared in 64% yield under similar reaction conditions (Scheme 77). All these coupled products successfully exemplified the possibility of orthogonal functionalisation of 4-bromoaniline.

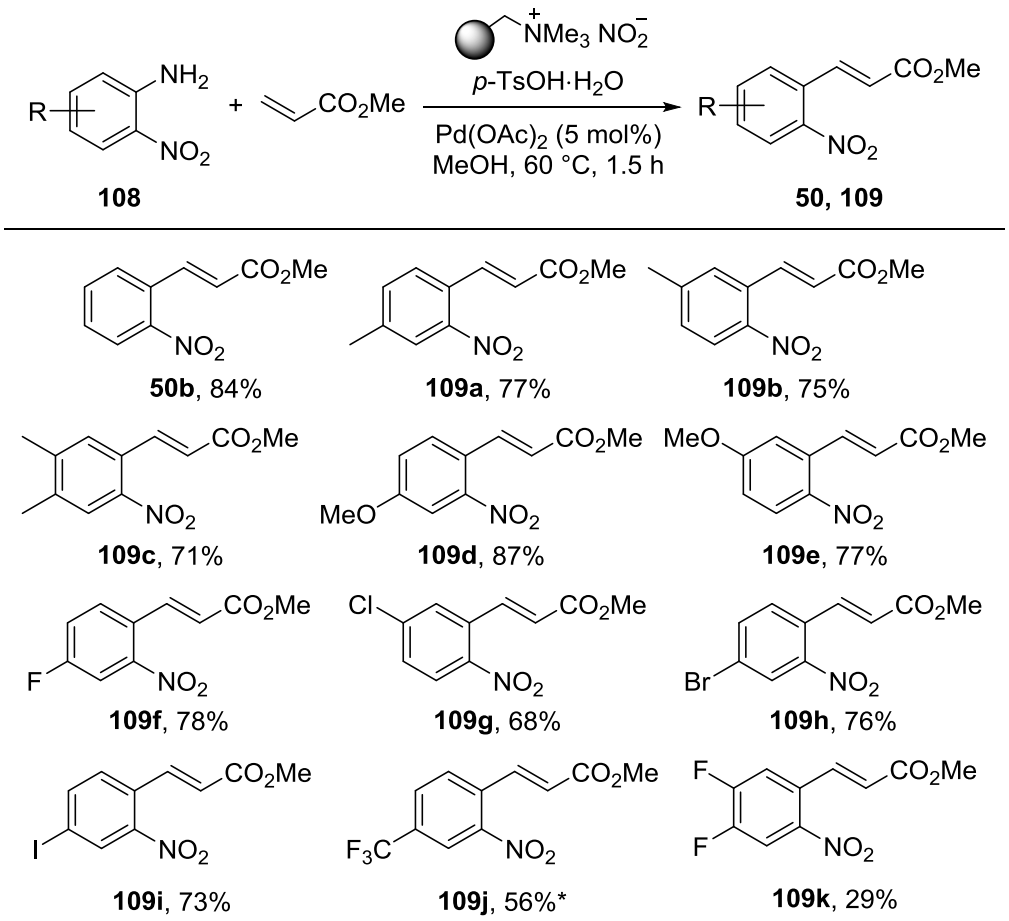


Scheme 77: Suzuki coupling of 98d with allylboronic acid pinacol ester

2.2.5 Heck-Matsuda reaction of 2-nitroanilines

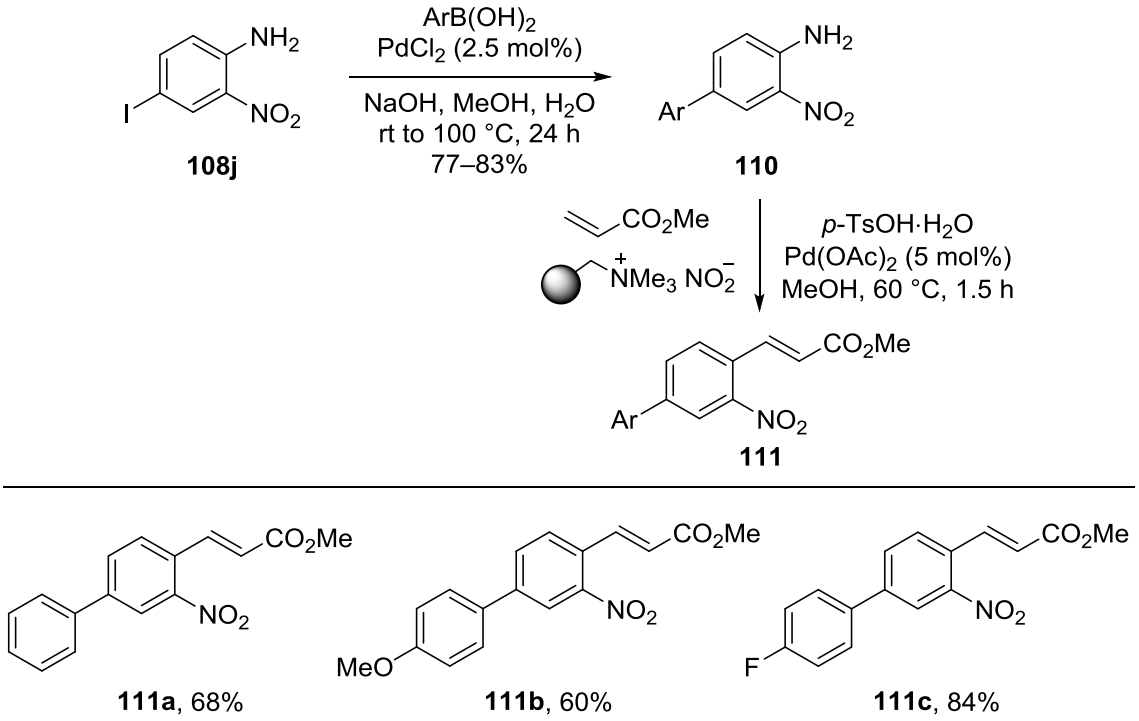
In order to successfully carry out the envisioned multi-bond forming synthetic route for the construction of 3,4-dihydroquinolin-2-ones, first the intermediate methyl cinnamates bearing an *ortho*-nitro group were synthesised from 2-nitroanilines **108** by the standard one-pot tandem reaction (Scheme 78). The second library of methyl (*E*)-cinnamates was built up using the same one-pot tandem conditions as before, and the standard 1.5 hour reaction time resulted in the corresponding coupled products **50b** and **109a–k** in good to high yields, showcasing these compounds as excellent substrates for the one-pot process. Compared to the first library, these substrates gave generally higher yields due to the increased reactivity of the *ortho*-nitroanilines. However, this was not unexpected as *ortho*-substituted aniline has previously shown a high-yielding process in the preparation of **98i** (Scheme 72). 2-Nitroaniline (**108a**) performed well in the one-pot process and **50b** was obtained in 84% yield. Both electron-rich and electron-deficient multi-substituted 2-nitroaniline starting materials were submitted to the one-pot process and it was found that these were also tolerated in the reaction. 2-Nitroanilines with additional electron-donating groups in the *para*-substitution led to higher yields compared to the same substituent at the meta-position. For example, **109d** and **109e** were synthesised in 87% and 77% yield, respectively. Again, halogen-containing 2-nitroaniline substrates led to chemoselective transformations, whereby all the halogen atoms remained intact in the one-pot diazotisation and Heck-Matsuda reaction. This led to the formation of methyl cinnamates **109g–i** in 68–76% yield, which have the potential role in additional chemoselective transition metal-catalysed coupling reactions. Under the standard conditions, the strongly electron-withdrawing trifluoromethyl-containing substrate showed a slow reaction with incomplete conversion to **109j**. The optimised conditions involved the use of

7.5 mol% catalyst loading and a longer reaction time (24 h), which then resulted in 56% yield for **109j**. Overall, the second library of compounds demonstrated the remarkably efficient one-pot preparation of methyl cinnamates bearing an *ortho*-nitro functionality, which has the synthetic potential for further transformations. It should be noted that compounds **109b**, **109d** and **109j** were synthesised by Megan Grace, a BSc project student.



Scheme 78: Scope of the one-pot tandem reaction using 2-nitroanilines; *7.5 mol% $Pd(OAc)_2$ was used over 24 hours

Starting material 4-aryl-2-nitroanilines **110a–c** for the last substrates were synthesised *via* the Suzuki coupling of 4-iodo-2-nitroaniline (**108j**) with several arylboronic acids (phenyl-, 4-methoxyphenyl- and 4-fluorophenylboronic acid, Scheme 79). This reaction gave biaryl compounds **110a–c** in 77–83% yield. These coupled products served as additional substrates for the scope and performed well in the one-pot tandem process, successfully leading to the target analogues **111a–c** in 60–84% yield under the standard conditions.



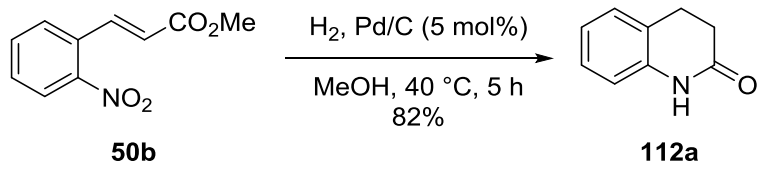
Scheme 79: Suzuki coupling of 108j with aryl boronic acids and the one-pot tandem synthesis of 111a–c

2.2.6 Multistep synthesis of 3,4-dihydroquinoline-2-ones

As the one-pot tandem process successfully showed the high-yielding preparation of 2-nitro bearing methyl cinnamates **50b**, **109a–k** and **111a–c** the scope of the 3,4-dihydroquinoline-2-one synthesis was next explored. This time, the aim was to progress the methyl cinnamate products of the one-pot tandem process further without isolation and expand the methodology to a multi-bond forming operation.

Prior to the multistep process, one test reaction was carried out in order to probe the reduction and cyclisation processes from **50b** (Scheme 80). As a possible palladium deactivation pathway of $Pd(OAc)_2$ in the Heck-Matsuda reaction involves the formation of palladium black, Pd/C was used as the catalyst for the hydrogenation of the double bond and reduction of the nitro group under a hydrogen atmosphere. The reaction was monitored with ^1H NMR spectroscopy, and the disappearance of the distinctive *E*-alkene doublet peaks indicated the formation of methyl 2-nitrophenylpropionate intermediate. After nitro reduction, the resulting compound spontaneously cyclised to quinolone

112a, leading to a clean reaction after 5 hours and **112a** was achieved in 82% yield.



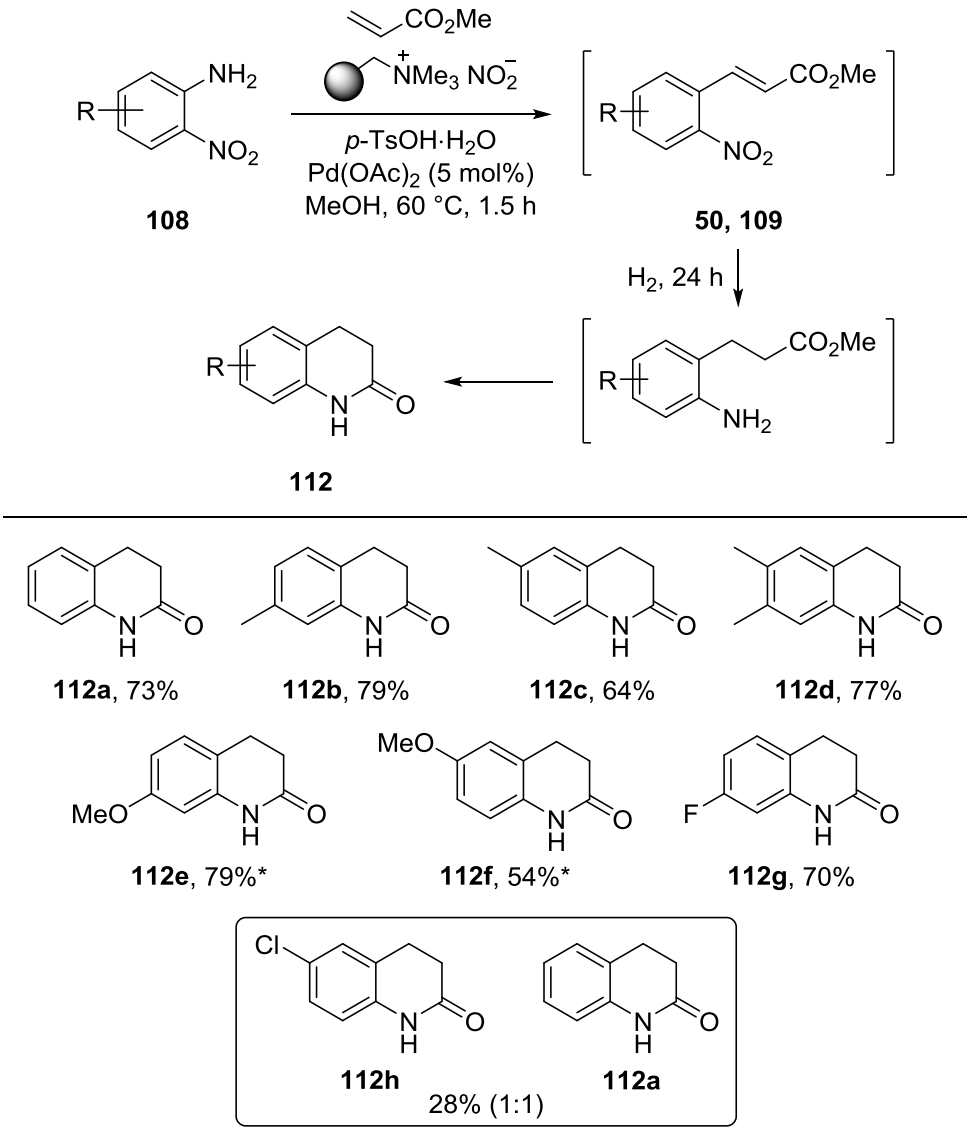
50b **112a**

Scheme 80: Synthesis of 3,4-dihydroquinoline-2-one 112a from 50b

The next stage was to explore the extended multistep process and prepare the quinolinones in one-pot from the 2-nitroanilines. This was successful and a range of 2-nitroaniline starting materials were transformed *via* diazotisation, Heck-Matsuda reaction, reduction under a hydrogen atmosphere and the subsequent cyclisation process resulting in the quinolinones (Scheme 81).

The unsubstituted quinolinone derivative **112a** performed well in the process and was isolated in 73% yield, which was comparable to that obtained earlier starting directly from the methyl cinnamate **50b**. This result represented the outstanding efficiency of the one-pot multistep process, as a high yield was achieved after 5 consecutive reaction steps. All substrates were synthesised in high yields, and **112e** performed excellently even on a gram scale. It has to be noted that depending on the scale of the electron-donating effects of substituted anilines, the hydrogenation/reduction steps were found to lead to the electron-rich methoxy derived quinolinones **112e** and **112f** more slowly. To achieve full conversion, the reaction for these compounds was repeated by conducting the reduction under pressure. For this, a Parr apparatus was used and the hydrogen pressure set to 2.5 bar. Changing the conditions for the latter steps successfully generated the quinolinones **112e** and **112f** in 79% and 54% yield, respectively. A limitation of this one-pot process was that 2-nitroanilines containing hydrogen-labile carbon–halogen bonds could lead to dehalogenation at the reduction step. Hydrodehalogenation can take place in the presence of palladium and the process results in carbon-halide bond cleavage. For example, applying 5-chloro-2-nitroaniline in our one-pot process gave 5-chloro-3,4-dihydroquinolin-2-one (**112h**) in a low 28% yield and as a 1:1 inseparable mixture

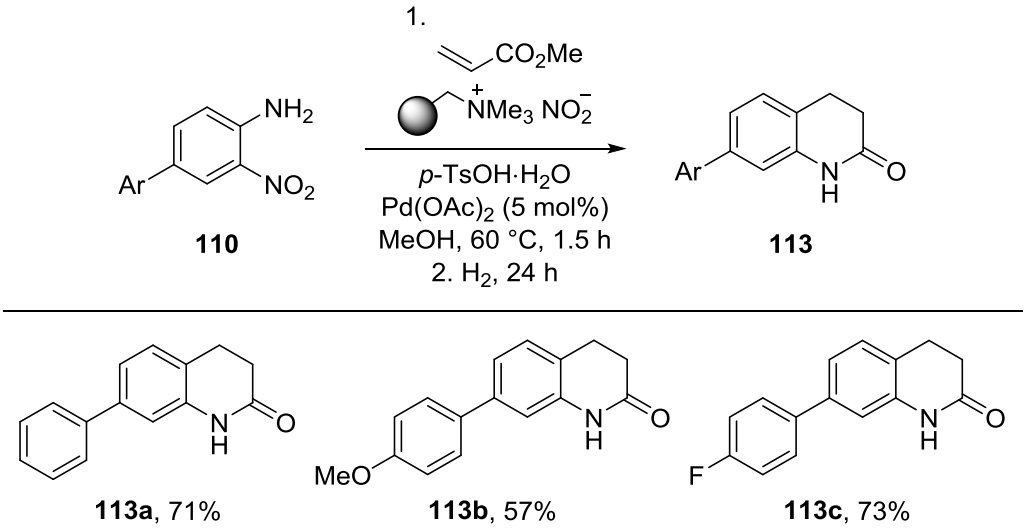
with the dechlorinated product **112a**. It should be noted that compound **112c** was synthesised by Megan Grace, a BSc project student.



Scheme 81: Scope of the one-pot multistep synthesis of 3,4-dihydroquionolin-2-ones 112a–h; *reduction and cyclisation reactions were performed under pressure using 2.5 bar of hydrogen in the Parr apparatus

As halogenated 3,4-dihydroquinolin-2-ones are interesting for their potential for further structural diversification through cross-coupling reactions we aimed to overcome this limitation. Thus, Suzuki–Miyaura reactions of 4-iodo-2-nitroaniline (**108j**) were carried out prior to the one-pot process as seen previously on Scheme 79. It was found when using the biaryl derivatives **110a–c** in the one-pot multistep process, that again the use of 2.5 bar of pressure for the hydrogenation and reduction steps was needed for the most efficient synthesis

of compounds **113a–c** (Scheme 82). However, this was ultimately successful giving the three target compounds in 57–73% yield. It should be noted that compound **113b** was synthesised by Megan Grace, a BSc project student.

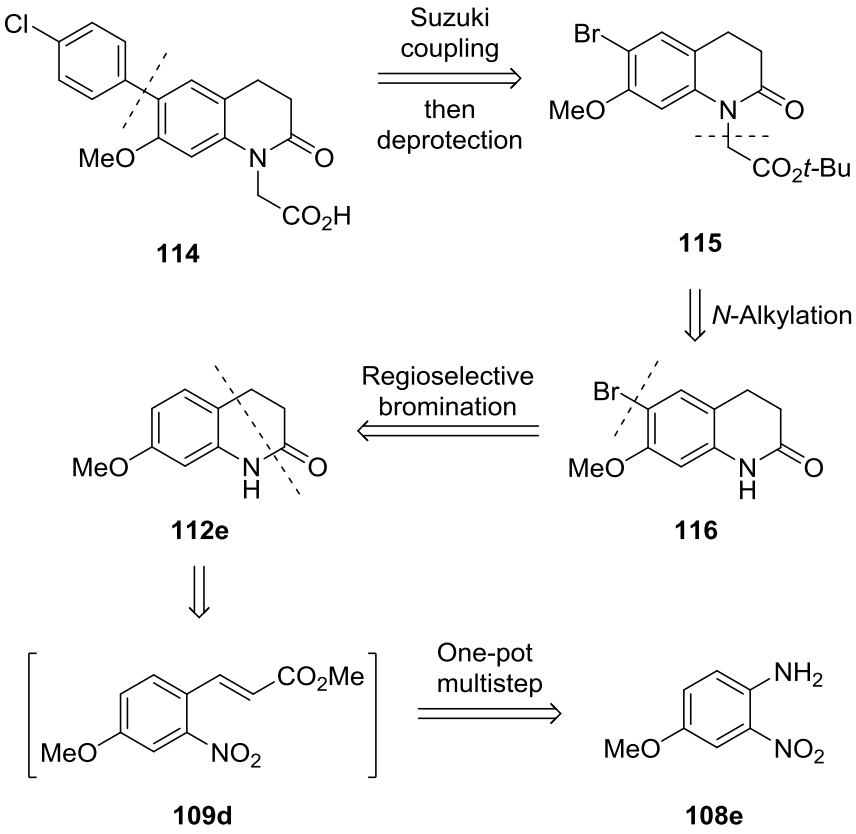


Scheme 82: Scope of the one-pot multistep synthesis of 7-aryl-3,4-dihydroquionolin-2-ones 113a–c

2.2.7 Synthesis of sodium channel modulator 114

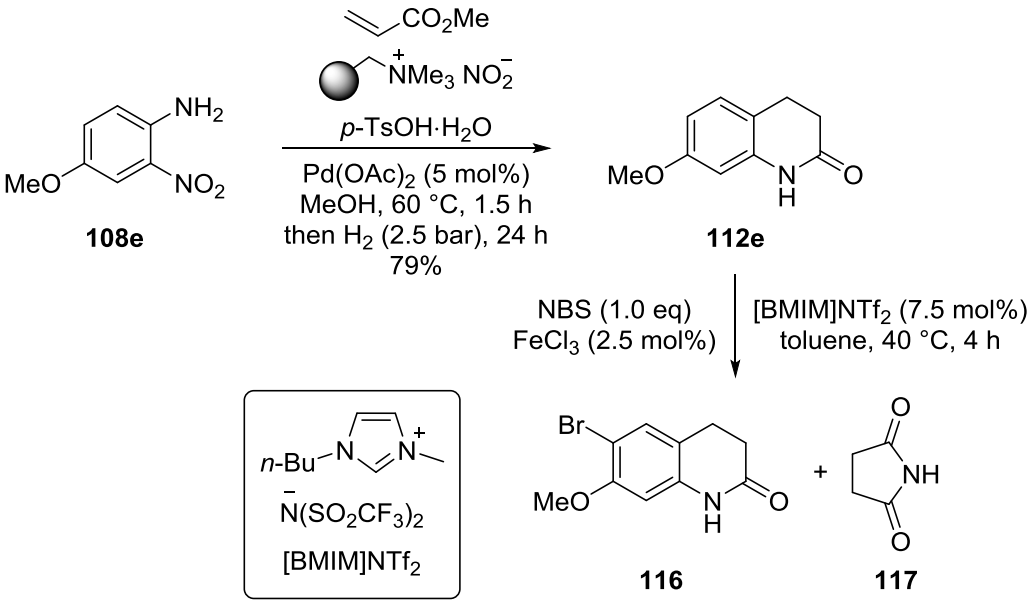
The final stage of this project was to show the synthetic potential of the one-pot multistep process. We aimed to demonstrate this *via* the total synthesis of a pharmaceutically important target. *N*-Acetic acid derived 3,4-dihydroquinolin-2-ones containing aryl groups either at the 6- or 7-position are late stage sodium channel blockers and have the potential to be used in the treatment of diabetes and cardiovascular diseases.[149]

Retrosynthetic analysis of sodium channel modulator **114** is shown in Scheme 83. The final compound could be achieved after ester hydrolysis and prior to this the Suzuki reaction would install the aryl group at the 6-position. *N*-Alkylation of the quinolinone core and the key iron(III)-catalysed regioselective bromination would lead to 3,4-dihydroquinolin-2-one **112e**. Finally, disconnection of this compound would afford 4-methoxy-2-nitroaniline (**108e**).



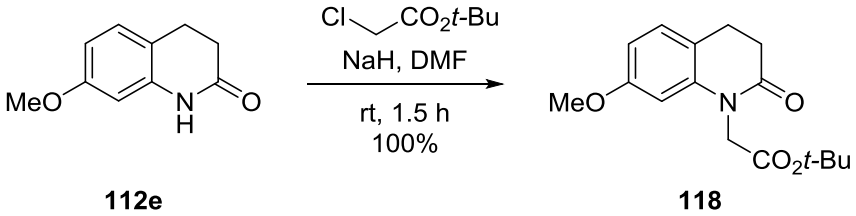
Scheme 83: Retrosynthetic analysis of 114

As shown in Scheme 81, the extended one-pot process was used to synthesise 7-methoxyquinolinone **112e** in the forward synthesis. More importantly, the successful scale-up of the one-pot multistep process was also accomplished and the core compound **112e** was synthesised in a 79% yield on a gram scale. This was beneficial as for the total synthesis of the ion channel modulator further transformations were necessary starting from this quinolinone scaffold. Compound **112e** was then submitted to the highly regioselective bromination with *N*-bromosuccinimide (NBS) in the presence of catalytic amounts of iron(III) chloride and ionic liquid [BMIM]NTf_2 (Scheme 84). As previously shown within the Sutherland research group, the combination of these forms iron(III) triflimide *in situ*, which acts as a powerful Lewis acid for the activation of NBS.[150] However, this reaction led to an unseparable mixture of the target compound 6-bromo-7-methoxy-3,4-dihydroquinolin-2-one (**116**) and the byproduct succinimide (**117**) due to their very similar polarity.



Scheme 84: One-pot synthesis of 7-methoxyquinolone 112e followed by the regioselective bromination

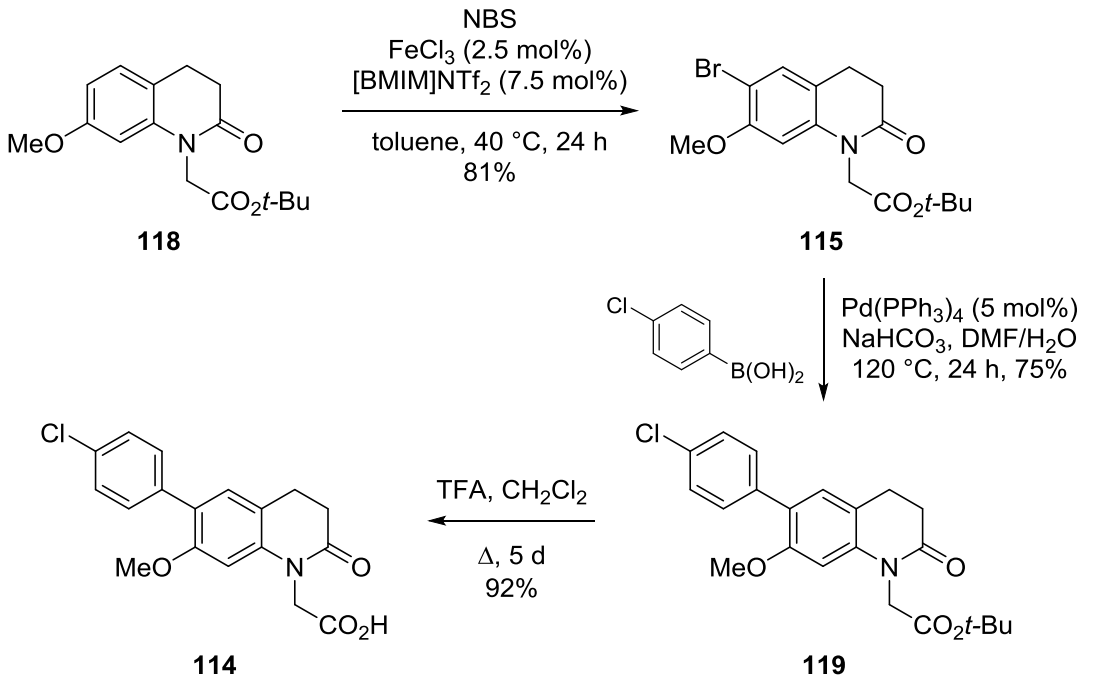
As the separation issues arising from the similar properties of the substituted 3,4- dihydroquinolin-2-one **116** and **117** could not be overcome, it was then decided to change the route and perform the *N*-alkylation step prior to the regioselective bromination (Scheme 85). Reaction of the quinolinone core **112e** with *t*-butyl chloroacetate and sodium hydride afforded the corresponding *N*-alkylated 3,4-dihydroquinolinone compound **118** in a quantitative yield after 1.5 hours.



Scheme 85: *N*-Alkylation of 112e

Following this, the highly regioselective iron(III) triflimide-catalysed bromination with NBS was used to functionalise the 6-position of the aryl ring (Scheme 86). This time, isolation of product **115** was achieved in 81% yield. Subsequent Suzuki–Miyaura coupling of **115** with 4-chlorophenylboronic acid using conditions previously described in literature gave 6-aryl-7-methoxy-3,4-dihydroquinolin-2-

one **119** in 75% yield.[149] Finally, TFA mediated hydrolysis of the *t*-butyl ester completed the synthesis and *N*-acetic acid derived compound **114** was achieved in nearly quantitative yield under mild conditions. Thus, the five-pot total synthesis of sodium ion channel modulator **114** was accomplished in 44% overall yield from 2-nitroaniline **108e**.



Scheme 86: Last three steps of the total synthesis of 114

2.2.8 Conclusions

In summary, a rapid and operationally simple one-pot tandem process involving diazotisation and base-free Heck–Matsuda reaction of anilines with methyl acrylate and styrenes was developed.[147] The particularly mild procedure for the formation of aryl diazonium tosylate salts using the polymer-supported nitrite reagent and *p*-tosic acid allowed for the efficient and environmentally benign synthesis of a number of Heck coupled products. Another key feature of the one-pot tandem process was the demonstration of the chemoselective coupling of brominated and iodinated anilines, which could then be further functionalised in other cross-coupling reactions, leading to orthogonally substituted arenes. It was also successfully shown, that by using 2-nitroanilines as starting materials, the one-pot process could be extended for the direct synthesis of the 3,4-dihydroquinolin-2-one core *via* the methyl cinnamate intermediates. Therefore,

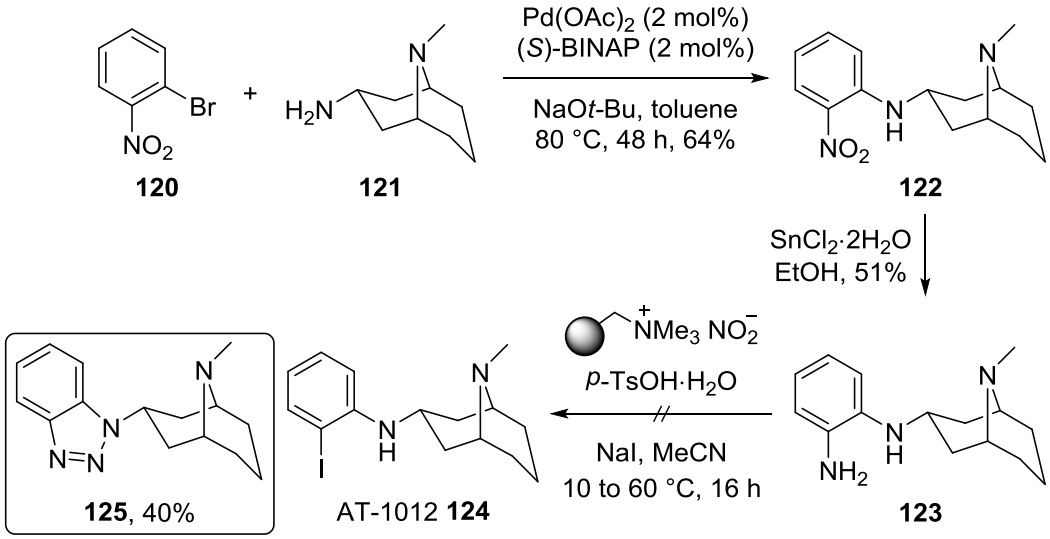
after the diazotisation and palladium-catalysed Heck–Matsuda steps, in the presence of the residual catalyst hydrogenation of the alkene, reduction of the nitro group, and *in situ* cyclisation furnished a library of 3,4-dihydroquinolin-2-ones in good yields. Furthermore, the environmental impact of this reaction was also reduced by the successful reutilisation of the catalyst during the final stage of the one-pot process. Finally, the synthetic utility of the one-pot multi-bond forming process was demonstrated with the total synthesis of a sodium ion channel modulator *via* a five-pot synthesis.

2.3 One-pot Rapid Synthesis of 1*H*-Benzotriazoles from 1,2-Aryldiamines

2.3.1 Previous work in the Sutherland group

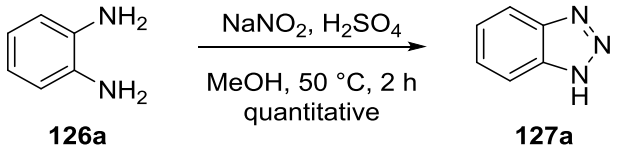
As described in the previous section (2.2 One-pot Tandem Reactions for the Synthesis of Methyl Cinnamates and 3,4-Dihydroquinolin-2-ones), the combination of a polymer-supported nitrite reagent and *p*-tosic acid has been used in the Sutherland group for the one-pot synthesis of aryl iodides from anilines.[136] This process involved the safe and rapid *in situ* formation of stable aryl diazonium tosylate salts and not only allowed the efficient late-stage iodination of more complex organic structures, but the syntheses of a series of SPECT imaging agents incorporated with iodine-125 were also developed.[137]

However, during the synthesis of AT-1012 (**124**),[151] a highly potent antagonist for $\alpha 3\beta 4$ nicotinic acetylcholine receptor, it was discovered that the final iodinated target did not form under the standard conditions (Scheme 87).[152] The core structure was synthesised *via* a Buchwald-Hartwig coupling of azabicyclononane **121** with 2-bromo-1-nitrobenzene (**120**), followed by tin(II) chloride-mediated reduction of the nitro group. This resulted in the aniline substrate **123** ready to undergo the one-pot diazotisation-iodination process. The attempted room temperature reaction did not result in any conversion of the precursor, therefore the reaction was heated to 60°C overnight. This time complete conversion of the starting material **123** was observed, and upon purification the analysis of the compound led to the discovery of the formation of the novel *N*-substituted 1*H*-benzotriazole **125** in 40% yield.



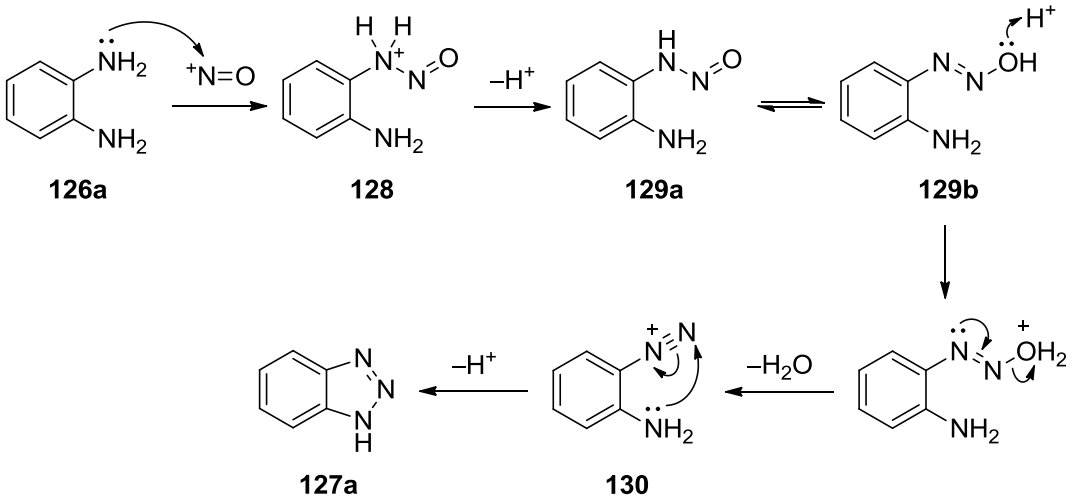
Scheme 87: Previous synthetic attempt of AT-1012 (124)

This was an unexpected result as the target molecule was the iodinated biologically active AT-1012, but was not unprecedented in literature. It is known, that 1,2-arylamines undergo diazotisation and subsequent intramolecular cyclisation to form benzotriazoles in the presence of a nitrite source under acidic conditions (Scheme 88). Therefore, diazotisation of **126a** followed by intramolecular cyclisation afforded **127a** in a quantitative yield.[153]



Scheme 88: Formation of 1*H*-benzotriazole (126a) from 1,2-phenylenediamine (127a)

The process leading to 1*H*-benzotriazoles proceeds *via* the diazotisation of an aromatic amine, and starts with the nitrogen-nitrogen bond-forming step (Scheme 89). This begins with the nucleophilic aniline lone pair of **126a** attacking the nitrosonium cation (formed previously from a nitrite reagent under acidic conditions). After deprotonation, the resulting nitrosamine **129a** tautomerises to **129b** which allows for the protonation of the diazohydroxyl oxygen and subsequent dehydration leads to the formation of the diazonium species **130**. The synthesis of 1*H*-benzotriazole (**127a**) is complete after intramolecular cyclisation and deprotonation.



Scheme 89: Proposed mechanism for the formation of 1*H*-benzotriazole (127a)

2.3.2 1*H*-Benzotriazole scaffolds; medicinal chemistry and synthesis

Benzotriazoles are important nitrogen heterocycles with a wide range of applications throughout organic synthesis,[154–156] medicinal chemistry[157–159] and material science.[160,161] The increasing clinical use of benzotriazole-based drugs prompts investigations to develop new and efficient syntheses of these derivatives in the hope for more effective treatments. These aromatic benzo-fused nitrogen heterocyclic compounds exhibit a broad range of biological activities and therefore are highly useful in medicinal applications.[162] The increasing synthetic effort towards constructing benzotriazole-containing drugs is due to their widespread antifungal, antiparasitic, anticancer, antibacterial, antiviral and antitubercular properties. The reason for the highly bioactive effect of the benzotriazole compounds is arising from their structure. Due to the fused benzene ring the bicycle possesses an extended conjugated system, therefore is able to interact *via* π-π stacking.[157] In addition to this, the three nitrogen-atom unit allows hydrogen bonding and coordination to metal ions easily.[163] These properties make benzotriazole derivatives bind more readily with a range of receptors and enzymes found in biological systems *via* diverse non-covalent interactions. Recently, promising new benzotriazole-containing drugs have been discovered with effective pharmacological properties such as low toxicity, few side effects, good water solubility as well as little multi-drug resistance.[164]

Several antifungal benzotriazole derivatives have emerged due to the wide spectrum activity of these compounds.[165] Azole drugs in general are very potent antifungal compounds, and fluconazole (**131**) has been used as an oral antifungal treatment since 1988, also listed by the World Health Organisation of essential medicines (Figure 6).[166] It has been shown active against most *Candida* species and *Cryptococcus neoformans* among others and operates *via* blocking the biosynthesis of ergosterol from lanosterol, the essential component of fungal cytoplasmic membrane. The structural modification of this first-generation triazole-based compound led to a more potent medication and it involved the introduction of a benzotriazole unit into the molecule. Indeed, benzotriazole derivative **132** showed improved bioactivity against *Candida glabrata*, with a two-fold potency compared to the parent fluconazole.[167] Other benzotriazole compounds with saturated alkyl chains were also reported to have excellent activity against *Candida neoformans*, such as *N*-nonylbenzotriazole (**133**). A study on the length of the alkyl chain revealed that optimum length was possessed by the nonyl compound **133**, while longer alkyl chain containing benzotriazoles showed no antifungal activity.

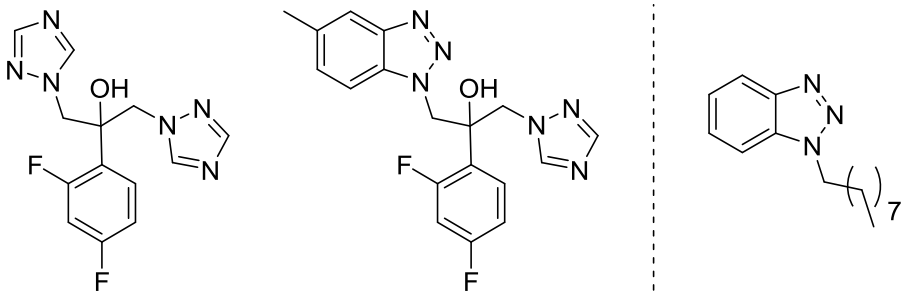
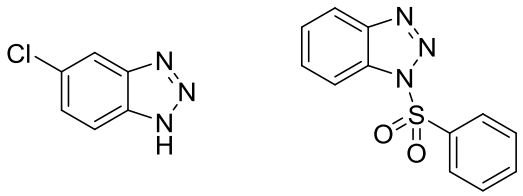


Figure 6: Antifungal benzotriazole compounds

Benzotriazole derivatives not only possess antifungal activities, but antiparasitic compounds have also been discovered (Figure 7).[157] Parasitic diseases cause damages to both society and economy, therefore an urgent requirement for novel treatments with better efficacy has arisen. To solve this problem, benzotriazole based drugs have been reported with advanced antiparasitic properties, such as 5-chlorobenzotriazole (**134**).[168] This showed great activity against *Entamoeba histolytica* with half maximal inhibitory concentration (IC_{50}

value) of 0.34 μg/mL. Moreover, *N*-phenylsulfonyl benzotriazole (**135**) has shown to inhibit the epimastigote developmental stage of *Trypanosoma cruzian*, the main cause of Chagas disease.[169]



134 **135**

Figure 7: Antiparasitic benzotriazole compounds 134 and 135

Due to several side effects of clinically used anticancer drugs that show toxicity to normal tissues and their dose-related accumulation which often leads to drug resistance, structurally new therapeutic agents are needed. The key to long-term effectiveness of anticancer agents is the design and development required from targeted research. Numerous benzotriazole derived compounds have been found to show anticancer activity. These include vorozole (**136**), which is under clinical trials and 4,5,6,7-tetrabromobenzotriazole (TBB, **137**), which has already been commercialised and has high selective inhibition against protein kinase CK2 (Figure 8).[170] As kinases play a significant role in cell multiplication, kinase inhibition bears utmost importance in cancer treatment.[171] The effective inhibition of kinase activity is possible *via* diverse non-covalent forces such as hydrophobic effect, ion-dipole, hydrogen bonding, coordination and so on. Human protein kinase CK2 plays an important role in regulating many cellular events, such as disruption of cell growth or promotion of cell death. As CK2 suppresses apoptosis, cancerous cells are allowed to escape cell death and continue proliferating. Therefore, this promotes the kinase being a potential therapeutic target. TBB **137** is a clinically used CK2 inhibitor with an IC_{50} value of 0.56 μg/mL.[172] Recently, other TBB derivatives were found to possess similar or better inhibitory effects, such as compound **138**. This compound differs from the parental **137** in a propanol functional group at the 1-position and has better inhibition with an IC_{50} value of 0.32 μg/mL.[173] Compound **138** is also able to cross the blood/brain barrier which has made this an important candidate for further studies.

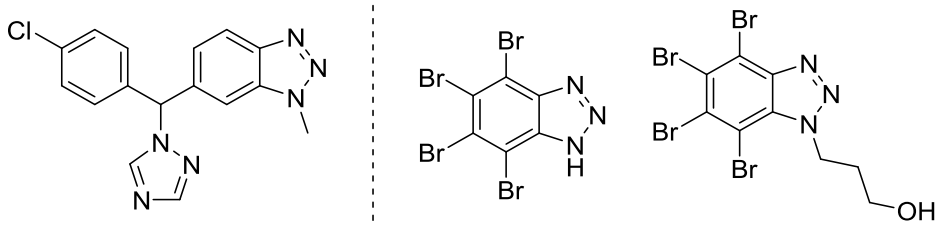


Figure 8: Anticancer vorozole (136), TBB (137) and its derivative 138

Histone deacetylases (HDACs) play an important role in carcinogenesis (cancer development).[174] Therefore, compounds with HDAC inhibitory effect are under clinical trials to treat a number of malignancies within the cell as they are able to block cell proliferation and induce apoptosis.[175] Two novel benzotriazole classes **139** and **140** were assayed for their antiproliferative activities against three types of human cancer cell lines (Figure 9).[176] All compounds possessed anticancer activity, among which benzotriazolyl trimethoxybenzoate **139** showing the most potent activity with an IC_{50} value of 1.7 n*M*. Investigation for HDAC inhibitory activity of these compounds was also evaluated. Finally, docking experiments confirmed their binding mode at the active site *via* π stacking between a tyrosine residue and the two benzene rings of **139** as well as possible hydrophobic interactions with phenylalanine, leucine, lysine and tyrosine residues of the enzyme.

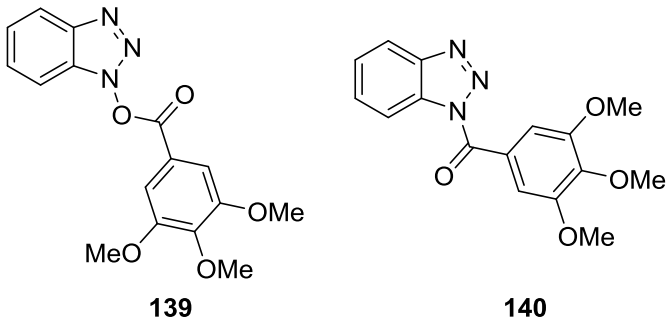
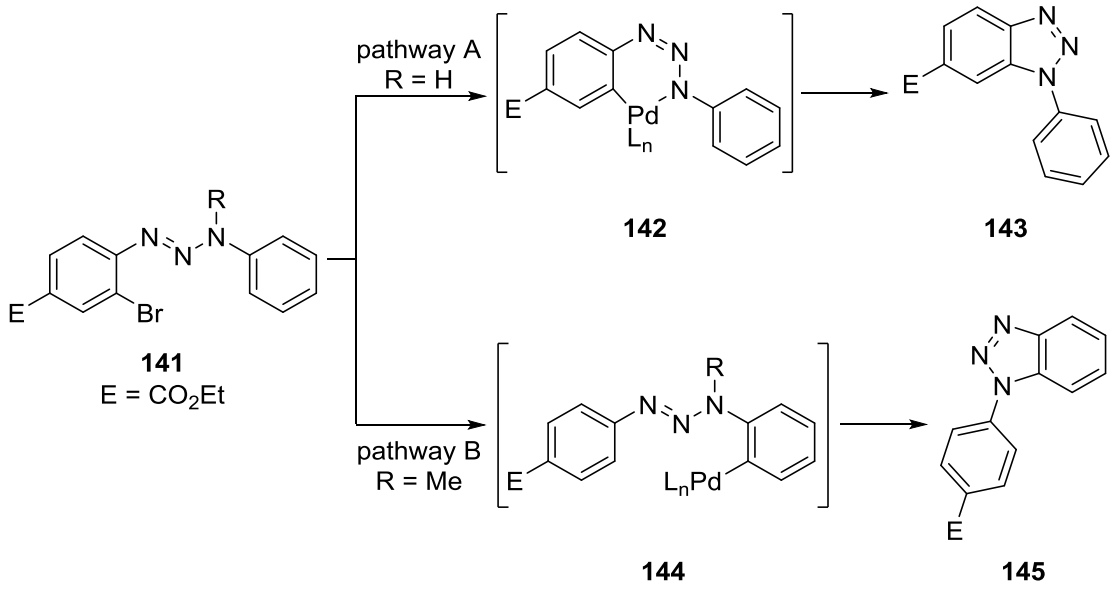


Figure 9: Antiproliferative agents

Traditionally, N_1-substituted benzotriazoles have been prepared by *N*-alkylation or arylation of benzotriazoles or click-type [3+2] cycloaddition of organic azides and arynes.[177–187] Due to the tautomeric nature of unsymmetrical benzotriazoles the alkylation/arylation approach can suffer from poorer regioselectivities and

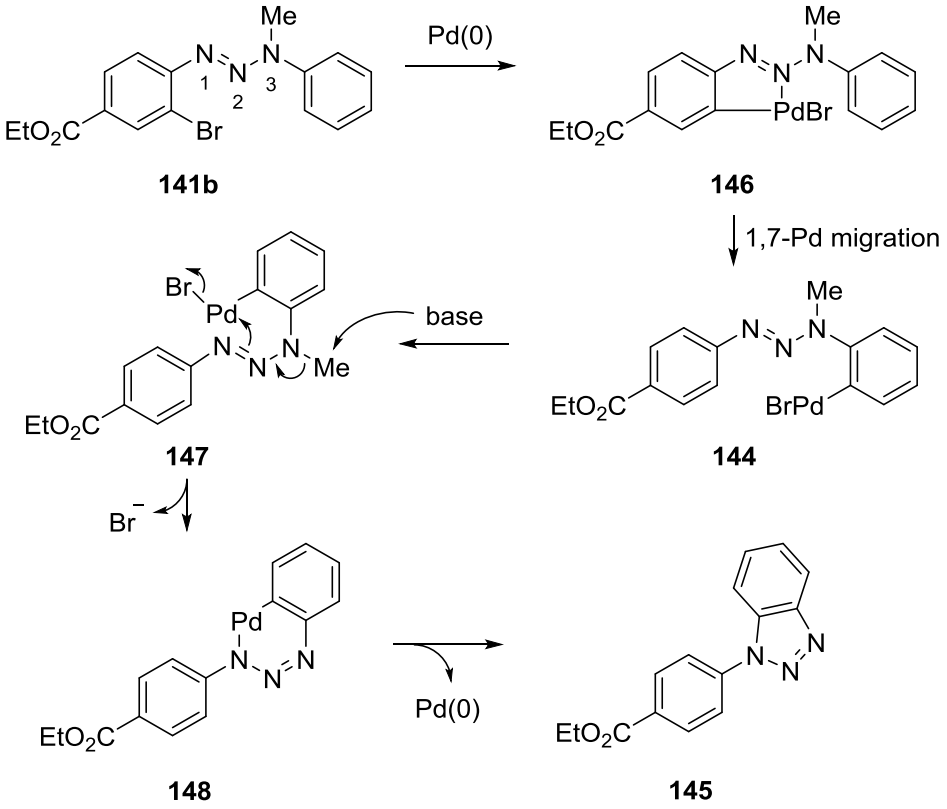
often limited to the use of activated aryl halides that possess strong electron-withdrawing groups.[179] Also, regioselectivity of 1,3-dipolar cycloadditions of azides is usually largely dependent on the steric and electronic properties of the benzynes, thus resulting in a mixture of N_1-, N_2-, and N_3-regioisomers.[180,181] Separation of these benzotriazoles is not straightforward as their physical properties are very similar. In addition to this, the large scale handling of reactive benzyne and azide derivatives can cause safety problems. Thus, the design and development of a safe and efficient approach to synthesise N_1-substituted benzotriazoles with regioselectivity is highly desirable.

Ren *et al.*, have reported the regioselective synthesis of *N*-substituted benzotriazoles **143** and **145** from N_3-substituted 1,3-diaryltriazene derivatives **141** (Scheme 90).[182] This reaction sequence involves a 1,7-palladium migration *via* C-H activation, intramolecular cyclisation and base induced dealkylation to furnish benzotriazoles with good yields and high regioselectivities. In this study, the regioselectivity was controlled by changing the substituent on N_3; if the nitrogen was unsubstituted (**141a**, R = H) and was only bearing a hydrogen atom, intramolecular amination occurred *via* a 6-membered palladacycle **142** (pathway A). However, when the substituent on N_3 was changed to a methyl group (**141b**, R = Me or other alkyl, even benzyl groups), under the optimised conditions, another regioisomer of the benzotriazole compound could be achieved (pathway B).



Scheme 90: Regioselective synthesis of benzotriazoles from 1,3-aryltriazenes

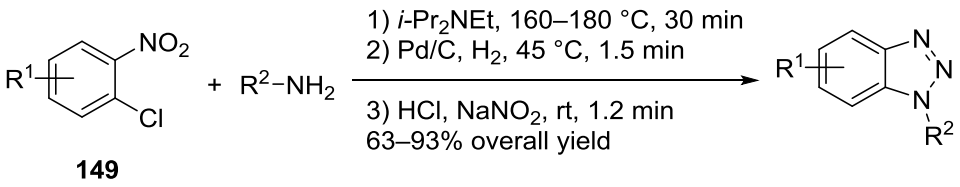
The authors also included a plausible mechanism to account for the change in selectivity (Scheme 91).[182] The first step is the fast oxidative addition of palladium(0) which leads to the 5-membered palladacycle **146** *via* Pd-N_2 coordination. As this brings the other aryl ring in close proximity, the subsequent 1,7-palladium migration *via* C-H activation results in compound **144**. This can then undergo a N_2-N_3 bond rotation and base induced demethylation results in the 6-membered palladacycle. The last step is the reductive elimination whereby product **145** is released and the catalyst regenerated.



Scheme 91: Proposed mechanism for the formation of *N*-substituted benzotriazole 145

Buchwald and co-workers published a paper on *N*-substituted benzotriazole formation in three steps from 2-chloro-1-nitrobenzenes in flow.[183] The reaction sequence consisted of the nucleophilic aromatic substitution (or palladium catalysed arylation) of 2-chloro-1-nitrobenzene, reduction of the nitro moiety, followed by diazotisation and spontaneous intramolecular cyclisation (Scheme 92). The stepwise synthetic approach allowed for the preparation of *N*-substituted benzotriazoles regioselectively. This continuous-flow process had the advantage of inexpensive starting materials and that the intermediates did not

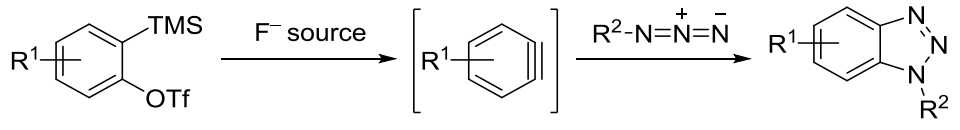
need to be isolated, thus being a cost and time efficient route to these building blocks.



149

Scheme 92: Stepwise benzotriazole synthesis in flow

One of the most important and frequently used method for preparing benzotriazoles is the [3+2] cycloaddition of benzynes with 1,3-dipolar compounds. Several research groups from the synthetic chemistry community published the use of benzyne click chemistry for the synthesis of N_1-substituted benzotriazoles. For example, in 2008, the research groups of Feringa, Larock and Reddy all reported the synthesis of such scaffolds using the same copper-free click-type approach (Scheme 93).[180,184,185] Their work showed similarities, as they all started from *ortho*-TMS-phenyltriflates **149** for *in situ* fluoride-induced *ortho*-elimination to achieve the benzyne intermediate which was then reacted with organic azides. As fluoride sources, the authors successfully used TBAF, KF and CsF either in combination with or without 18-crown-6 at ambient temperature. However, the major limitation of this kind of approach is the formation of N_1- and N_3-benzotriazole regioisomers from unsymmetrically substituted benzynes.

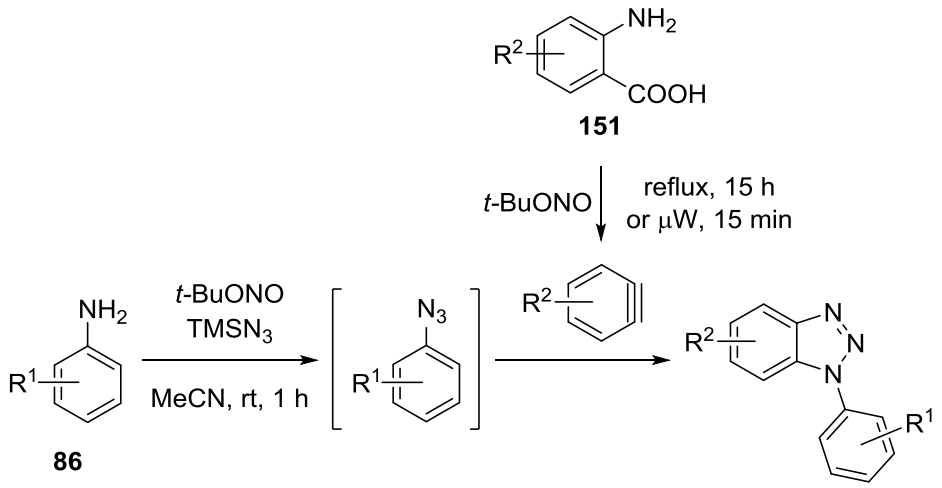


150

Scheme 93: Benzyne-azide cycloaddition for the formation of benzotriazoles

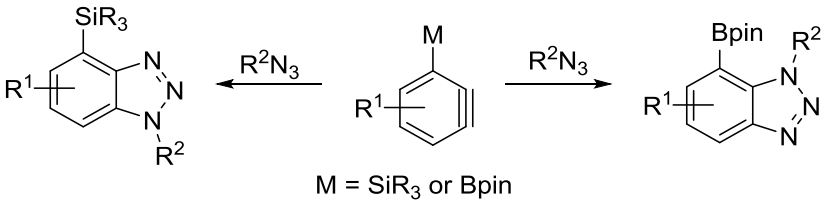
One year later, Moses and co-workers reported the synthesis of benzotriazoles using a very similar approach, this time however, both the azide and benzyne were prepared *in situ* to avoid safety issues arising from the reactive nature of these compounds (Scheme 94).[186] The azide fragments in this study were prepared from anilines **86** with $TMSN_3$ at room temperature and anthranilic acids **151** were used as precursors for benzyne synthesis, for which heating was

required. Later it was also shown that microwave irradiation can also be used for the cycloaddition step. With this, the reaction time of this one-pot process could be reduced from hours to minutes.



Scheme 94: Benzyne-azide cycloaddition using *in situ* prepared reagents

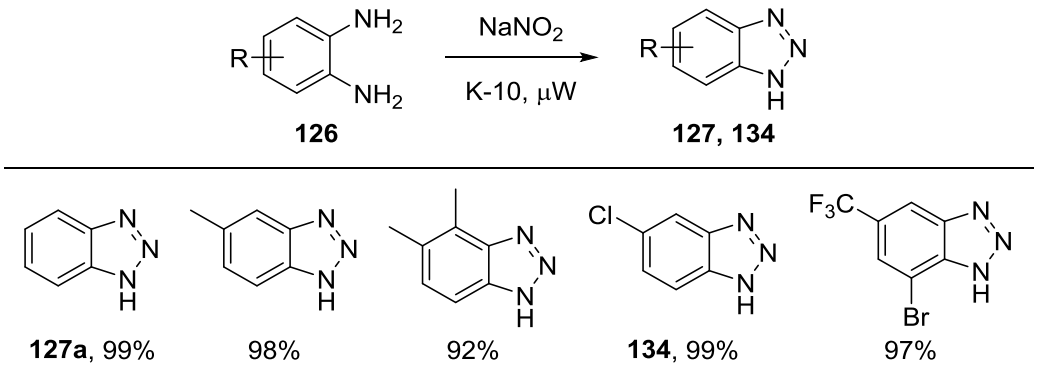
In 2013, a research group from Japan published the first proximal-selective examples of the cycloaddition reaction between 3-substituted benzynes and azides (Scheme 95).[187] This was achieved by the unique substituent effects of the boryl and silyl groups on the benzyne fragment. It was found, after analysis based on DFT calculations, that cycloaddition of 3-borylbenzynes was electrostatically controlled, while for 3-silylbenzyne derivatives sterical properties dominated the reaction outcome.



Scheme 95: Proximal and distal selective benzotriazole syntheses

More recently, Kokel and Török reported the microwave-assisted formation of 1*H*-benzotriazoles from *ortho*-phenylenediamines using sodium nitrite and K-10 montmorillonite (Scheme 96).[188] This involved the solid-phase diazotisation of anilines followed by the intramolecular cyclisation to form the triazole ring under Brønsted acidic conditions. With this, the acidic K-10 clay was used in a

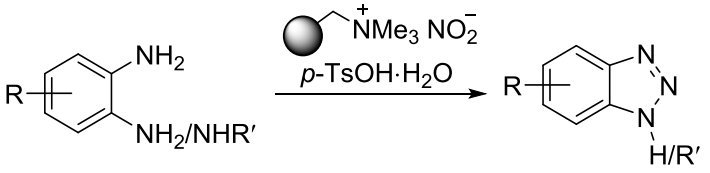
multifunctional way as it was not only the medium of the reaction but it also served as the reagent for the transformation.



Scheme 96: Benzotriazole synthesis from 1,2-phenylenediamines using a solid-supported acid clay

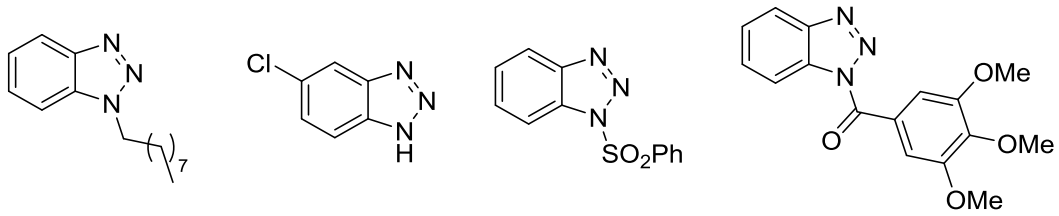
2.3.3 Proposed research

The ultimate aim of this project was to develop a rapid and operationally simple diazotisation and intramolecular cyclisation sequence of 1,2-aryldiamines to prepare 1*H*-benzotriazoles efficiently (Scheme 97). As a key objective, the use of the solid-supported nitrite reagent would allow for an easy separation by filtration and the resin could be recycled to show the cost-efficiency of this one-pot process. The polymer-supported nitrite reagent would be synthesised as described previously, by ion-exchange of the commercially available tetramethylammonium hydroxide functionalised resin, Amberlyst® A26 with sodium nitrite in an aqueous solution.[69,141] Once a general method was optimised, using the polymer-supported nitrite reagent and *p*-tosic acid under mild conditions, the diamine-precursors would all be converted into the corresponding 1*H*-benzotriazoles.



Scheme 97: Proposed synthesis of 1*H*-benzotriazoles from 1,2-aryldiamines

After optimisation, the substrate scope of *N*-unsubstituted benzotriazoles would be explored using a variety of commercially available 1,2-phenylenediamines. This first library would also showcase the synthesis of the antiparasitic agent 5-chlorobenzotriazole (**134**, Figure 10). Another key objective of this project was to extend the scope with several, structurally diverse N_1-substituted benzotriazoles using not only traditional nitrogen protecting groups such as tosyl and benzyloxycarbonyl (Cbz) but also alkyl, benzyl and acyl functionalities. The diazotisation and cyclisation approach would also demonstrate that it is able to facilitate the general preparation of a number of benzotriazole containing pharmaceutical compounds, such as the antifungal agent *N*-nonylbenzotriazole (**133**), the antiparasitic *N*-phenylsulfonyl derivative **135** and the anticancer *N*-(trimethoxybenzoyl)-1*H*-benzotriazole (**140**).[157]



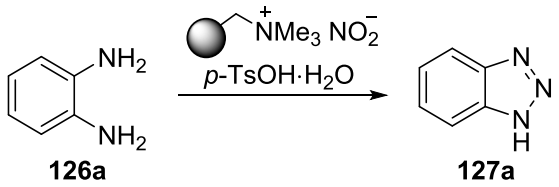
133 **134** **135** **140**

Figure 10: Biologically active 1*H*-benzotriazole targets

2.3.4 Synthesis of 1*H*-benzotriazoles

Synthetic work started with optimising the conditions for the preparation of 1*H*-benzotriazole (**127a**) from 1,2-phenylenediamine (**126a**) (Table 5).[189] As seen in Scheme 87, the conditions under which the benzotriazole derivative **125** formed, included acetonitrile as solvent and high temperature over 16 h. Because of this, it was decided that similar conditions would be used for the formation of **127a** (entry 1). The target benzotriazole **127a** was synthesised in 46% isolated yield after 1.5 h in acetonitrile, at 80 °C. In order to achieve a higher yield, a longer reaction time (18 h) was then investigated and this resulted in 71% yield (entry 2). However, the aim was to find conditions which would allow the formation of **127a** in a shorter reaction time, so next the solvent was switched to methanol. This, in combination with cooling down the temperature upon addition of reagents and slowly letting to warm to room temperature resulted in 66% yield after 6 h (entry 3), which could not be significantly improved even with longer

reaction time (entry 4). Following this, the ratio of the reagents to starting material was investigated, and a detrimental effect was seen on the yield when 1 equivalent of both polymer-supported nitrite and *p*-tosic acid were used (entry 5). Finally, a comparable yield was achieved when using 6 equivalents of reagents (entry 6) to that previously achieved with 3 equivalents. It was ultimately decided that conditions found in entry 3 would be used for the rest of the substrate scope.



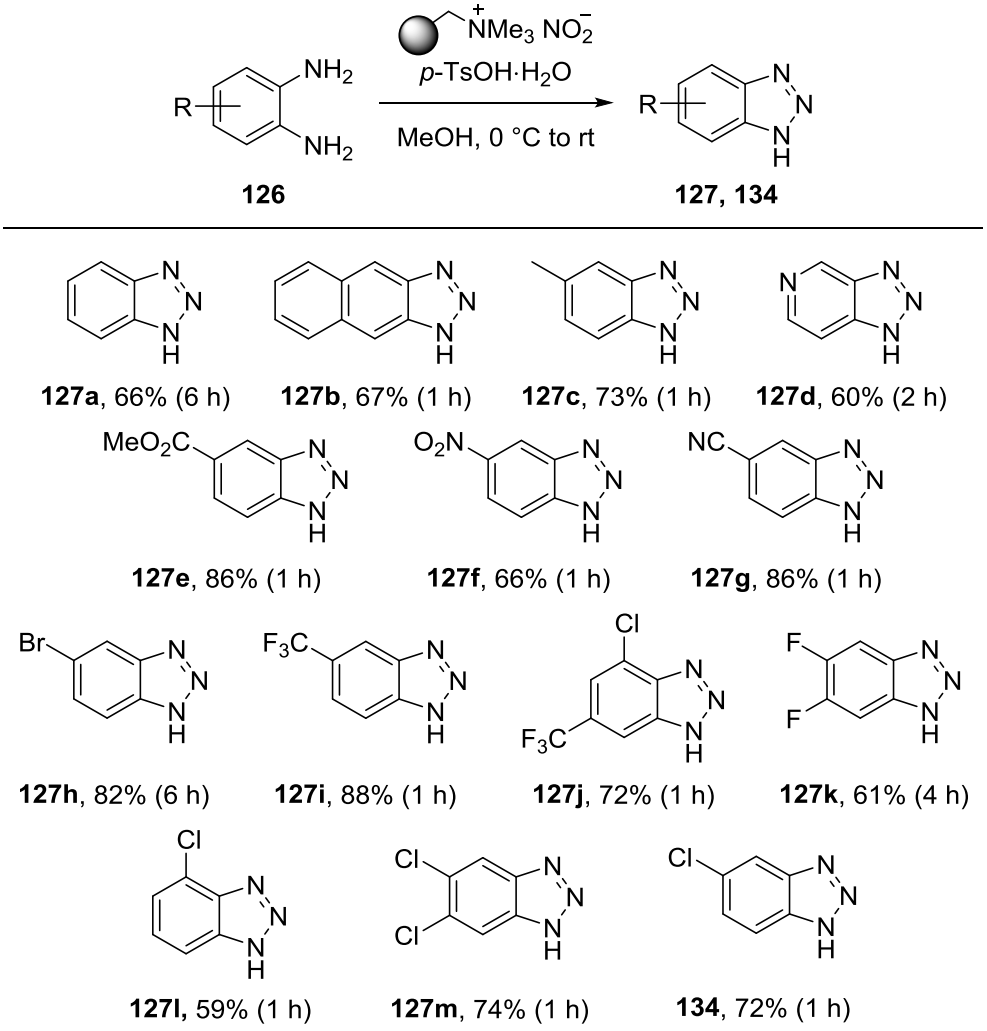
126a **127a**

Entry	Reagents (equiv.)	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	3	MeCN	80	1.5	46
2	3	MeCN	80	18	71
3	**3**	**MeOH**	**0 to rt**	**6**	**66**
4	3	MeOH	0 to rt	48	69
5	1	MeOH	0 to rt	6	29
6	6	MeOH	0 to rt	6	62

Table 5: Optimisation of 1*H*-benzotriazole (127a) formation

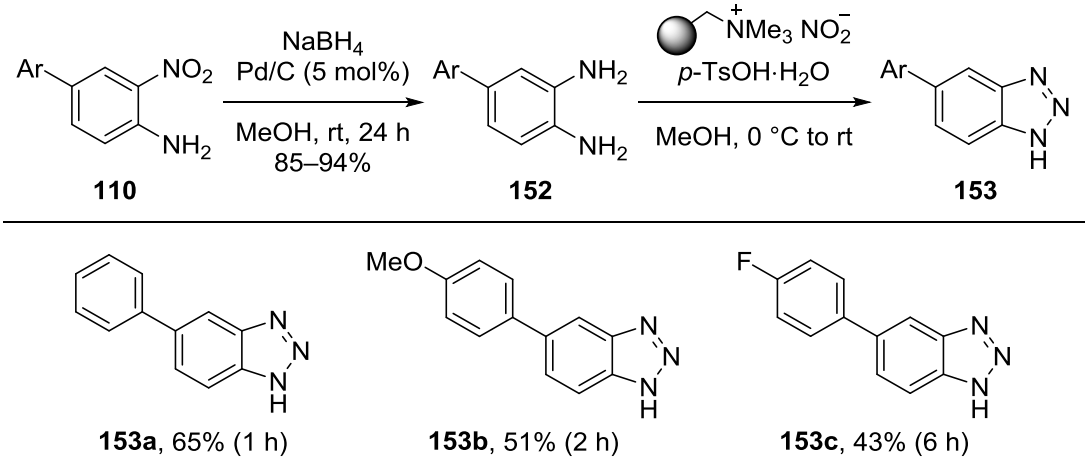
With the optimised conditions in hand, next the scope of the reaction was explored. Various commercially available 1,2-arylamines **126** with both electron-rich and electron-deficient substituents were submitted to the one-pot diazotisation and cyclisation process (Scheme 98). During evaluation, it was found that the majority of the starting materials were fully converted within an hour at 0 °C. The quick reaction allowed for the preparation of a range of benzotriazoles in good to high yields after an easy work-up by filtration followed by purification on silica-gel. Methyl 3,4-diaminobenzoate **126e** and 3,4-diaminobenzonitrile **126g** were found to be excellent substrates for the one-pot procedure and the corresponding benzotriazoles **127e** and **127g** were both

achieved in 86% isolated yield after only 1 hour. It was also shown that a heterocycle analogue, pyridine derived benzotriazole **127d** could be prepared, and also a range of halogenated compounds were successfully synthesised using this one-pot process. Thus, the scope included the high-yielding synthesis of 5-bromobenzotriazole (**127h**) and 5-trifluoromethylbenzotriazole (**127i**), which were prepared in 82% and 88% yield, respectively. Among these substrates, other halogenated compounds were also synthesised efficiently, including the antiparasitic agent **134**, which was prepared in 71% yield. This biologically active compound was found to be more effective against the protozoan parasite *Entamoeba histolytica* than metronidazole, the already existing clinical treatment for amebiosis.[168]



Scheme 98: The scope of 1*H*-benzotriazoles

Benzotriazoles bearing 5-aryl functionality can be used as substrates for carbonylative-Suzuki coupling and denitrogenative-Suzuki coupling reactions, therefore three more compounds of this kind were also incorporated in the scope (**153a–c**).[190] Thus, 4-iodo-2-nitroaniline (**108j**) was submitted to a Suzuki-Miyaura coupling with various arylboronic acids as seen earlier on Scheme 79, and the resulting biaryl compounds **110a–c** were reduced using sodium borohydride and 10% palladium on carbon to give compounds **152a–c** bearing 3,4-diamino functionality (Scheme 99). These were used as substrates for the one-pot diazotisation and cyclisation reaction. Using the standard conditions, the corresponding 5-aryl-benzotriazoles were successfully synthesised, although different reactivity patterns was observed based on the electronic properties of the molecules. While 5-phenyl derivative **153a** was synthesised in 1 hour at 0°C, the electron-rich 5-(4-methoxyphenyl)benzotriazole **153b** needed 2 hours to form, and the 4-fluorophenyl analogue **153c** required a longer reaction time.



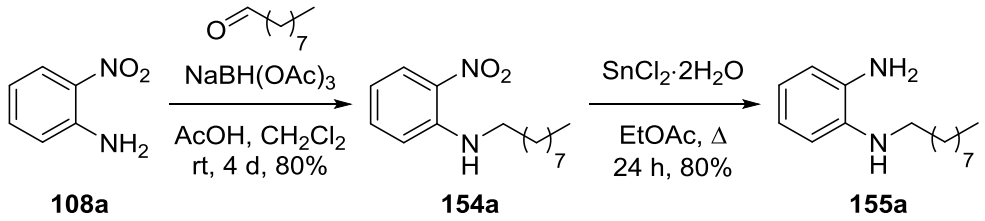
Scheme 99: The scope of 5-aryl benzotriazoles 153a–c

2.3.5 Preparation of *N*-substituted 1,2-phenylenediamine precursors

Prior to the synthesis of an additional library containing *N*-substituted benzotriazoles, the substrates for the one-pot process had to be prepared in advance. The aim was to incorporate several kinds of *N*-protecting groups and doing so, a variety of benzotriazole structures could be achieved.

Firstly, alkyl protecting groups were considered, and this led to the investigation of the preparation of the *N*-nonyl and *N*-allyl 1,2-phenylenediamine compounds

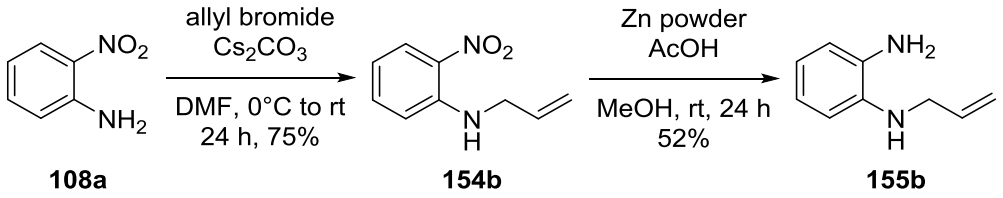
155a and **155b** (Scheme 100 and 101). For both compounds, the synthetic route started with the mono substitution of 2-nitroaniline (**108a**) followed by reduction of the nitro group, however, different chemical transformations were carried out regarding the *N*-substitution reactions. Preparation of *N*-nonyl-2-nitroaniline (**154a**) proceeded *via* reductive amination of 2-nitroaniline (**108a**) with nonanal using sodium triacetoxyborohydride (Scheme 100). The use of the mild reducing agent was necessary as previously, a complex mixture was observed upon using sodium borohydride, which presumably led to the reduction of the starting material nonanal. Although it is known that aldehydes more readily undergo reductive amination reactions, the combination of an aldehyde with a long alkyl chain and an aniline bearing an *ortho*-nitro functionality led to a very slow reaction. The reductive amination was complete after 4 days at room temperature and several equivalents of reagents were needed in order to successfully obtain *N*-nonyl-2-nitroaniline (**154a**) in 80% yield. The nitro group was then reduced using tin(II) chloride under reflux temperature, and the resulting substituted 1,2-diamine **155a** was isolated in 80% yield.



108a **154a** **155a**

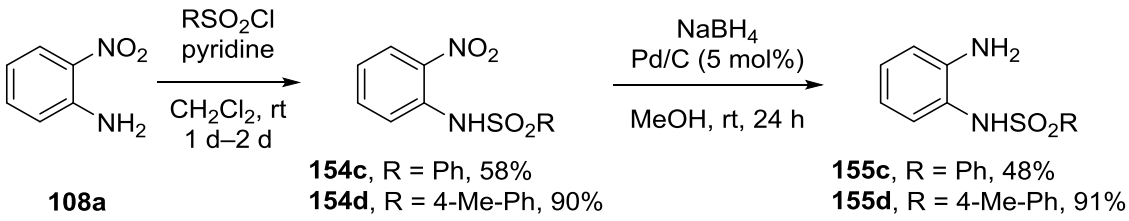
Scheme 100: Synthesis of *N*-nonyl phenylenediamine 155a

The *N*-allyl substrate **155b** was also prepared in a two-step synthetic route, whereby the first step was the allylation of **108a** with allyl bromide (Scheme 101). As allylation of amines can result in both the mono and double protected anilines, it was decided that allyl bromide would be used as the limiting reagent and **108a** would be in excess. With this, the double allylation was fully avoided and *N*-allyl-2-nitroaniline (**154b**) was the sole product of the reaction. For nitro group reduction, zinc powder was used in combination with acetic acid and this resulted in product **155b** in 52% yield.



Scheme 101: Synthesis of *N*-allyl phenylenediamine 155b

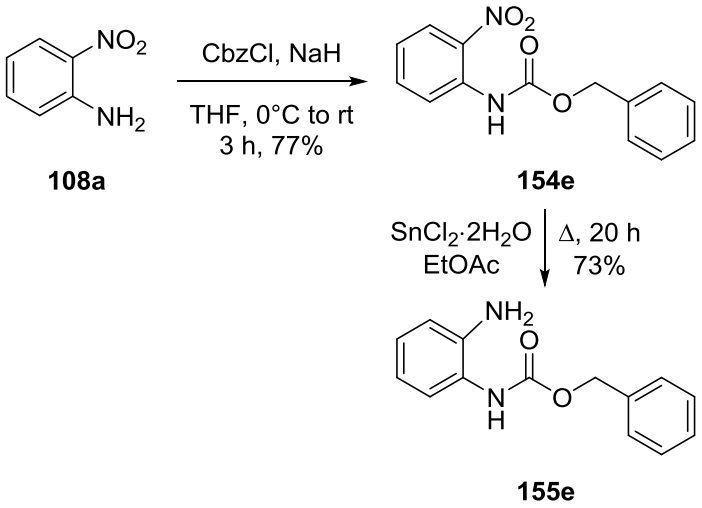
Next, sulfonyl protecting groups were considered and therefore, the preparations of **155c** and **155d** were carried out using sulfonamide formation followed by nitro reduction for both cases (Scheme 102). The sulfonamides **154c** and **154d** were synthesised using **108a** and sulfonyl chlorides in the presence of pyridine and were achieved in 58% and 90% yield, respectively. The corresponding *N*-substituted 1,2-diamine compounds **155c** and **155d** were then obtained *via* reduction of the nitro group using 10% palladium on carbon and sodium borohydride.



Scheme 102: Synthesis of 1,2-phenylenediamines 155c and 155d

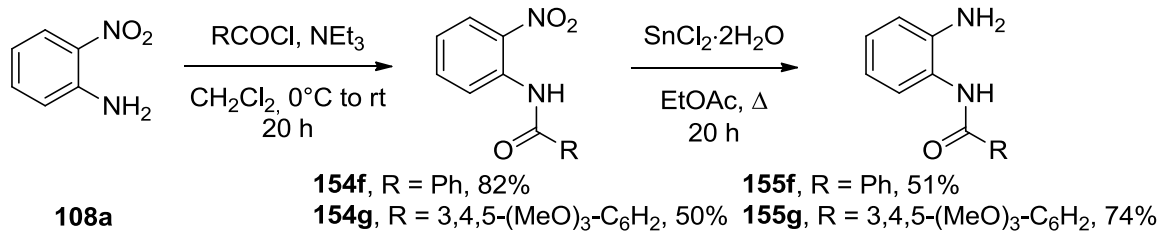
As one traditional *N*-protecting group containing substrate was already incorporated in the scope with the synthesis of the *N*-tosyl derivative **155d**, the preparation of another class of such compounds was aimed for. In peptide chemistry, along with sulfonamides, carbamate *N*-protecting groups are also frequently used. For example, in solid phase peptide chemistry the *N*-terminus of α-amino acids can be protected temporarily with benzyloxycarbonyl (Cbz) and used for coupling.[191,192] Therefore, the next 1,2-diamine target was the Cbz derivative **155e**, which was synthesised in a similar two-step procedure as before (Scheme 103). First *N*-substitution of 2-nitroaniline (**108a**) had to be optimised, as during the reaction, both mono and double protections were also possible. The use of the optimal conditions, which included the careful dropwise addition of benzyl chloroformate to the deprotonated 2-nitroaniline at 0°C, as

well as short reaction time to avoid double substitution, resulted in **154e** in 77% yield. Following this, upon nitro reduction of **154e,** an additional 1,2-diamine substrate was synthesised in 73% yield.



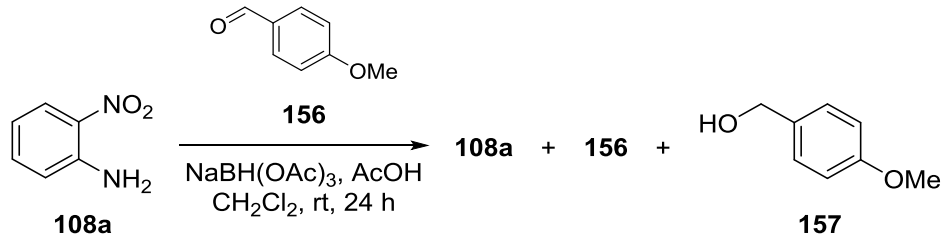
Scheme 103: Synthesis of Cbz protected phenylenediamine 155e

In addition to the previous substrates, *N*-acyl compounds were also obtained for the scope, such as **155f** and **155g** (Scheme 104). *N*-Benzoylation of **108a** was successful with both benzoyl chloride and 3,4,5-trimethoxybenzoyl chloride and the resulting *N*-substituted 2-nitroanilines **154f** and **154g** were achieved in 82% and 50% yield, respectively. Although it should be noted, that using 3,4,5-trimethoxybenzoyl chloride led to a much slower reaction compared to that with benzoyl chloride, and the use of excess reagents were needed. Even with this, the reaction stopped at 50% conversion of the starting material **108a** according to ^{1}H NMR spectroscopy. The target substrates **155f** and **155g** were then obtained after nitro reduction using tin(II) chloride in 51% and 74% yield, respectively.



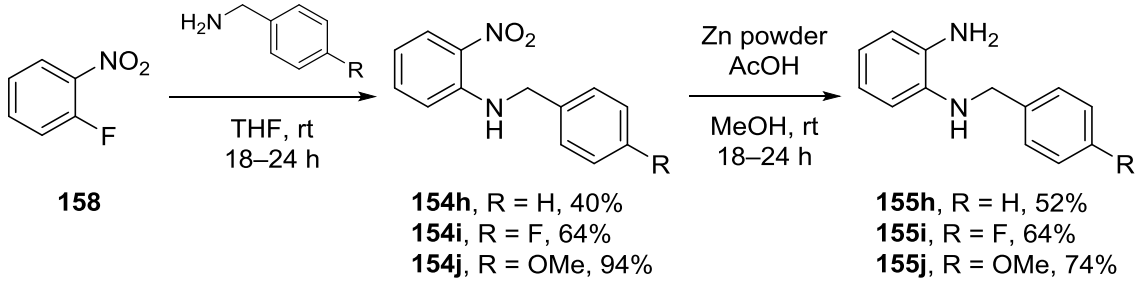
Scheme 104: Synthesis of *N*-benzoyl-1,2-phenylenediamine (155f) and *N*-(3,4,5-trimethoxybenzoyl)-1,2-phenylenediamine (155g)

The final compounds for the *N*-substituted benzotriazole scope were the ones with *N*-benzyl functional groups. For this, the corresponding *N*-benzyl 1,2-phenylenediamines had to be prepared, and this was investigated *via* a two-step procedure starting from 2-nitroaniline (**108a**). The aim was to perform a reductive amination of **108a** followed by nitro group reduction, but the preliminary results were not satisfying. During reductive amination of **108a** with *p*-methoxybenzaldehyde (**156**), a mixture of unreacted starting materials **108a** and **156** along with the reduced benzaldehyde **157** was observed in a 3:3:1 ratio according to ^{1}H NMR spectroscopy (Scheme 105).



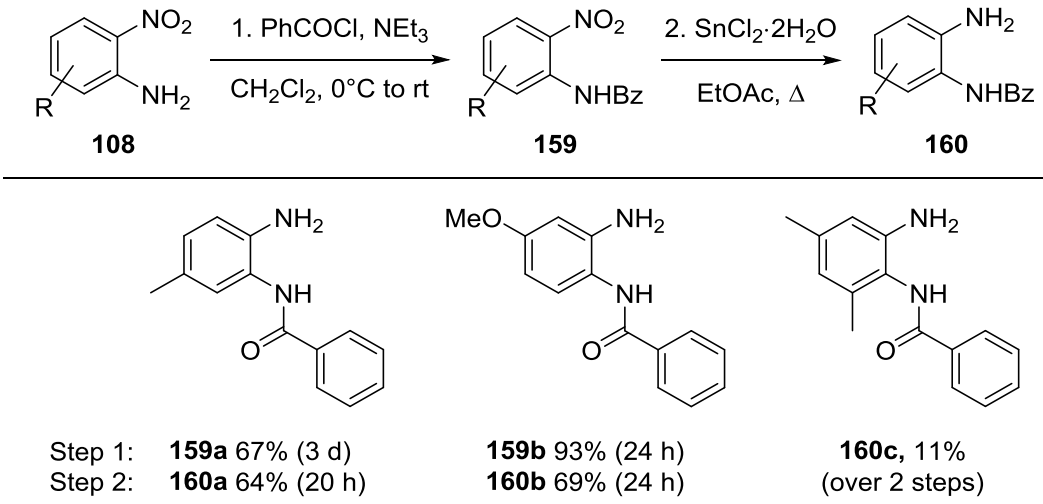
Scheme 105: Attempted reductive amination of 108a

At this point, the reductive amination reaction was not pursued any further and another route was taken into consideration towards the target compounds. This led to the nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene (**158**) with benzylamine (Scheme 106). This reaction allowed the formation of three additional *N*-substituted 2-nitroanilines **154h–j** in 40–94% yield. Benzylamine and 4-methoxybenzylamine derivatives **154h** and **154j** were prepared using the same conditions, while *N*-(4''-fluorobenzyl)-2-nitroaniline (**154i**) was synthesised in the presence of triethylamine and under reflux conditions. All three substrates were reduced using zinc powder and acetic acid and the resulting 1,2-phenylenediamine compounds **155h–j** were obtained in good yields.



Scheme 106: Synthesis of *N*-benzyl 1,2-phenylenediamines 155h–j

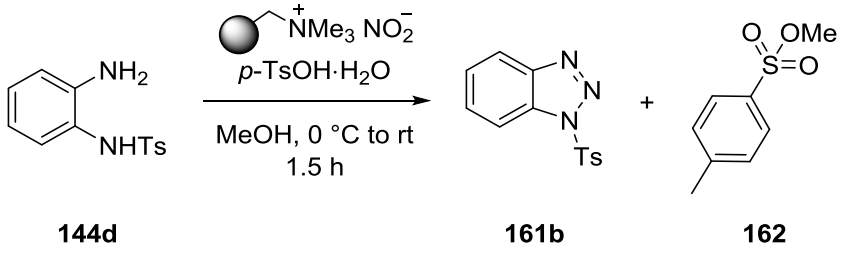
The final stage of the project was highly important, as we wanted to demonstrate that regioselectivity issues could be easily overcome by the synthesis of selectively N_1-protected 1,2-aryldiamines with non-symmetrically substituted aryl rings. Therefore, a series of *N*-benzoyl protected 1,2-aryldiamines were synthesised which had various substitution patterns on the aniline ring (Scheme 107). The synthetic route for these compounds was similar as mentioned before (Scheme 104). 5-Methyl-, 4-methoxy- and 4,6-dimethyl-2-nitroanilines were submitted to the benzoyl protection using standard conditions, and upon nitro reduction, the starting materials **160a–c** for the one-pot diazotisation and cyclisation process were achieved. It has to be noted, that benzoylation of 5-methyl-2-nitroaniline required a longer reaction time (3 days) and excess reagent in order to go to completion. Also, the reaction from 4,6-dimethyl-2-nitroaniline led to an inseparable mixture of mono- and di-benzoyl protected anilines, and it was decided to take this mixture further for the reduction step without purification. The low yield also contributes to the incomplete conversion of the starting material. However, after nitro group reduction, product **160c** could easily be separated and isolated.



Scheme 107: Synthesis of *N*-benzoyl 1,2-phenylenediamines 160a–c

2.3.6 Synthesis of *N*-substituted 1*H*-benzotriazoles

Following the synthesis of the *N*-unsubstituted benzotriazole library, the standard one-pot process was then applied to these *N*-substituted 1,2-aryldiamines **155a–j**. A wide range of benzotriazoles was prepared with alkyl, acyl, sulfonyl and benzyl *N*-protecting groups. Upon using the *N*-substituted 1,2-aryldiamines **155a–j** in the general process, the use of methanol as solvent led to the formation of a byproduct, methyl tosylate (**162**). According to ^{1}H NMR spectroscopy, in the preparation of the *N*-tosyl derivative **161b**, **162** was the major product in a 3:1 ratio (Scheme 108). After this result was obtained, it was decided to switch the solvent for the formation of these less polar *N*-substituted substrates to acetonitrile.

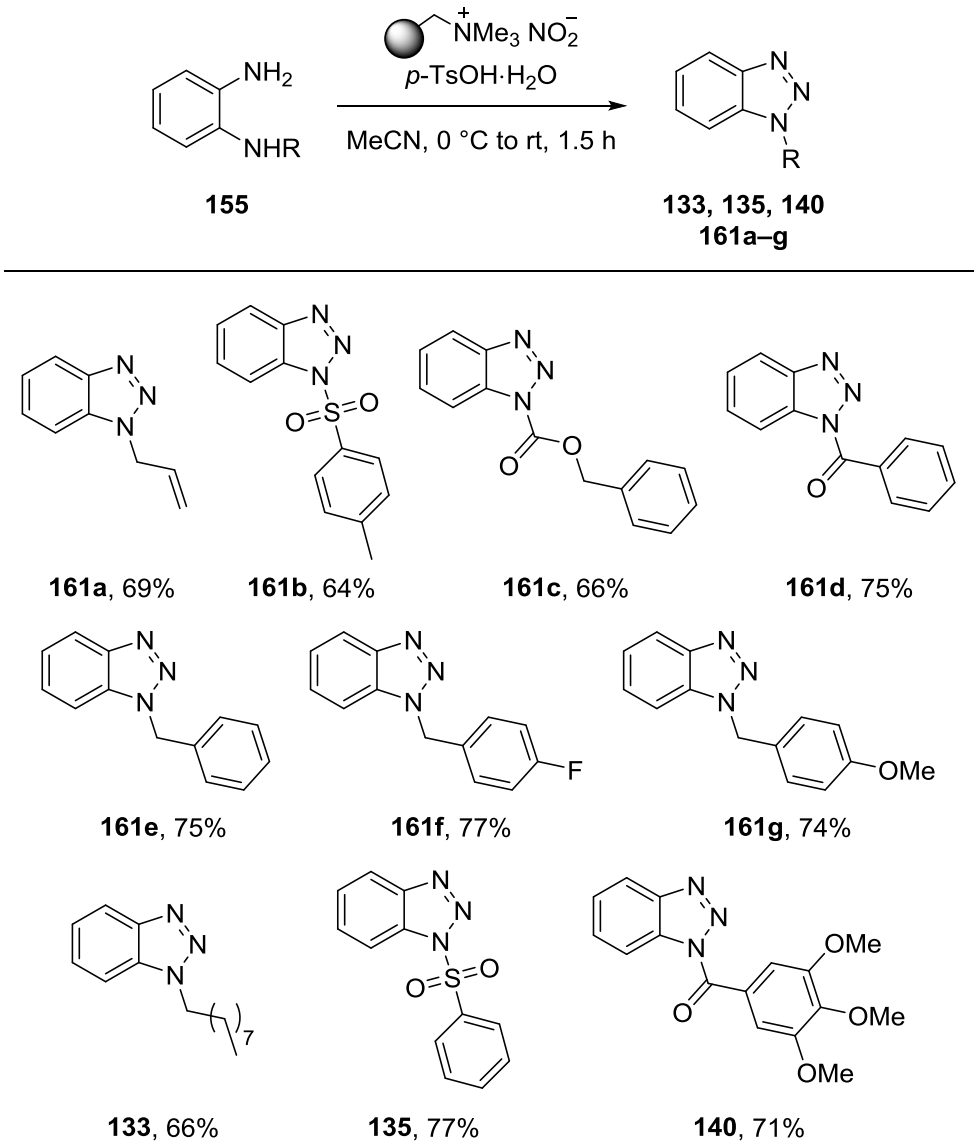


144d **161b** **162**

Scheme 108: Methyl tosylate formation in methanol

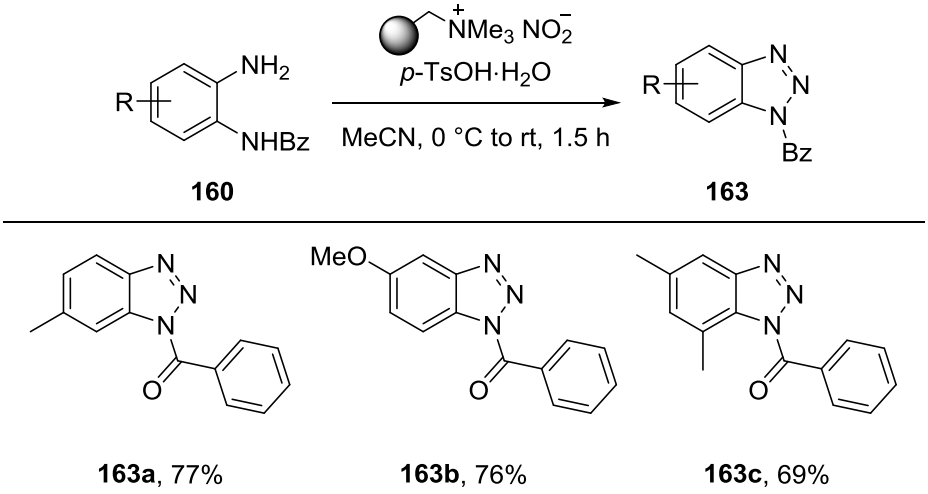
Thus, from this point on, the solvent of the reaction was acetonitrile and all the diamine substrates submitted to the process were fully converted in 1.5 hours. This meant, that the reagents were added at 0°C and after 0.5 hours, the reaction mixture was allowed to slowly warm to room temperature for another hour. This allowed the synthesis of the second benzotriazole library with good to high yields. It was found that the use of these conditions were optimal for the formation all of the benzotriazole substrates (Scheme 109). Various substituents on the N_1-position were all generally applicable in this process and the compounds were achieved in 64–77% yields. Thus, 1-allyl-1*H*-benzotriazole (**161a**) was achieved using the standard conditions in 69% yield. Only the *N*-tosyl benzotriazole (**161b**) needed further optimisation, as incomplete reaction was observed under the standard conditions (up to 50% conversion according to ^{1}H NMR spectroscopy). Thus, extra equivalents of reagents were used to drive the reaction to completion (4.5 equivalents of both polymer supported nitrite and *p*-

tosic acid instead of 3 equivalents). These new conditions eventually led to the formation of the target compound **161b** in 64% yield after 5 hours. The standard conditions also afforded the Cbz-protected analogue **161c** and 1-benzoyl-1*H*-benzotriazole (**161d**) in 66% and 75% yield, respectively. Benzyl-protected diamines **155h–j** were excellent substrates for the diazotisation-intramolecular cyclisation reaction and the resulting benzotriazole compounds **161e–g** were achieved in 74–77% yield. The scope also included the preparation of biologically active benzotriazoles, such as the antifungal agent **133**, which has shown inhibition of the growth of *Cryptococcus neoformans*, an organism resistant towards the already existing treatment, fluconazole (**131**, Figure 6).[167] Another important example prepared was the antiparasitic *N*-benzenesulfonyl benzotriazole (**135**), which is a highly active agent against the protozoan parasite, *Trypanosoma cruzi*, responsible for Chagas disease.[169] Finally, 3,4,5-trimethoxybenzoyl derivative **140** was also successfully included in the scope, which displays antiproliferative activity against stomach carcinoma MKN45 cells in humans.[176]



Scheme 109: The scope of *N*-substituted benzotriazoles

The regioselective synthesis of unsymmetrically substituted benzotriazoles was also considered using a route starting from differently substituted 2-nitroanilines (as shown in Scheme 107). The formation of the 1,2-phenylenediamine substrates **160a–c** *via* the two-step synthetic route meant that the regioselectivity was fully controlled in the preparation of these compounds. With this, the problem associated with lack of regioselectivity was overruled and benzotriazoles **163a–c** could be achieved as single regioisomers in 69–77% yield using the standard one-pot diazotisation-cyclisation conditions (Scheme 110).



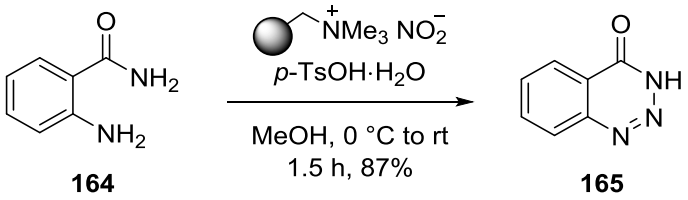
Scheme 110: Regioselective synthesis of *N*-benzoyl benzotriazoles 163a–c

2.3.7 Conclusions

To conclude, a facile and efficient one-pot synthesis was developed using the recyclable polymer-supported nitrite reagent in combination with *p*-tosic acid which led to a very mild process.[189] This protocol allowed the rapid formation of a range of benzotriazoles, both *N*-unsubstituted and *N*-substituted *via* diazotisation and intramolecular cyclisation. A variety of *N*-unsubstituted benzotriazoles were synthesised using methanol as the solvent in good to high yields with reaction times ranging between 1 and 6 hours. Among these, 5-chlorobenzotriazole (**134**) was also prepared in 71% yield, a biologically important compound with antiparasitic activity. An additional library of *N*-substituted benzotriazoles was also synthesised, which utilised the *N*-substituted 1,2-phenylenediamines prepared in advance *via* a two-step route. Again, the preparation of a number of antifungal (**133**), antiparasitic (**135**) and anticancer (**140**) compounds demonstrated the importance of this one-pot process. Finally, regioselectivity issues associated with the preparation of N_1-functionalised non-symmetrically substituted benzotriazoles were successfully overcome with the synthesis of the 1,2-phenylenediamine substrates from the corresponding 2-nitroanilines.

2.3.8 Outlook

In order to open up new synthetic applications for this one-pot diazotisation and intramolecular cyclisation protocol, a new class of substrates was considered as starting materials. It was proposed that the use of the one-pot process with anthranilamides would allow the preparation of 1,2,3-benzotriazin-4-ones (Scheme 111). The use of anthranilamide (**164**) resulted in the successful formation of benzotriazinone **165** in a high 87% yield after the first attempt, under the standard one-pot conditions.



164 **165**

Scheme 111: 1,2,3-Benzotriazin-4-one synthesis

This promising initial result was important as this nitrogen-containing heterocyclic scaffold can be found in a number of biologically active compounds with a wide range of medicinal and agrochemical applications (Figure 11).[193–198] Among the many pharmaceutical properties of the triazinone-containing compounds reported are anesthetic (**166**), antitubercular, anticancer and antiarthritic. For example, compound **167** has a high affinity and selectivity for 5-HT_{1A} subtype receptor for serotonin, a subtype that is present in high concentrations in limbic systems and has a role in emotional processes and hence could be a potential treatment for anxiety.[195] Compound class **168** containing either an ether or thioether linkage was found to be a successful inhibitor of matrix metalloproteinases MMP-2, 3, 9 and 13, enzymes that are involved in the regeneration and degradation of the extracellular matrix.[196] Compounds exploiting the benzotriazinone core are also late sodium current inhibitors (**169,** R = heterocycles such as oxazole, isoxazole and imidazole).[197] Moreover, derivatives **170** and **171** containing the benzotriazinone core and either a thiourea or acylthiourea linkage showed high nematicidal activity against *Meloidogyne incognita*, a root-knot plant-parasitic nematode.[198]

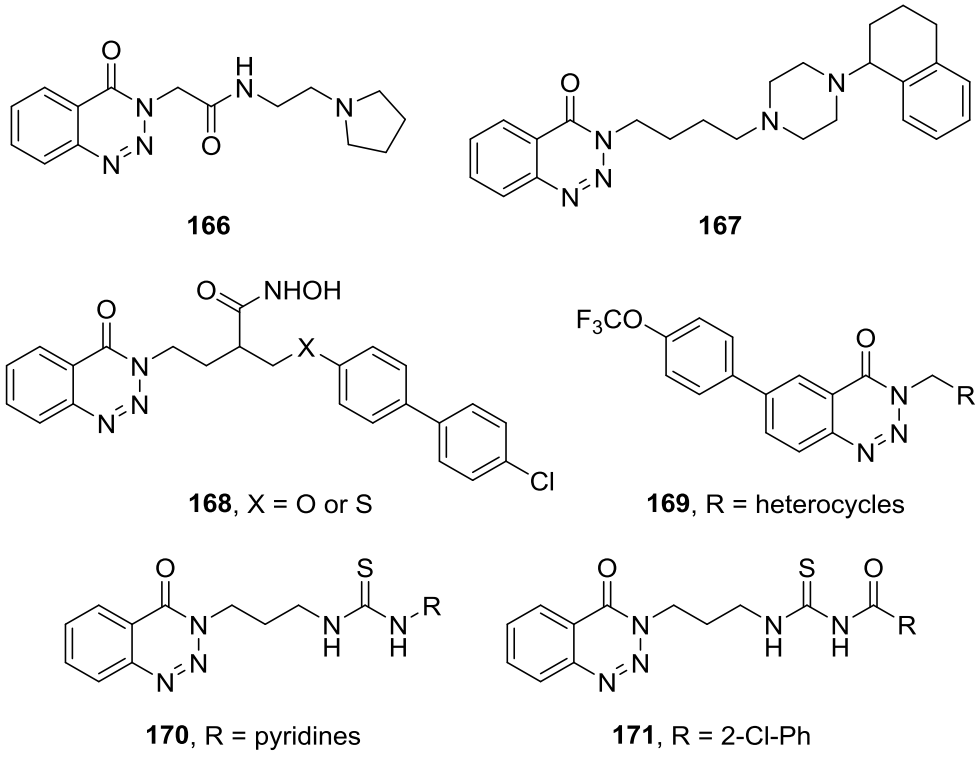
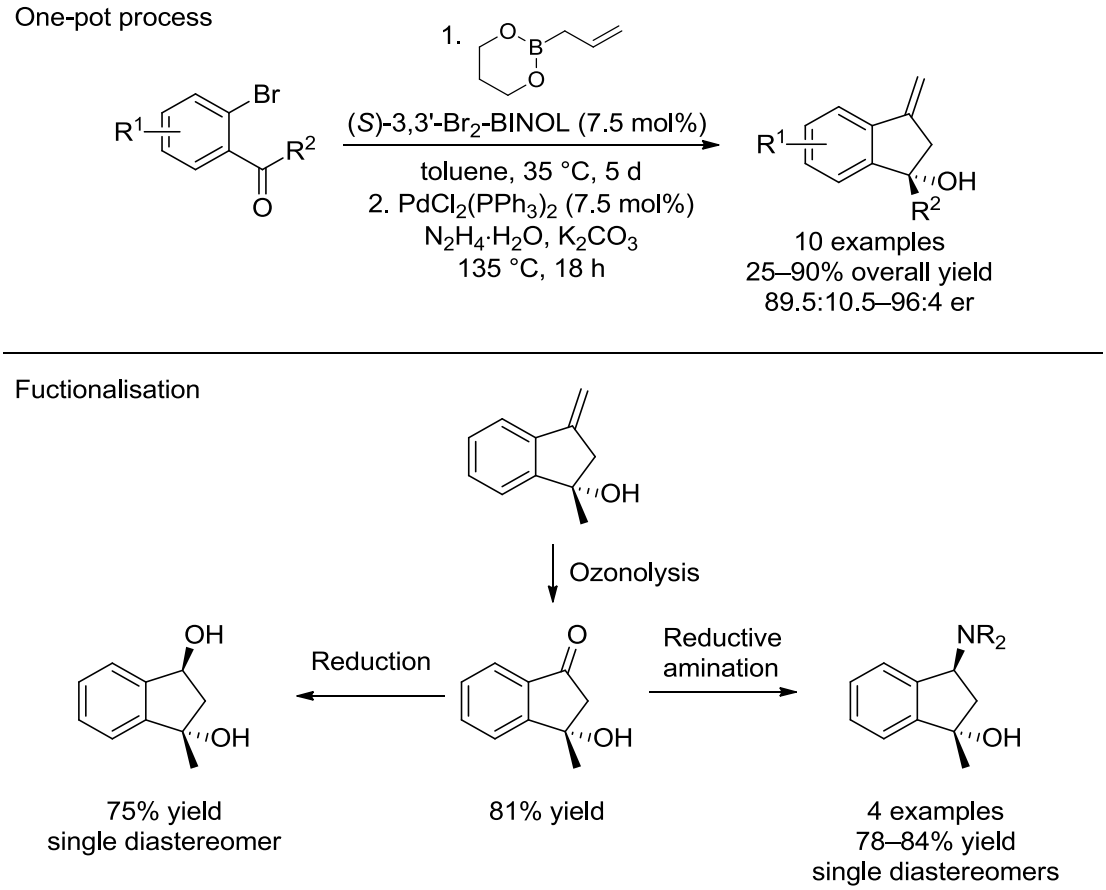


Figure 11: Benzotriazinone-containing biologically active compounds 166–171

2.4 Summary

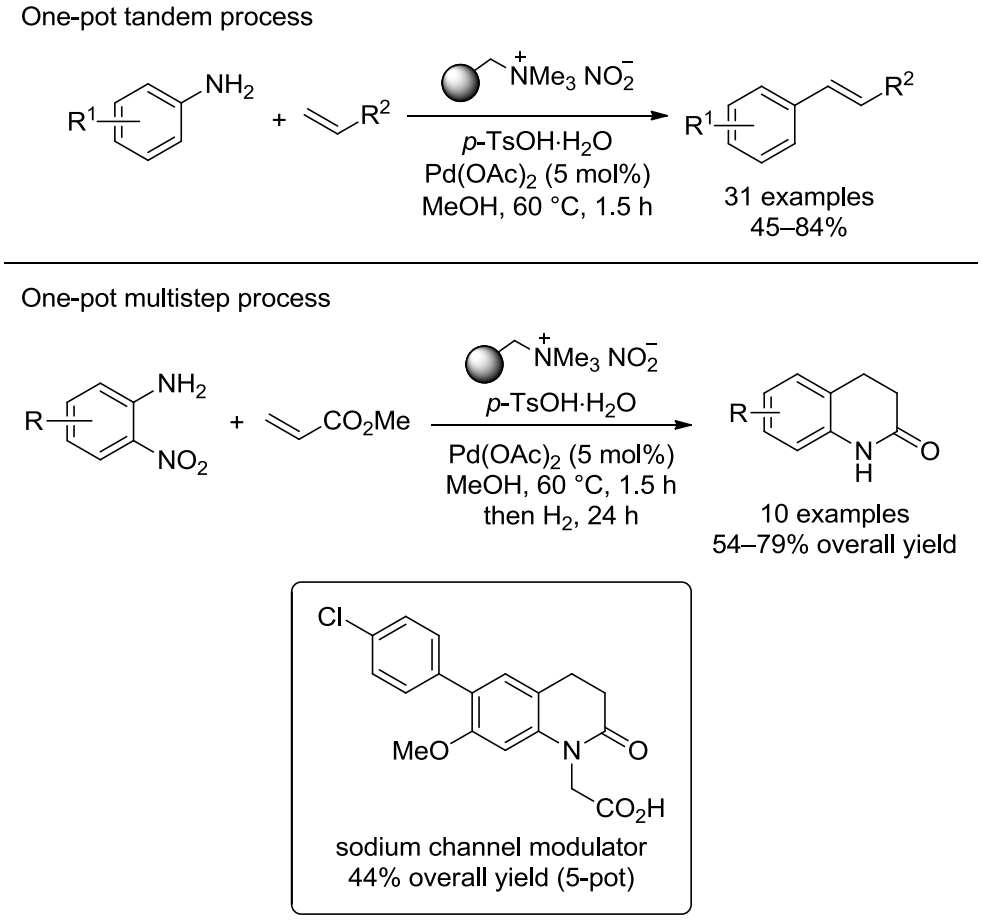
Chapter 2 showed the detailed results of three successful projects on the preparation of carbocyclic and heterocyclic structures from optimisation to substrate scope evaluation and demonstration of their synthetic utility. As a common feature of the synthetic routes, the syntheses were all carried out in a one-pot fashion.

The first section described the one-pot asymmetric Brønsted-acid catalysed allylboration of 2'-bromoaryl alkyl ketones followed by palladium-catalysed intramolecular Heck cyclisation for the preparation of optically active indanols featuring a tertiary alcohol stereocentre and an *exo*-methylene moiety (Scheme 112). The 1,1-disubstituted alkene was then easily converted into a ketone *via* ozonolysis, and opened up additional synthetic pathways. Thus, the indanone core was further functionalised using highly diastereoselective reductive reactions to access 3-hydroxyindanol and 3-aminoindanol compounds.



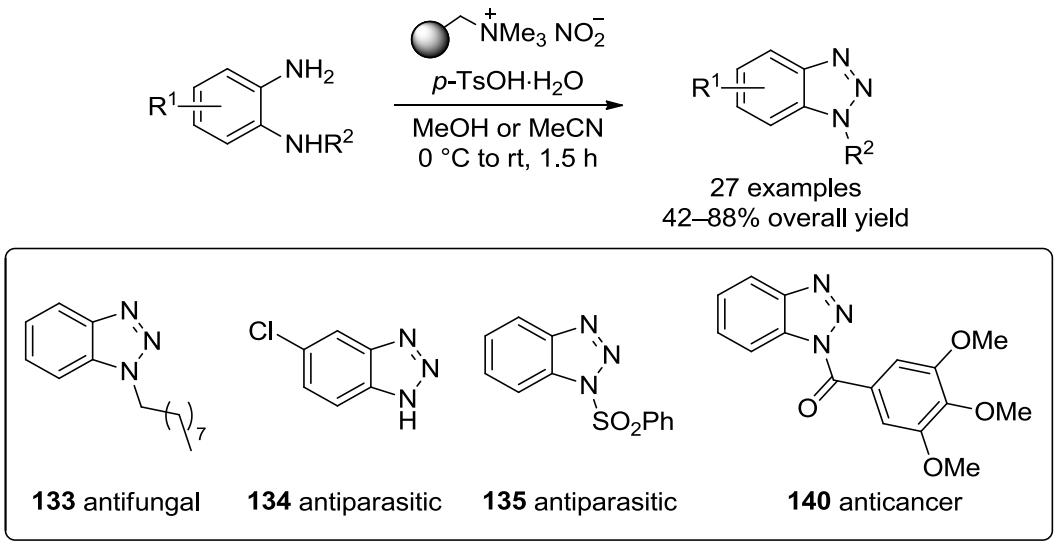
Scheme 112: Asymmetric one-pot synthesis of indanols and their synthetic utility

The next section then described the mild *in situ* formation of aryl diazonium tosylate salts from anilines and their coupling with activated alkenes using a palladium-catalysed Heck reaction (Scheme 113). The one-pot tandem diazotisation/Heck-Matsuda process was carried out with a solid-supported nitrite reagent in combination with *p*-tosic acid and the coupled compounds were all prepared with loss of dinitrogen in the cross-coupling step. The results showed the super-electrophilic nature of diazonium salts in the presence of aryl halide functionality which allowed for chemoselective transformations. Moreover, the procedure was extended to a one-pot multistep process for the synthesis of quinolone heterocycles with reutilisation of the palladium catalyst. The total synthesis of a sodium channel modulator successfully demonstrated the synthetic utility of the one-pot process.



Scheme 113: One-pot procedures for the synthesis of methyl cinnamates and quinolones

The last section focused on the mild diazotisation of 1,2-phenylenediamines and the preparation of benzotriazoles (Scheme 114). The one-pot diazotisation/intramolecular cyclisation process required the diazonium dinitrogen unit to be incorporated in the final 1*H*-benzotriazole structures. Among the synthesised 1*H*-benzotriazoles were important biologically active examples, such as anticancer, antiparasitic and antifungal agents. Finally, the common regioselectivity issue associated with benzotriazole synthesis was ultimately overcome with the two-step synthesis of 1,2-phenylenediamine precursors. This allowed the preparation of N_1-functionalised non-symmetrically substituted benzotriazoles.



Scheme 114: One-pot synthesis of 1*H*-benzotriazoles

3.0 Experimental

3.1 General information

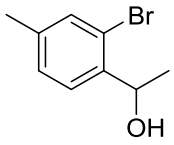
All reagents and starting materials were obtained from commercial sources and used as received unless otherwise stated. Dry solvents were purified using a PureSolv 500 MD solvent purification system or by distillation. Brine refers to a saturated solution of sodium chloride. All reactions were performed in oven-dried glassware under an atmosphere of argon unless otherwise stated. Flash column chromatography was carried out using Merck Geduran Si 60 (40–63 μm) and neutral aluminium oxide (Acros Organics, Brockmann I, 50–200 μm). Merck aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised under ultraviolet light and by staining with $KMnO_4$, vanillin or ninhydrin. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVI 400, AVIII 400 or AVIII 500 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0), residual chloroform (δ_H 7.26 and δ_C 77.2), methanol (δ_H 3.31 and δ_C 49.0) or dimethylsulfoxide (δ_H 2.50 and δ_C 39.5) as standard. Assignment of ^{1}H and ^{13}C NMR signals are based on two-dimensional COSY, HSQC, and DEPT experiments. Mass spectra were obtained using a JEOL JMS-700 spectrometer or a Bruker microTOFq High Resolution Mass Spectrometer. Infrared spectra were recorded on a Shimadzu FTIR-84005. Melting points were determined on a Gallenkamp melting point apparatus. Optical rotations were determined as solutions irradiating at the sodium D line (λ = 589 nm) using a polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC methods were calibrated with their corresponding racemic mixtures.

3.2 Indanol Experimental

General procedure for the synthesis of secondary alcohols

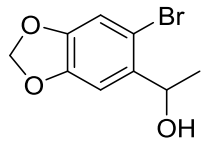
To a stirred solution of a 2-bromobenzaldehyde (1 equiv.) in dry diethyl ether (2 mL/mmol) at –78 °C, under an argon atmosphere was added dropwise, a solution of methylmagnesium bromide (1 M in dibutyl ether, 2 equiv.), ethylmagnesium bromide (1 M in THF, 2 equiv.) or isopropylmagnesium bromide (1 M in THF, 2 equiv.). After addition, the reaction mixture was allowed to warm to 0 °C and stirred for 3 h. The reaction mixture was then quenched with a saturated solution of aqueous ammonium chloride (10–15 mL/mmol). The product was extracted using diethyl ether (3 × 20 mL/mmol). The combined organic layers were washed with brine (2 × 20 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash column chromatography, eluting with diethyl ether in petroleum ether gave the secondary alcohols.

1-(2'-Bromo-4'-methylphenyl)ethan-1-ol (75a)



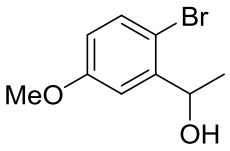
The reaction was performed according to the general procedure using 2-bromo-4-methylbenzaldehyde (0.40 g, 2.0 mmol) and methylmagnesium bromide solution (4.0 mL, 4.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-4'-methylphenyl)ethan-1-ol (**75a**) (0.42 g, 98%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3335 (OH), 2974 (CH), 1609, 1488, 1098, 1037, 821; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.5 Hz, 2-H_3), 1.95 (1H, d, *J* 3.5 Hz, 1-OH), 2.32 (3H, s, 4'-CH_3), 5.21 (1H, qd, *J* 6.5, 3.5 Hz, 1-H), 7.15 (1H, br d, *J* 8.0 Hz, 5'-H), 7.35 (1H, br d, *J* 0.9 Hz, 3'-H), 7.46 (1H, d, *J* 8.0 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 20.7 (CH_3), 23.6 (CH_3), 69.0 (CH), 121.6 (C), 126.4 (CH), 128.7 (CH), 133.1 (CH), 138.9 (C), 141.5 (C); *m/z* (ESI) 236.9882 (MNa^+. $C_9H_{11}{}^{79}BrNaO$ requires 236.9885).

1-(2'-Bromo-4',5'-methylenedioxyphenyl)ethan-1-ol (75b)[199]



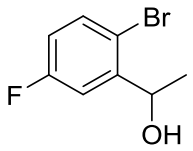
The reaction was performed according to the general procedure using 2-bromo-4,5-methylenedioxybenzaldehyde (0.69 g, 3.0 mmol) and methylmagnesium bromide solution (6.0 mL, 6.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-4',5'-methylenedioxyphenyl)ethan-1-ol (**75b**) (0.63 g, 86%) as a colourless oil which solidified upon standing to give a white solid. Mp 51–53 °C (lit.[199] 52–53 °C); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.4 Hz, 2-H_3), 1.87 (1H, d, *J* 3.3 Hz, 1-OH), 5.18 (1H, qd, *J* 6.4, 3.3 Hz, 1-H), 5.97 (1H, d, *J* 1.6 Hz, OC*H*HO), 5.98 (1H, d, *J* 1.6 Hz, OCH*H*O), 6.96 (1H, s, 6'-H), 7.09 (1H, s, 3'-H); δ_c (101 MHz, $CDCl_3$) 23.6 (CH_3), 69.1 (CH), 101.7 (CH_2), 106.6 (CH), 111.8 (C), 112.4 (CH), 138.1 (C), 147.4 (C), 147.8 (C); *m/z* (ESI) 269 (MNa^+. 100%), 267 (98).

1-(2'-Bromo-5'-methoxyphenyl)ethan-1-ol (75c)[104]



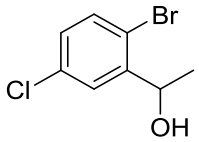
The reaction was performed according to the general procedure using 2-bromo-5-methoxybenzaldehyde (0.44 g, 3.0 mmol) and methylmagnesium bromide solution (6.0 mL, 6.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-methoxyphenyl)ethan-1-ol (**75c**) (0.63 g, 90%) as a colourless oil. Spectroscopic data were consistent with the literature.[104] δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.4 Hz, 2-H_3), 1.98 (1H, d, *J* 3.4 Hz, 1-OH), 3.81 (3H, s, 5'-OCH_3), 5.19 (1H, qd, *J* 6.4, 3.4 Hz, 1-H), 6.69 (1H, dd, *J* 8.8, 3.1 Hz, 4'-H), 7.16 (1H, d, *J* 3.1 Hz, 6'-H), 7.39 (1H, d, *J* 8.8 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 23.6 (CH_3), 55.5 (CH_3), 69.2 (CH), 111.8 (C), 112.0 (CH), 114.7 (CH), 133.2 (CH), 145.8 (C), 159.4 (C); *m/z* (EI) 232 (M^+. 39%), 230 (40).

1-(2'-Bromo-5'-fluorophenyl)ethan-1-ol (75d)



The reaction was performed according to the general procedure using 2-bromo-5-fluorobenzaldehyde (0.61 g, 3.0 mmol) and methylmagnesium bromide solution (6.0 mL, 6.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-fluorophenyl)ethan-1-ol (**75d**) (0.58 g, 88%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3323 (OH), 2974 (CH), 1580, 1465, 1261, 1153, 1029, 808, 625; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.4 Hz, 2-H_3), 2.05 (1H, d, *J* 3.5 Hz, 1-OH), 5.14–5.23 (1H, m, 1-H), 6.86 (1H, ddd, *J* 8.6, 8.0, 3.2 Hz, 4'-H), 7.34 (1H, dd, *J* 9.8, 3.2 Hz, 6'-H), 7.46 (1H, dd, *J* 8.6, 5.2 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 23.5 (CH_3), 69.1 (CH), 114.0 (d, $^2J_{C\text{-}F}$ 24.0 Hz, CH), 115.3 (C), 115.9 (d, $^2J_{C\text{-}F}$ 22.8 Hz, CH), 133.8 (d, $^3J_{C\text{-}F}$ 7.8 Hz, CH), 147.0 (d, $^3J_{C\text{-}F}$ 6.7 Hz, C), 162.5 (d, $^1J_{C\text{-}F}$ 247.2 Hz, C); *m/z* (EI) 217.9731 (M^+. $C_8H_8{}^{79}BrFO$ requires 217.9743), 205 (82), 203 (100), 175 (16), 152 (38), 123 (11), 96 (60).

1-(2'-Bromo-5'-chlorophenyl)ethan-1-ol (75e)



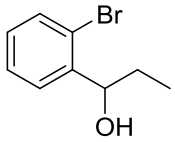
The reaction was performed according to the general procedure using 2-bromo-5-chlorobenzaldehyde (0.66 g, 3.0 mmol) and methylmagnesium bromide solution (6.0 mL, 6.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-chlorophenyl)ethan-1-ol (**75e**) (0.68 g, 96%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3336 (OH), 2976 (CH), 2360, 1449, 1194, 1102, 1025, 808; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.4 Hz, 2-H_3), 2.01 (1H, d, *J* 3.7 Hz, 1-OH), 5.18 (1H, qd, *J* 6.4, 3.7 Hz, 1-H), 7.11 (1H, dd, *J* 8.4, 2.6 Hz, 4'-H), 7.43 (1H, d, *J* 8.4 Hz, 3'-H), 7.60 (1H, d, *J* 2.6 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 23.6 (CH_3), 69.0 (CH), 119.2 (C),

127.0 (CH), 128.8 (CH), 133.7 (CH), 134.1 (C), 146.5 (C); *m/z* (EI) 235.9430 (M^+. $C_8H_8{}^{81}Br^{35}ClO$ requires 235.9425), 234 (29), 223 (24), 221 (100), 219 (81), 112 (56), 75 (27).

1-(2'-Bromo-3'-pyridyl)ethan-1-ol (75f)

The reaction was performed according to the general procedure using 2-bromopyridine-3-carboxaldehyde (1.00 g, 5.40 mmol) and methylmagnesium bromide solution (11.0 mL, 10.8 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-3'-pyridyl)ethan-1-ol (**75f**) (0.94 g, 87%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3410 (OH), 2932 (CH), 1651 (C=C), 1389, 1096, 656; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.4 Hz, 2-H_3), 3.76 (1H, br s, 1-OH), 5.12–5.20 (1H, m, 1-H), 7.28 (1H, dd, *J* 7.6, 4.8 Hz, 5'-H), 7.93 (1H, dd, *J* 7.6, 2.0 Hz, 6'-H), 8.16 (1H, dd, *J* 4.8, 2.0 Hz, 4'-H); δ_c (101 MHz, $CDCl_3$) 23.7 (CH_3), 67.9 (CH), 123.4 (CH), 135.8 (CH), 140.9 (C), 142.6 (C), 148.4 (CH); *m/z* (ESI) 223.9674 (MNa^+. $C_7H_8{}^{79}BrNNaO$ requires 223.9681).

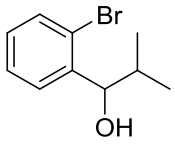
1-(2'-Bromophenyl)propan-1-ol (75g)[200]



The reaction was performed according to the general procedure using 2-bromobenzaldehyde (1.0 mL, 8.0 mmol) and ethylmagnesium bromide solution (16 mL, 16 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromophenyl)propan-1-ol (**75g**) (1.40 g, 81%) as a colourless oil. Spectroscopic data were consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 1.01 (3H, td, *J* 7.4, 0.8 Hz, 3-H_3), 1.65–1.90 (2H, m, 2-H_2), 1.95–2.05 (1H, m, 1-OH), 5.01 (1H, dt, *J* 8.0, 4.0 Hz, 1-H), 7.12 (1H, br t, *J* 7.5 Hz, ArH), 7.33 (1H, br t, *J* 7.5 Hz, ArH), 7.49–7.56 (2H,

m, ArH); δ_c (101 MHz, $CDCl_3$) 10.1 (CH_3), 30.5 (CH_2), 74.2 (CH), 122.2 (C), 127.4 (CH), 127.6 (CH), 128.7 (CH), 132.6 (CH), 143.6 (C); *m/z* (ESI) 239 (MNa^+. 95%), 237 (100).

1-(2'-Bromophenyl)-2-methylpropan-1-ol (75h)[201]



The reaction was performed according to the general procedure using 2-bromobenzaldehyde (1.0 mL, 8.0 mmol) and isopropylmagnesium bromide solution (16 mL, 16 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromophenyl)-2-methylpropan-1-ol (**75h**) (0.91 g, 57%) as a colourless oil. Spectroscopic data were consistent with the literature.[201] δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8 Hz, 3-H_3), 0.97 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.85 (1H, br s, 1-OH), 2.00–2.14 (1H, m, 2-H), 4.87 (1H, d, *J* 8.0 Hz, 1-H), 7.12 (1H, td, *J* 7.6, 4.0 Hz, ArH), 7.29–7.36 (1H, m, ArH), 7.51 (2H, td, *J* 7.6, 4.0 Hz, ArH); δ_c (101 MHz, $CDCl_3$) 16.8 (CH_3), 19.5 (CH_3), 34.0 (CH), 77.6 (CH), 122.7 (C), 127.4 (CH), 128.3 (CH), 128.7 (CH), 132.7 (CH), 142.9 (C); *m/z* (EI) 230 (M^+. 8%), 228 (10), 187 (81), 185 (100), 172 (17), 157 (9), 105 (9), 84 (23), 77 (43).

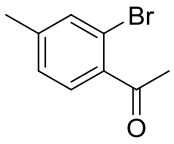
General procedure A for oxidation to 2'-bromoaryl ketones

To a stirred solution of a secondary alcohol (1 equiv.) in chloroform (3 mL/mmol) at room temperature was added manganese(IV) oxide (10 equiv.). The reaction mixture was stirred for 18 h under reflux. After cooling to room temperature, the mixture was filtered through a pad of Celite®, which was washed with diethyl ether (2 × 15 mL/mmol). The filtrate was then concentrated *in vacuo*. The crude product was purified using silica gel flash column chromatography, eluting with diethyl ether in petroleum ether to give the corresponding ketone derivatives.

General procedure B for oxidation to 2'-bromoaryl ketones

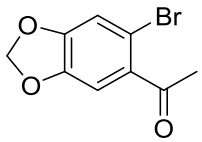
To a stirred solution of a secondary alcohol (1 equiv.) in dichloromethane (5 mL/mmol) at room temperature was added a homogeneous mixture of PCC and silica gel (1:1 by mass) (3 equiv.). The resulting suspension was stirred for 2 h. The mixture was filtered through a pad of silica gel, which was washed with dichloromethane (2 × 30 mL/mmol). The filtrate was then concentrated *in vacuo*. The crude product was purified using silica gel flash column chromatography, eluting with diethyl ether in petroleum ether to give the corresponding ketone derivatives.

1-(2'-Bromo-4'-methylphenyl)ethan-1-one (69b)[202]



The reaction was performed according to general procedure A using 1-(2'-bromo-4'-methylphenyl)ethan-1-ol (**75a**) (0.42 g, 2.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-4'-methylphenyl)ethan-1-one (**69b**) (0.33 g, 79%) as a yellow oil. Spectroscopic data were consistent with the literature.[202] δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, 4'-CH_3), 2.62 (3H, s, 2-H_3), 7.17 (1H, dd, *J* 8.0, 0.8 Hz, 5'-H), 7.43 (1H, d, *J* 8.0 Hz, 6'-H), 7.45 (1H, d, *J* 0.8 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 21.0 (CH_3), 30.2 (CH_3), 119.3 (C), 128.2 (CH), 129.4 (CH), 134.5 (CH), 138.1 (C), 142.9 (C), 200.7 (C); *m/z* (CI) 215 (MH^+. 48%), 213 (51), 136 (100), 71 (33), 69 (35).

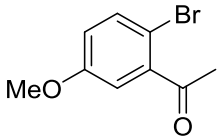
1-(2'-Bromo-4',5'-methylenedioxyphenyl)ethan-1-one (69c)[203]



The reaction was performed according to general procedure B using 1-(2'-bromo-4',5'-methylenedioxyphenyl)ethan-1-ol (**75b**) (0.50 g, 2.0 mmol). Purification by

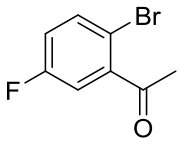
flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-4',5'-methylenedioxyphenyl)ethan-1-one (**69c**) (0.39 g, 79%) as a colourless oil. Spectroscopic data were consistent with the literature.[203] δ_H (400 MHz, $CDCl_3$) 2.61 (3H, s, 2-H_3), 6.04 (2H, s, OCH_2O), 7.03 (1H, s, ArH), 7.05 (1H, s, ArH); δ_c (101 MHz, $CDCl_3$) 30.3 (CH_3), 102.5 (CH_2), 109.3 (CH), 112.0 (C), 113.9 (CH), 134.3 (C), 147.4 (C), 150.4 (C), 199.5 (C); *m/z* (ESI) 267 (MNa^+. 100%), 265 (99).

1-(2'-Bromo-5'-methoxyphenyl)ethan-1-one (69d)[104]



The reaction was performed according to general procedure A using 1-(2'-bromo-5'-methoxyphenyl)ethan-1-ol (**75c**) (0.62 g, 2.7 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-methoxyphenyl)ethan-1-one (**69d**) (0.46 g, 74%) as a colourless oil. Spectroscopic data were consistent with the literature.[104] δ_H (400 MHz, $CDCl_3$) 2.63 (3H, s, 2-H_3), 3.81 (3H, s, 5'-OCH_3), 6.85 (1H, dd, *J* 8.8, 3.1 Hz, 4'-H), 6.98 (1H, d, *J* 3.1 Hz, 6'-H), 7.48 (1H, d, *J* 8.8 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 30.3 (CH_3), 55.7 (CH_3), 109.1 (C), 114.2 (CH), 117.9 (CH), 134.6 (CH), 142.3 (C), 158.9 (C), 201.3 (C); *m/z* (EI) 230 (M^+. 54%), 228 (55), 215 (99), 213 (100), 187 (17), 185 (17), 172 (14), 157 (15), 78 (18), 63 (35).

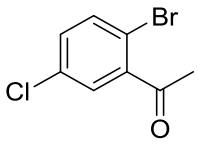
1-(2'-Bromo-5'-fluorophenyl)ethan-1-one (69e)[104]



The reaction was performed according to general procedure A using 1-(2'-bromo-5'-fluorophenyl)ethan-1-ol (**75d**) (0.55 g, 2.5 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-fluorophenyl)ethan-1-one (**69e**) (0.40 g, 74%) as a colourless oil. Spectroscopic data were consistent with the literature.[104] δ_H (400

MHz, $CDCl_3$) 2.64 (3H, s, 2-H_3), 7.04 (1H, ddd, *J* 8.8, 7.6, 3.1 Hz, 4'-H), 7.18 (1H, dd, *J* 8.4, 3.1 Hz, 6'-H), 7.58 (1H, dd, *J* 8.8, 4.9 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 30.2 (CH_3), 113.1 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 116.1 (d, $^2J_{C\text{-}F}$ 24.1 Hz, CH), 119.1 (d, $^2J_{C\text{-}F}$ 22.5 Hz, CH), 135.4 (d, $^3J_{C\text{-}F}$ 7.8 Hz, CH), 142.9 (d, $^3J_{C\text{-}F}$ 5.8 Hz, C), 161.4 (d, $^1J_{C\text{-}F}$ 250.3 Hz, C), 199.9 (C); *m/z* (EI) 218 (M^+. 35%), 216 (36), 203 (98), 201 (100), 175 (33), 173 (34), 94 (58), 86 (38), 84 (60).

1-(2'-Bromo-5'-chlorophenyl)ethan-1-one (69f)[199]



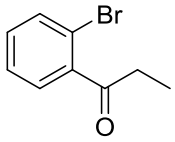
The reaction was performed according to general procedure A using 1-(2'-bromo-5'-chlorophenyl)ethan-1-ol (**75e**) (0.43 g, 1.8 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromo-5'-chlorophenyl)ethan-1-one (**69f**) (0.33 g, 78%) as a yellow oil. Spectroscopic data were consistent with the literature.[199] δ_H (400 MHz, $CDCl_3$) 2.63 (3H, s, 2-H_3), 7.28 (1H, dd, *J* 8.5, 2.5 Hz, 4'-H), 7.43 (1H, d, *J* 2.5 Hz, 6'-H), 7.55 (1H, d, *J* 8.5 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 30.2 (CH_3), 116.8 (C), 128.9 (CH), 131.8 (CH), 133.8 (C), 135.0 (CH), 142.7 (C), 199.9 (C); *m/z* (EI) 234 (M^+. 45%), 232 (33), 219 (100), 217 (77), 191 (39), 189 (24), 110 (16), 84 (12), 75 (33).

1-(2'-Bromo-3'-pyridyl)ethan-1-one (69g)

To a stirred solution of 1-(2'-bromo-3'-pyridyl)ethan-1-ol (**75f**) (0.940 g, 4.70 mmol) in DMF (5 mL) at room temperature was added a solution of PDC (2.65 g, 7.05 mmol) in DMF (5 mL). The resulting suspension was stirred for 18 h then filtered through a pad of Celite®, washed with diethyl ether (2 × 30 mL) and concentrated *in vacuo*. The crude product was then purified using silica gel flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–

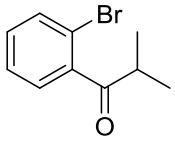
60) to give 1-(2'-bromo-3'-pyridyl)ethan-1-one (**69g**) (0.69 g, 74%) as a yellow oil. ν_{max}/cm^{-1} (neat) 1697 (C=C), 1566, 1389, 1273, 1111, 1042, 741, 648; δ_H (400 MHz, $CDCl_3$) 2.69 (3H, s, 2-H_3), 7.37 (1H, dd, *J* 7.6, 4.7 Hz, 5'-H), 7.76 (1H, dd, *J* 7.6, 2.0 Hz, 6'-H), 8.46 (1H, dd, *J* 4.7, 2.0 Hz, 4'-H); δ_c (101 MHz, $CDCl_3$) 30.3 (CH_3), 122.7 (CH), 137.4 (CH), 138.1 (C), 138.5 (C), 151.4 (CH), 199.8 (C); *m/z* (ESI) 199.9710 (MH^+. $C_7H_7{}^{79}BrNO$ requires 199.9706).

2'-Bromopropiophenone (69h)[200]



The reaction was performed according to general procedure B using 1-(2'-bromophenyl)propan-1-ol (**75g**) (1.30 g, 6.00 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2'-bromopropiophenone (**69h**) (1.15 g, 90%) as a yellow oil. Spectroscopic data were consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2 Hz, 3-H_3), 2.93 (2H, q, *J* 7.2 Hz, 2-H_2), 7.25–7.31 (1H, m, ArH), 7.33–7.39 (2H, m, ArH), 7.57–7.62 (1H, m, ArH); δ_c (101 MHz, $CDCl_3$) 8.1 (CH_3), 36.1 (CH_2), 118.5 (C), 127.4 (CH), 128.2 (CH), 131.3 (CH), 133.6 (CH), 142.0 (C), 205.1 (C); *m/z* (ESI) 237 (MNa^+. 98%) 235 (100).

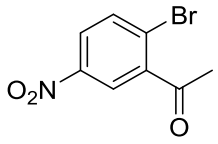
1-(2'-Bromophenyl)-2-methylpropan-1-one (69i)[201]



The reaction was performed according to general procedure B using 1-(2'-bromophenyl)-2-methylpropan-1-ol (**75h**) (0.90 g, 3.9 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 1-(2'-bromophenyl)-2-methylpropan-1-one (**69i**) (0.73 g, 83%) as a yellow oil. Spectroscopic data were consistent with the literature.[201] δ_H (400 MHz, $CDCl_3$) 1.20 (6H, d, *J* 7.0 Hz, 3-H_3 and 2-CH_3), 3.32 (1H, sept, *J* 7.0 Hz, 2-H), 7.25–7.31 (2H, m, ArH), 7.33–7.39 (1H, m, ArH), 7.57–7.62 (1H, m, ArH); δ_c

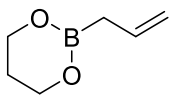
(101 MHz, $CDCl_3$) 18.1 (2 × CH_3), 40.2 (CH), 118.7 (C), 127.2 (CH), 128.1 (CH), 131.0 (CH), 133.4 (CH), 142.1 (C), 208.7 (C); *m/z* (ESI) 251 (MNa^+. 98%) 249 (100).

1-(2'-Bromo-5'-nitrophenyl)ethan-1-one (69j)[116]



1-(2'-Bromophenyl)ethan-1-one (**69a**) (0.54 mL, 4.0 mmol) was added to a solution of potassium nitrate (0.50 g, 5.0 mmol) in concentrated sulfuric acid (4 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for 1.5 h. The mixture was quenched with water (5 mL) and extracted with dichloromethane (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) yielded 1-(2'-bromo-5'-nitrophenyl)ethan-1-one (**69j**) (0.53 g, 54%) as a white powder. Mp 86–87 °C (lit.[116] 85–87 °C); δ_H (400 MHz, $CDCl_3$) 2.69 (3H, s, 2-H_3), 7.83 (1H, d, *J* 8.7 Hz, 3'-H), 8.15 (1H, dd, *J* 8.7, 2.7 Hz, 4'-H), 8.31 (1H, d, *J* 2.7 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 30.1 (CH_3), 123.8 (CH), 125.9 (CH), 126.2 (C), 135.2 (CH), 142.4 (C), 147.0 (C), 198.7 (C); *m/z* (EI) 245 (M^+. 27%), 243 (27), 230 (100), 182 (22), 151 (28), 105 (17), 75 (44).

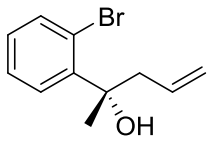
***B*-Allyl-1,3,2-dioxaborinane (73)**[114]



Trimethyl borate (**77**) (5.6 mL, 50 mmol) was dissolved in dry diethyl ether (50 mL) under an argon atmosphere and cooled to –78 °C. Allylmagnesium bromide solution (50 mL, 1 M in diethyl ether) was added dropwise over 0.5 h. After addition, the reaction mixture was stirred for 2 h at –78 °C, then acidified at 0 °C with a 3 M aqueous solution of hydrochloric acid (60 mL). The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 50

mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to approximately 100 mL. To this solution was added 1,3-propanediol (3.6 mL, 50 mmol) as well as oven dried 4Å molecular sieves (10 g) and the resulting mixture was stirred for 16 h at room temperature. The molecular sieves were filtered and washed with diethyl ether (2 × 50 mL). The solvent was removed *in vacuo*, and the crude product was then dissolved in *n*-pentane (100 mL). The resulting cloudy suspension was filtered through a pad of Celite®, washed and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 35% diethyl ether in *n*-pentane gave a pale yellow oil. Further purification by short-path Kugelrohr distillation gave *B*-allyl-1,3,2-dioxaborinane (**73**) (4.0 g, 63%) as a colourless oil. Spectroscopic data were consistent with the literature.[114] δ_H (400 MHz, $CDCl_3$) 1.63 (2H, br d, *J* 7.6 Hz, 1'-H_2), 1.93 (2H, quin, *J* 5.5 Hz, 5-H_2), 3.98 (4H, t, *J* 5.5 Hz, 4-H_2 and 6-H_2), 4.88 (1H, ddt, *J* 10.0, 2.4, 1.2 Hz, 3'-*H*H), 4.92 (1H, ddt, *J* 15.2, 2.4, 1.2 Hz, 3'-H*H*), 5.85 (1H, ddt, *J* 15.2, 10.0, 7.6 Hz, 2'-H); δ_c (101 MHz, $CDCl_3$) 22.0 (d, $^1J_{C\text{-}B}$ 64.6 Hz, CH_2) 27.3 (CH_2), 61.9 (2 × CH_2), 113.9 (CH_2) 135.5 (CH); *m*/*z* (CI) 127 (MH^+, 12%), 113 (32), 103 (44), 97 (40), 85 (83), 71 (100), 69 (71).

(2*S*)-2-(2'-Bromophenyl)pent-4-en-2-ol [(*S*)-76a][104]



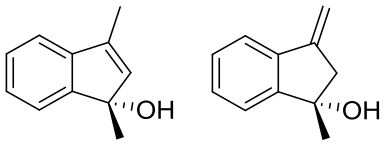
B-Allyl-1,3,2-dioxaborinane (**73**) (0.026 ml, 0.21 mmol) and (*S*)-(−)-3,3'-dibromo-1,1'-bi-2-naphthol [**(*S*)-74**] (0.0050g, 0.011 mmol) was dissolved in distilled toluene (1 mL) and stirred for 0.1 h at 35 °C in an oven dried microwave vial. A solution of 1-(2'-bromophenyl)ethan-1-one (**69a**) (0.020 mL, 0.15 mmol) in distilled toluene (0.75 mL) was the added and the reaction mixture was stirred for 5 days at 35 °C under an argon atmosphere. Purification by flash column chromatography eluting with 10% diethyl ether in petroleum ether (40–60) gave (2*S*)-2-(2'-bromophenyl)pent-4-en-2-ol [**(S)-76a**] (0.036 g, 100%) as a colourless oil. Spectroscopic data were consistent with the literature.[104] $[\alpha]_D^{31}$ −34.3 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.72 (3H, s, 1-H_3), 2.62 (1H, s, 2-OH), 2.64 (1H, br dd, *J* 14.0, 8.4 Hz, 3-*H*H), 3.29 (1H, ddt, *J* 14.0, 6.3, 1.1 Hz, 3-H*H*), 5.06–5.19

(2H, m, 5-H_2), 5.55 (1H, dddd, *J* 17.0, 10.1, 8.4, 6.3 Hz, 4-H), 7.10 (1H, td, *J* 7.8, 1.7 Hz, ArH), 7.30 (1H, td, *J* 7.8, 1.3 Hz, ArH), 7.58 (1H, dd, *J* 7.8, 1.3 Hz, ArH) 7.70 (1H, dd, *J* 7.8, 1.7 Hz, ArH); δ_c (101 MHz, $CDCl_3$) 27.3 (CH_3), 45.1 (CH_2), 74.7 (C), 119.4 (CH_2), 120.0 (C), 127.4 (CH), 128.3 (CH), 128.6 (CH), 133.7 (CH), 135.1 (CH), 145.0 (C); *m*/*z* (ESI) 265 (MNa^+. 100%), 263 (97). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{minor} = 1.78 min, t_{major} = 1.96 min; 98:2 er.

General procedure for the asymmetric synthesis of 1-alkyl-1-indanols

B-Allyl-1,3,2-dioxaborinane (**73**) (1.4 equiv.) and (*S*)-(–)-3,3'-dibromo-1,1'-bi-2-naphthol [**(*S*)-74**] (7.5 mol%) was dissolved in distilled toluene (5 mL/mmol) and stirred for 0.1 h at 35 °C in an oven dried microwave vial. A solution of 2'-bromophenyl alkyl ketone (1.0 equiv.) in distilled toluene (5 mL/mmol) was the added and the reaction mixture was stirred for 5 days at 35 °C. Bis(triphenylphosphine)palladium(II) dichloride (7.5 mol%), potassium carbonate (2 equiv.) and hydrazine monohydrate (0.4 equiv.) were added to the reaction mixture. The vial was sealed and heated to 135 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (2 mL/mmol), filtered through a pad of Celite® and concentrated *in vacuo*. Purification of the crude product using silica gel flash chromatography, eluting with diethyl ether or ethyl acetate in petroleum ether or ethyl acetate in hexane gave the corresponding 1-alkyl-1-indanols.

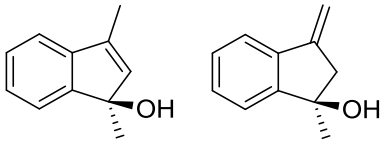
(1*S*)-1,3-Dimethylinden-1-ol [(*S*)-82a][104] and (1*S*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [(S)-70a][104]



The reaction was performed according to the general procedure using 1-(2'-bromophenyl)ethan-1-one (**69a**) (0.067 mL, 0.50 mmol) and (*S*)-(–)-3,3'-dibromo-1,1'-bi-2-naphthol [**(*S*)-74**] (0.016 g, 0.040 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in

petroleum ether (40–60) to yield first (1*S*)-1,3-dimethylinden-1-ol [**(*S*)-82a**] (0.012 g, 15%), and then (1*S*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70a**] (0.060 g, 75%) as colourless oils, which solidified upon standing. Spectroscopic data were consistent with the literature.[104] Data for (1*S*)-1,3-dimethylinden-1-ol [**(*S*)-82a**]: Mp 95–97 °C; $[\alpha]_D^{31}$ +55.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.58 (3H, s, 1-CH_3), 1.67 (1H, s, 1-OH), 2.06 (3H, d, *J* 1.6 Hz, 3-CH_3), 5.99 (1H, q, *J* 1.6 Hz, 2-H), 7.15 (1H, br d, *J* 7.3 Hz, ArH), 7.22 (1H, td, *J* 7.3, 1.0 Hz, ArH), 7.28 (1H, td, *J* 7.3, 1.0 Hz, ArH), 7.40 (1H, br d, *J* 7.3 Hz, ArH); δ_c (101 MHz, $CDCl_3$) 12.7 (CH_3), 23.8 (CH_3), 81.1 (C), 119.3 (CH), 121.2 (CH), 126.3 (CH), 128.3 (CH), 137.7 (CH), 138.9 (C), 143.0 (C), 150.0 (C); *m*/*z* (ESI) 183 (MNa^+. 100%). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 2.43 min, t_{minor} = 2.80 min; 96:4 er. Data for (1*S*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70a**]: Mp 79–81 °C; $[\alpha]_D^{31}$ +10.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.59 (3H, s, 1-CH_3), 1.95 (1H, s, 1-OH), 2.88 (1H, dt, *J* 16.5, 2.1 Hz, 2-*H*H), 2.95 (1H, dt, *J* 16.5, 2.1 Hz, 2-H*H*), 5.09 (1H, t, *J* 2.1 Hz, 3-C*H*H), 5.52 (1H, t, *J* 2.1 Hz, 3-CH*H*), 7.28–7.34 (2H, m, ArH), 7.39–7.44 (1H, m, ArH), 7.46–7.52 (1H, m, ArH); δ_c (101 MHz, $CDCl_3$) 28.1 (CH_3), 49.4 (CH_2), 78.7 (C), 104.5 (CH_2), 120.6 (CH), 122.9 (CH), 128.6 (CH), 129.1 (CH), 139.4 (C), 145.9 (C), 150.4 (C); *m*/*z* (ESI) 183 (MNa^+. 100%). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 2.58 min, t_{minor} = 2.96 min; 96:4 er.

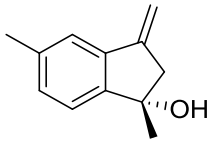
(1*R*)-1,3-Dimethylinden-1-ol [(*R*)-82a] and (1*R*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [(*R*)-70a]



The reaction was performed according to the general procedure using 1-(2'-bromophenyl)ethan-1-one (**69a**) (0.067 mL, 0.50 mmol) and (*R*)-(+)-3,3'-dibromo-1,1'-bi-2-naphthol [**(*R*)-74**] (0.016 g, 0.040 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield first (1*R*)-1,3-dimethylinden-1-ol [**(*R*)-82a**]

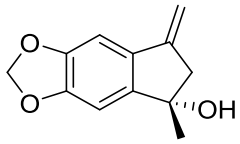
(0.014 g, 18%) and then (1*R*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [**(*R*)-70a**] (0.056 g, 70%) as colourless oils, which solidified upon standing. Melting point and spectroscopic data were as recorded for **(*S*)-82a** and **(*S*)-70a**. Additional data for **(*R*)-82a**: $[\alpha]_D^{31}$ –56.2 (*c* 0.5, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{minor} = 2.38 min, t_{major} = 2.75 min; 96:4 er. Additional data for **(*R*)-70a**: $[\alpha]_D^{31}$ –13.0 (*c* 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{minor} = 2.53 min, t_{major} = 2.94 min; er = 96:4.

(1*S*)-2,3-Dihydro-1,5-dimethyl-3-(methylene)indan-1-ol [(*S*)-70b]



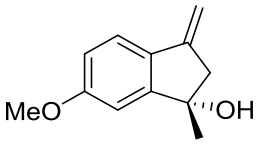
The reaction was performed according to the general procedure using 1-(2'-bromo-4'-methylphenyl)ethan-1-one (**69b**) (0.10 g, 0.47 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 8% ethyl acetate in hexane to yield (1*S*)-2,3-dihydro-1,5-dimethyl-3-(methylene)indan-1-ol [**(*S*)-70b**] (0.050 g, 61%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3352 (OH), 2969 (CH), 1644 (C=C), 1444, 1367, 1179, 1077, 945, 863, 817; $[\alpha]_D^{31}$ +24.4 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.56 (3H, s, 1-CH_3), 1.90 (1H, s, 1-OH), 2.37 (3H, s, 5-CH_3), 2.87 (1H, dt, *J* 16.4, 2.1 Hz, 2-*H*H), 2.93 (1H, dt, *J* 16.4, 2.1 Hz, 2-H*H*), 5.05 (1H, t, *J* 2.1 Hz, 3-C*H*H), 5.48 (1H, t, *J* 2.1 Hz, 3-CH*H*), 7.13 (1H, br d, *J* 7.9 Hz, 7-H), 7.28–7.32 (2H, m, 4-H and 6-H); δ_c (101 MHz, $CDCl_3$) 21.4 (CH_3), 28.1 (CH_3), 49.6 (CH_2), 78.4 (C), 104.1 (CH_2), 121.0 (CH), 122.7 (CH), 130.1 (CH), 138.5 (C), 139.6 (C), 146.0 (C), 147.8 (C); *m/z* (ESI) 197.0933 (MNa^+. $C_{12}H_{14}NaO$ requires 197.0937). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 99:1, flow rate 1.0 mL/min), t_{minor} = 12.88 min, t_{major} = 13.57 min; 96:4 er.

(1*S*)-2,3-Dihydro-5,6-(methylenedioxy)-1-methyl-3-(methylene)indan-1-ol [(*S*)-70c]



The reaction was performed according to the general procedure using 1-(2'-bromo-4',5'-methylenedioxyphenyl)ethan-1-one (**69c**) (0.12 g, 0.50 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-5,6-(methylenedioxy)-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70c**] (0.071 g, 69%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3403 (OH), 2970 (CH), 2359 (CH), 1474, 1337, 1271, 1084, 1038, 939; $[\alpha]_D^{30}$+35.3 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 1.45 (3H, s, 1-CH_3), 2.86 (2H, t, *J* 2.0 Hz, 2-H_2), 4.89 (1H, t, *J* 2.0 Hz, 3-C*H*H), 5.29 (1H, t, *J* 2.0 Hz, 3-CH*H*), 5.94 (1H, d, *J* 1.2 Hz, OC*H*HO), 5.95 (1H, d, *J* 1.2 Hz, OCH*H*O), 6.82 (1H, s, ArH), 6.90 (1H, s, ArH); δ_c (101 MHz, CD_3OD) 27.6 (CH_3), 49.0 (CH_2), 77.4 (C), 99.6 (CH), 100.5 (CH_2), 101.4 (CH_2), 102.5 (CH), 133.4 (C), 145.3 (C), 146.0 (C), 148.7 (C), 149.0 (C); *m*/*z* (ESI) 227.0672 (MNa^+. $C_{12}H_{12}NaO_3$ requires 227.0679). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{minor} = 6.04 min, t_{major} = 6.59 min; 89.5:10.5 er.

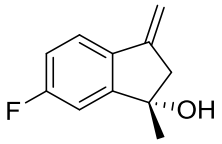
(1*S*)-2,3-Dihydro-6-methoxy-1-methyl-3-(methylene)indan-1-ol [(*S*)-70d][104]



The reaction was performed according to the general procedure using 1-(2'-bromo-5'-methoxyphenyl)ethan-1-one (**69d**) (0.12 g, 0.50 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-6-methoxy-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70d**] (0.044 g, 47%) as a yellow oil. Spectroscopic data were consistent with the literature.[104] $[\alpha]_D^{30}$ +30.8 (*c* 1.0, MeOH); δ_H (400

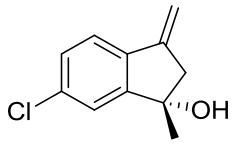
MHz, CD_3OD) 1.48 (3H, s, 1-CH_3), 2.84 (1H, td, *J* 16.4, 1.6 Hz, 2-*H*H), 2.89 (1H, td, *J* 16.4, 1.6 Hz, 2-H*H*), 3.80 (3H, s, 6-OCH_3), 4.90 (1H, t, *J* 1.6 Hz, 3-C*H*H), 5.32 (1H, t, *J* 1.6 Hz, 3-CH*H*), 6.85 (1H, dd, *J* 8.5, 2.3 Hz, 5-H), 6.94 (1H, d, *J* 2.3 Hz, 7-H), 7.39 (1H, d, *J* 8.5 Hz, 4-H); δ_c (101 MHz, CD_3OD) 27.7 (CH_3), 49.1 (CH_2), 54.5 (CH_3), 77.6 (C), 100.4 (CH_2), 106.7 (CH), 115.2 (CH), 121.2 (CH), 132.1 (C), 145.9 (C), 152.5 (C), 160.9 (C); *m/z* (EI) 190 (84%), 175 (100), 160 (10), 132 (11), 115 (14), 88 (12), 61 (17). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 2.99 min, t_{minor} = 3.67 min; 93.5:6.5 er.

(1*S*)-2,3-Dihydro-6-fluoro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70e]



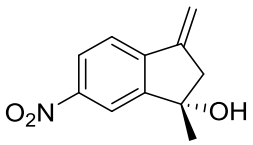
The reaction was performed according to the general procedure using 1-(2'-bromo-5'-fluorophenyl)ethan-1-one (**69e**) (0.054 g, 0.25 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-6-fluoro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70e**] (0.020 g, 46%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3356 (OH), 2970 (CH), 1643 (C=C), 1605, 1481, 1258, 1080, 872, 826, 687; $[\alpha]_D^{31}$ +18.3 (*c* 0.5, $CDCl_3$); δ_H (400 MHz, CD_3OD) 1.48 (3H, s, 1-CH_3), 2.87 (1H, dt, *J* 16.4, 2.1 Hz, 2-*H*H), 2.92 (1H, dt, *J* 16.4, 2.1 Hz, 2-H*H*), 5.02 (1H, t, *J* 2.1 Hz, 3-C*H*H), 5.45 (1H, t, *J* 2.1 Hz, 3-CH*H*), 7.01 (1H, ddd, *J* 9.2, 8.6, 2.4 Hz, 5-H), 7.10 (1H, dd, *J* 8.8, 2.4 Hz, 7-H), 7.51 (1H, dd, *J* 8.6, 5.2 Hz, 4-H); δ_c (101 MHz, CD_3OD) 27.5 (CH_3), 48.9 (CH_2), 77.3 (d, $^4J_{C\text{-}F}$ 2.2 Hz, C), 102.5 (CH_2), 109.3 (d, $^2J_{C\text{-}F}$ 23.2 Hz, CH), 115.3 (d, $^2J_{C\text{-}F}$ 24.2 Hz, CH), 121.9 (d, $^3J_{C\text{-}F}$ 9.1 Hz, CH), 135.3 (d, $^4J_{C\text{-}F}$ 2.0 Hz, C), 145.3 (C), 153.3 (d, $^3J_{C\text{-}F}$ 7.1 Hz, C), 163.5 (d, $^1J_{C\text{-}F}$ 247.5 Hz, C); *m/z* (EI) 178.0801 (M^+. $C_{11}H_{11}FO$ requires 178.0794), 163 (100%), 133 (33), 88 (12), 61 (17). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 10.50 min, t_{minor} = 12.92 min; 94:6 er.

(1*S*)-2,3-Dihydro-6-chloro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70f]



The reaction was performed according to the general procedure using 1-(2'-bromo-5'-chlorophenyl)ethan-1-one (**69f**) (0.10 g, 0.43 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-6-chloro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70f**] (0.044 g, 52% yield) as a colourless oil. ν_{max}/cm^{-1} (neat) 3372 (OH), 2924 (CH), 1628 (C=C), 1458, 1366, 1103, 1080, 826; $[\alpha]_D^{31}$ +19.5 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, CD_3OD) 1.48 (3H, s, 1-CH_3), 2.89 (1H, t, *J* 2.0 Hz, 2-H_2), 5.08 (1H, t, *J* 2.0 Hz, 3-C*H*H), 5.52 (1H, t, *J* 2.0 Hz, 3-CH*H*), 7.27 (1H, dd, *J* 8.2, 1.9 Hz, 5-H), 7.39 (1H, d, *J* 1.9 Hz, 7-H), 7.48 (1H, d, *J* 8.2 Hz, 4-H); δ_c (101 MHz, CD_3OD) 27.5 (CH_3), 48.7 (CH_2), 77.4 (C), 103.7 (CH_2), 121.6 (CH), 123.1 (CH), 128.2 (CH), 134.0 (C), 137.9 (C), 145.3 (C), 152.8 (C); *m*/*z* (EI) 194.0491 (M^+. $C_{11}H_{11}{}^{35}ClO$ requires 194.0498), 179 (100%), 159 (71), 144 (23), 115 (43), 84 (18). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 5.33 min, t_{minor} = 5.72 min; 95:5 er.

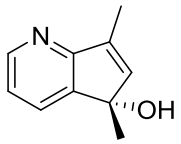
(1*S*)-2,3-Dihydro-6-nitro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70g]



The reaction was performed according to the general procedure using 1-(2'-bromo-5'-nitrophenyl)ethan-1-one (**69j**) (0.029 g, 0.10 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 30% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-6-nitro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70g**] (0.0090 g, 19%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3372 (OH), 2970 (CH), 2932 (CH), 1598, 1520, 1342, 1103, 903, 741; $[\alpha]_D^{30}$ +45.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, CD_3OD) 1.55 (3H, s, 1-CH_3), 2.92–3.04 (2H, m, 2-H_2),

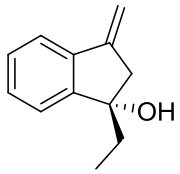
5.32 (1H, t, *J* 2.2 Hz, 3-C*H*H), 5.78 (1H, t, *J* 2.2 Hz, 3-CH*H*), 7.73 (1H, d, *J* 8.5 Hz, 4-H), 8.18 (1H, dd, *J* 8.5, 2.2 Hz, 5-H), 8.26 (1H, d, *J* 2.2 Hz, 7-H); δ_c (101 MHz, CD_3OD) 27.5 (CH_3), 48.5 (CH_2), 77.2 (C), 108.0 (CH_2), 118.5 (CH), 121.2 (CH), 123.5 (CH), 144.8 (C), 145.3 (C), 148.4 (C), 152.3 (C); *m*/*z* (ESI) 228.0625 (MNa^+. $C_{11}H_{11}NNaO_3$ requires 228.0631). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 93:7, flow rate 2.0 mL/min), t_{major} = 3.84 min, t_{minor} = 4.18 min; 93.5:6.5 er.

(5*S*)-5,7-Dimethylcyclopenta[b]pyridin-5-ol [(*S*)-82h]



The reaction was performed according to the general procedure using 1-(2'-bromo-3'-pyridyl)ethan-1-one (**69g**) (0.080 g, 0.40 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% ethyl acetate in petroleum ether (40–60) to yield (5*S*)-5,7-dimethyl-cyclopenta[b]pyridin-5-ol [**(*S*)-82h**] (0.040 g, 63%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3322 (OH), 2972 (CH), 1603 (C=C), 1572, 1474, 1337, 1086, 1038, 750; $[\alpha]_D^{31}$ +24.2 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, CD_3OD) 1.53 (3H, s, 5-CH_3), 2.10 (3H, d, *J* 1.6 Hz, 7-CH_3), 6.36 (1H, q, *J* 1.6 Hz, 6-H), 7.19 (1H, dd, *J* 7.4, 5.3 Hz, 3-H), 7.74 (1H, dd, *J* 7.4, 1.4 Hz, 4-H), 8.30 (1H, dd, *J* 5.3, 1.4 Hz, 2-H); δ_c (101 MHz, CD_3OD) 10.4 (CH_3), 22.8 (CH_3), 77.7 (C), 120.7 (CH), 128.8 (CH), 138.8 (C), 144.5 (CH), 145.0 (C), 147.4 (CH), 161.9 (C); *m*/*z* (EI) 161.0835 (M^+. $C_{10}H_{11}NO$ requires 161.0841), 146 (100%), 132 (12), 117 (14). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 15.69 min, t_{minor} = 22.38 min; 92.5:7.5 er.

(1*S*)-2,3-Dihydro-1-ethyl-3-(methylene)indan-1-ol [(*S*)-70i]



The reaction was performed according to the general procedure using 2'-bromopropiophenone (**69h**) (0.10 g, 0.47 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield (1*S*)-2,3-dihydro-1-ethyl-3-(methylene)indan-1-ol [**(*S*)-70i**] (0.048 g, 59%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3348 (OH), 2932 (CH), 1628 (C=C), 1458, 1381, 1018, 972, 748; $[\alpha]_D^{31}$ +8.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, CD_3OD) 0.81 (3H, t, *J* 7.5 Hz, 1-CH_2CH_3), 1.76 (1H, dq, *J* 13.3, 7.5 Hz, 1-C*H*H), 1.88 (1H, dq, *J* 13.3, 7.5 Hz, 1-CH*H*), 2.77 (1H, dt, *J* 16.4, 2.1 Hz, 2-*H*H), 2.96 (1H, dt, *J* 16.4, 2.1 Hz, 2-H*H*), 5.04 (1H, t, *J* 2.1 Hz, 3-C*H*H), 5.49 (1H, t, *J* 2.1 Hz, 3-CH*H*), 7.25–7.32 (2H, m, ArH), 7.35–7.40 (1H, m, ArH), 7.48–7.53 (1H, m, ArH); δ_c (101 MHz, CD_3OD) 7.5 (CH_3), 33.9 (CH_2), 45.7 (CH_2), 80.7 (C), 102.3 (CH_2), 120.0 (CH), 123.3 (CH), 128.0 (CH), 128.3 (CH), 140.0 (C), 146.8 (C), 149.6 (C); *m/z* (ESI) 197.0932 (MNa^+. $C_{12}H_{14}NaO$ requires 197.0937). Enantiomeric excess was determined by HPLC analysis with a chiralcel OD-H column (hexane:*i*-PrOH 95:5, flow rate 1.0 mL/min), t_{major} = 2.38 min, t_{minor} = 2.80 min; 94:6.

Two-step racemic synthesis of 1-alkyl-3-(methylene)indan-1-ols for chiral HPLC Analysis

Step 1: Synthesis of homoallylic alcohol derivatives 76a–j

General procedure A

To a stirred solution of a 2'-bromophenyl alkyl ketone (1.0 equiv.) in dry diethyl ether (3 mL/mmol) at –78 °C was added dropwise, a solution of allylmagnesium bromide (1 M in diethyl ether, 3.0 equiv.) under an argon atmosphere. After addition, the reaction mixture was warmed to 0 °C and was stirred for 4 h at this temperature. The reaction mixture was then quenched with a saturated solution of aqueous ammonium chloride (10–15 mL/mmol). After phase

separation, the aqueous layer was extracted with diethyl ether (3 × 15 mL/mmol). The combined organic layers were washed with brine (2 × 15 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash column chromatography, eluting with diethyl ether in petroleum ether gave the corresponding racemic homoallylic alcohol derivatives.

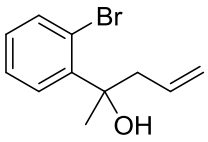
General procedure B

To a sonicated suspension of zinc dust (4 equiv.) in dry THF (4 mL/mmol) was added a solution of allyl bromide solution (4 equiv.) in dry THF (5 mL/mmol) under an argon atmosphere and the mixture was further sonicated for 0.5 h at room temperature. 2'-Bromophenyl alkyl ketone (1 equiv.) in dry THF (1 mL/mmol) was then added and the sonication was continued for 4 h. After diluting the reaction with ethyl acetate (10 mL/mmol), the reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (10 mL/mmol). After phase separation, the product was extracted with ethyl acetate (2 × 10 mL/mmol). The combined organic layers were washed with brine (2 × 15 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash column chromatography, eluting with ethyl acetate in petroleum ether gave the corresponding racemic homoallylic alcohol derivatives.

General procedure C

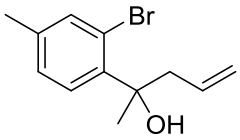
2'-Bromophenyl alkyl ketone (1 equiv.), indium powder (3 mol%) and allylboronic acid pinacol ester (1.5 equiv.) was dissolved in water (1 mL/mmol). The reaction was vigorously stirred at room temperature for 3 days before addition of dichloromethane (10 mL/mmol). After phase separation, the aqueous layer was extracted with dichloromethane (3 × 10 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash chromatography, eluting with diethyl ether in petroleum ether gave the corresponding racemic homoallylic alcohol derivatives.

2-(2'-Bromophenyl)pent-4-en-2-ol (76a)



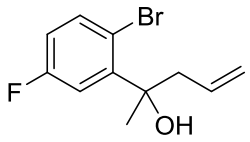
The reaction was performed according to general procedure A using 1-(2'-bromophenyl)ethan-1-one (**69a**) (0.40 mL, 3.0 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2-(2'-bromophenyl)pent-4-en-2-ol (**76a**) (0.72 g, 99%) as a colourless oil. Spectroscopic data were consistent with **(*S*)-76a**.

2-(2'-Bromo-4'-methylphenyl)pent-4-en-2-ol (76b)



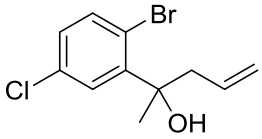
The reaction was performed according to general procedure A using 1-(2'-bromo-4'-methylphenyl)ethan-1-one (**69b**) (0.10 g, 0.47 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2-(2'-bromo-4'-methylphenyl)pent-4-en-2-ol (**76b**) (0.10 g, 80%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3464 (OH), 2976 (CH), 1607 (C=C), 1481, 1375, 1265, 916, 839, 823; δ_H (400 MHz, $CDCl_3$) 1.70 (3H, s, 1-H_3), 2.30 (3H, s, 4'-CH_3), 2.61 (1H, s, 2-OH), 2.62 (1H, br dd, *J* 14.0, 8.3 Hz, 3-*H*H), 3.26 (1H, ddt, *J* 14.0, 6.4, 0.9 Hz, 3-H*H*), 5.06–5.17 (2H, m, 5-H_2), 5.55 (1H, dddd, *J* 17.2, 10.1, 8.3, 6.4 Hz, 4-H), 7.10 (1H, dd, *J* 8.0, 0.9 Hz, 5'-H), 7.41 (1H, d, *J* 0.9 Hz, 3'-H), 7.55 (1H, d, *J* 8.0 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 20.3 (CH_3), 27.4 (CH_3), 45.2 (CH_2), 74.5 (C), 119.2 (CH_2), 119.7 (C), 128.0 (CH), 128.1 (CH), 133.8 (CH), 135.5 (CH), 138.6 (C), 141.9 (C); *m/z* (ESI) 277.0196 (MNa^+. $C_{12}H_{15}{}^{79}BrNaO$ requires 277.0198).

2-(2'-Bromo-5'-fluorophenyl)pent-4-en-2-ol (76c)



The reaction was performed according to general procedure A using 1-(2'-bromo-5'-fluorophenyl)ethan-1-one (**69e**) (0.10 g, 0.46 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2-(2'-bromo-5'-fluorophenyl)pent-4-en-2-ol (**76c**) (0.10 g, 84%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3466 (OH), 2978 (CH), 1576 (C=C), 1458, 1260, 1022, 919, 810, 607; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, s, 1-H_3), 2.52 (1H, s, 2-OH), 2.61 (1H, br dd, *J* 14.0, 8.6 Hz, 3-*H*H), 3.31 (1H, ddt, *J* 14.0, 6.2, 0.9 Hz, 3-H*H*), 5.10–5.20 (2H, m, 5-H_2), 5.53 (1H, dddd, *J* 17.2, 10.1, 8.6, 6.2 Hz, 4-H), 6.83 (1H, ddd, *J* 8.7, 7.1, 3.1 Hz, 4'-H), 7.49 (1H, dd, *J* 11.0, 3.1 Hz, 6'-H), 7.52 (1H, dd, *J* 8.7, 5.4 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 27.0 (CH_3), 44.6 (CH_2), 74.4 (C), 113.6 (d, $^4J_{C\text{-}F}$ 2.9 Hz, C), 115.5 (d, $^2J_{C\text{-}F}$ 22.4 Hz, CH), 115.9 (d, $^2J_{C\text{-}F}$ 25.0 Hz, CH), 119.9 (CH_2), 133.2 (CH), 136.2 (d, $^3J_{C\text{-}F}$ 7.7 Hz, CH), 147.9 (d, $^3J_{C\text{-}F}$ 6.3 Hz, C), 162.1 (d, $^1J_{C\text{-}F}$ 246.1 Hz, C); *m/z* (CI) 241.0036 (MH^+-H_2O. $C_{11}H_{11}{}^{79}BrF$ requires 241.0028), 219 (34%), 217 (37), 166 (37), 140 (84), 95 (37), 81 (42), 74 (79), 69 (62).

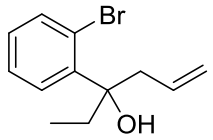
2-(2'-Bromo-5'-chlorophenyl)pent-4-en-2-ol (76d)



The reaction was performed according to general procedure A using 1-(2'-bromo-5'-chlorophenyl)ethan-1-one (**69f**) (0.12 g, 0.50 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2-(2'-bromo-5'-chlorophenyl)pent-4-en-2-ol (**76d**) (0.14 g, 97%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3470 (OH), 2976 (CH), 1640 (C=C), 1449, 1375, 1263, 1107, 1017, 920, 810; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, s, 1-H_3), 2.49 (1H, s, 2-OH), 2.61 (1H, ddt, *J* 14.1, 8.4, 0.8 Hz, 3-*H*H), 3.31 (1H, ddt, *J* 14.1, 6.3, 0.8 Hz, 3-H*H*), 5.11–5.20 (2H, m, 5-H_2), 5.53 (1H, dddd, *J* 17.1, 10.1, 8.4, 6.3 Hz, 4-

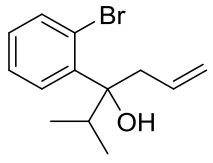
H), 7.08 (1H, dd, *J* 8.4, 2.7 Hz, 4'-H), 7.50 (1H, d, *J* 8.4 Hz, 3'-H), 7.75 (1H, d, *J* 2.7 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 27.1 (CH_3), 44.7 (CH_2), 74.4 (C), 117.6 (C), 120.0 (CH_2), 128.5 (CH), 128.6 (CH), 133.1 (CH), 133.8 (C), 136.1 (CH), 147.1 (C); *m/z* (ESI) 269.9644 (MNa^+. $C_{11}H_{12}{}^{79}Br^{35}ClNaO$ requires 296.9652).

3-(2'-Bromophenyl)hex-5-en-3-ol (76e)



The reaction was performed according to general procedure A using 2'-bromopropiophenone (**69h**) (0.20 g, 0.94 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 3-(2'-bromophenyl)hex-5-en-3-ol (**76e**) (0.20 g, 82%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3549 (OH), 2970 (CH), 1636 (C=C), 1458, 1427, 1358, 1265, 1150, 1018, 972, 918, 756; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, t, *J* 7.4 Hz, 1-H_3), 1.85 (1H, dq, *J* 14.1, 7.4 Hz, 2-*H*H), 2.33 (1H, s, 3-OH), 2.44–2.58 (2H, m, 2-H*H* and 4-*H*H), 3.40 (1H, ddt, *J* 14.1, 6.0, 0.9 Hz, 4-H*H*), 5.06–5.19 (2H, m, 6-H_2), 5.51 (1H, dddd, *J* 17.2, 10.0, 8.7, 6.0 Hz, 5-H), 7.09 (1H, td, *J* 7.8, 1.8 Hz, ArH), 7.30 (1H, td, *J* 7.8, 1.4 Hz ArH), 7.57 (1H, dd, *J* 7.8, 1.4 Hz, ArH), 7.71 (1H, dd, *J* 7.8, 1.8 Hz ArH); δ_c (126 MHz, $CDCl_3$) 7.9 (CH_3), 31.8 (CH_2), 44.0 (CH_2), 77.1 (C), 119.4 (CH_2), 119.7 (C), 127.2 (CH), 128.4 (CH), 129.6 (CH), 133.6 (CH), 134.9 (CH), 143.5 (C); *m/z* (ESI) 277.0196 (MNa^+. $C_{12}H_{15}{}^{79}BrNaO$ requires 227.0198).

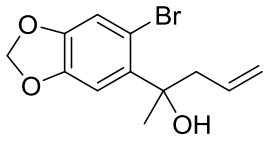
3-(2'-Bromophenyl)-2-methylhex-5-en-3-ol (76f)



The reaction was performed according to general procedure A using 1-(2'-bromophenyl)-2-methylpropan-1-one (**69i**) (0.20 g, 0.88 mmol). Purification by flash column chromatography, eluting with 5% diethyl ether in petroleum ether (40–60) gave 3-(2'-bromophenyl)-2-methylhex-5-en-3-ol (**76f**) (0.17 g, 72%) as a

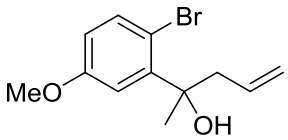
yellow oil. ν_{max}/cm^{-1} (neat) 3557 (OH), 2970 (CH), 1636 (C=C), 1458, 1427, 1234, 1165, 995, 918, 741; δ_H (500 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.9 Hz, 1-H_3), 1.07 (3H, d, *J* 6.9 Hz, 2-CH_3), 2.08 (1H, s, 3-OH), 2.44 (1H, dd, *J* 14.2, 9.1 Hz, 4-*H*H), 2.85 (1H, sept, *J* 6.9 Hz, 2-H), 3.62 (1H, br d, *J* 14.2 Hz, 4-H*H*), 5.00 (1H, br d, *J* 11.0 Hz, 6-*H*H), 5.11 (1H, br d, *J* 17.0 Hz, 6-H*H*), 5.29–5.40 (1H, m, 5-H), 7.06 (1H, td, *J* 7.8, 1.8 Hz, ArH), 7.27 (1H, td, *J* 7.8, 1.3 Hz, ArH), 7.56 (1H, dd, *J* 7.8, 1.3 Hz, ArH), 7.69 (1H, br d, *J* 7.8 Hz, ArH); δ_c (126 MHz, $CDCl_3$) 16.5 (CH_3), 17.5 (CH_3), 33.2 (CH), 41.4 (CH_2), 78.7 (C), 118.9 (CH_2), 119.5 (C), 127.3 (CH), 128.2 (CH), 129.9 (CH), 134.2 (CH), 135.0 (CH), 144.2 (C); *m/z* (ESI) 291.0359 (MNa^+. $C_{13}H_{17}{}^{79}BrNaO$ requires 291.0355).

2-(2'-Bromo-4',5'-methylenedioxyphenyl)pent-4-en-2-ol (76g)



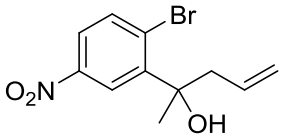
The reaction was performed according to general procedure B using 1-(2'-bromo-4',5'-methylenedioxyphenyl)ethan-1-one (**69c**) (0.10 g, 0.41 mmol). Purification by flash column chromatography, eluting with 10% ethyl acetate in petroleum ether (40–60) gave 2-(2'-bromo-4',5'-methylenedioxyphenyl)pent-4-en-2-ol (**76g**) (0.10 g, 85%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3545 (OH), 2976 (CH), 1639 (C=C), 1502, 1475, 1230, 1036, 932, 846, 734; δ_H (400 MHz, $CDCl_3$) 1.68 (3H, s, 1-H_3), 2.58 (1H, br dd, *J* 13.9, 8.2 Hz, 3-*H*H), 2.60 (1H, s, 2-OH), 3.25 (1H, ddt, *J* 13.9, 6.4, 1.0 Hz, 3-H*H*), 5.07–5.17 (2H, m, 5-H_2), 5.57 (1H, dddd, *J* 16.9, 10.3, 8.2, 6.4 Hz, 4-H), 5.96 (2H, s, OCH_2O), 7.02 (1H, s, 6'-H), 7.26 (1H, s, 3'-H); δ_c (101 MHz, $CDCl_3$) 27.5 (CH_3), 45.1 (CH_2), 74.5 (C), 101.8 (CH_2), 108.4 (CH), 110.1 (C), 114.7 (CH), 119.4 (CH_2), 133.7 (CH), 139.0 (C), 147.0 (C), 147.4 (C); *m/z* (ESI) 306.9940 (MNa^+. $C_{12}H_{13}{}^{79}BrNaO_3$ requires 306.9940).

2-(2'-Bromo-5'-methoxyphenyl)pent-4-en-2-ol (76h)[104]



The reaction was performed according to general procedure B using 1-(2'-bromo-5-methoxyphenyl)ethan-1-one (**69d**) (0.10 g, 0.44 mmol). Purification by flash column chromatography, eluting with 10% ethyl acetate in petroleum ether (40–60) gave 2-(2'-bromo-5'-methoxyphenyl)pent-4-en-2-ol (**76h**) (0.10 g, 84%) as a colourless oil. Spectroscopic data were consistent with the literature.[7] δ_H (400 MHz, $CDCl_3$) 1.70 (3H, s, 1-H_3), 2.60 (1H, br dd, *J* 14.0, 8.3 Hz, 3-*H*H), 2.61 (1H, s, 2-OH), 3.29 (1H, ddt, *J* 14.0, 6.3, 0.9 Hz, 3-H*H*), 3.78 (3H, s, 5'-OCH_3), 5.07–5.18 (2H, m, 5-H_2), 5.56 (1H, dddd, *J* 17.2, 10.1, 8.3, 6.3 Hz, 4-H), 6.64 (1H, dd, *J* 8.7, 3.1 Hz, 4'-H), 7.30 (1H, d, *J* 3.1 Hz, 6'-H), 7.45 (1H, d, *J* 8.7 Hz, 3'-H); δ_c (101 MHz, $CDCl_3$) 27.2 (CH_3), 44.9 (CH_2), 55.4 (CH_3), 74.5 (C), 110.1 (C), 113.7 (CH), 114.5 (CH), 119.4 (CH_2), 133.6 (CH), 135.7 (CH), 146.4 (C), 158.9 (C); *m*/*z* (ESI) 295 (MNa^+. 100%), 293 (98).

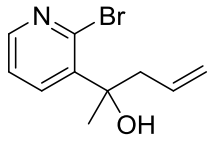
2-(2'-Bromo-5'-nitrophenyl)pent-4-en-2-ol (76i)



The reaction was performed according to general procedure C using 1-(2'-bromo-5'-nitrophenyl)ethan-1-one (**69j**) (0.05 g, 0.2 mmol). Purification by flash column chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) gave 2-(2'-bromo-5'-nitrophenyl)pent-4-en-2-ol (**76i**) (0.04 g, 68%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3528 (OH), 2978 (CH), 2361, 1568 (C=C), 1522, 1343, 1285, 1022, 918, 831, 740; δ_H (400 MHz, $CDCl_3$) 1.77 (3H, s, 1-H_3), 2.57 (1H, s, 2-OH), 2.68 (1H, ddt, *J* 14.1, 8.3, 0.9 Hz, 3-*H*H), 3.32 (1H, ddt, *J* 14.1, 6.6, 0.9 Hz, 3-H*H*), 5.10–5.23 (2H, m, 5-H_2), 5.54 (1H, dddd, *J* 17.2, 9.9, 8.3, 6.6 Hz, 4-H), 7.77 (1H, d, *J* 8.6 Hz, 3'-H), 7.95 (1H, dd, *J* 8.6, 2.8 Hz, 4'-H), 8.67 (1H, d, *J* 2.8 Hz, 6'-H); δ_c (101 MHz, $CDCl_3$) 27.1 (CH_3), 44.4 (CH_2), 74.6 (C), 120.5 (CH_2),

123.0 (CH), 123.7 (CH), 126.9 (C), 132.5 (CH), 136.1 (CH), 147.3 (C), 147.7 (C); *m/z* (ESI) 307.9880 (MNa^+. $C_{11}H_{12}{}^{79}BrNNaO_3$ requires 307.9893).

2-(2'-Bromo-3'-pyridyl)pent-4-en-2-ol (76j)

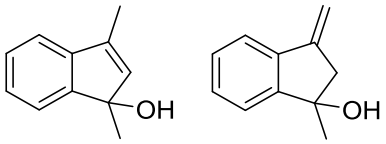


The reaction was performed according to general procedure C using 1-(2'-bromo-3'-pyridyl)ethan-1-one (**69g**) (0.10 g, 0.50 mmol). Purification by flash column chromatography, eluting with 15% ethyl acetate in petroleum ether (40–60) gave 2-(2'-bromo-3'-pyridyl)pent-4-en-2-ol (**76j**) (0.05 g, 41%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3372 (OH), 2970 (CH), 1697 (C=C), 1558, 1381, 1034, 918, 810, 741; δ_H (400 MHz, $CDCl_3$) 1.75 (3H, s, 1-H_3), 2.54 (1H, s, 2-OH), 2.69 (1H, br dd, *J* 14.0, 8.3 Hz, 3-*H*H), 3.31 (1H, br dd, *J* 14.0, 6.6 Hz, 3-H*H*), 5.10–5.21 (2H, m, 5-H_2), 5.56 (1H, dddd, *J* 17.3, 10.0, 8.3, 6.6 Hz, 4-H), 7.28 (1H, dd, *J* 7.8, 4.6 Hz, 5'-H), 8.06 (1H, dd, *J* 7.8, 1.9 Hz, 6'-H), 8.26 (1H, dd, *J* 4.6, 1.9 Hz, 4'-H); δ_c (101 MHz, $CDCl_3$) 27.2 (CH_3), 44.7 (CH_2), 73.5 (C), 120.1 (CH_2), 122.7 (CH), 132.9 (CH), 137.1 (CH), 139.8 (C), 142.8 (C), 148.2 (CH); *m/z* (ESI) 263.9990 (MNa^+. $C_{10}H_{12}{}^{79}BrNNaO$ requires 263.9994).

Step 2: General procedure for Heck reaction and synthesis of racemic 1-alkyl-1-indanols

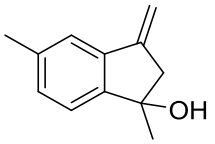
To a stirred solution of a racemic homoallylic alcohol (1 equiv.) in distilled toluene (10 mL/mmol) was added bis(triphenylphosphine)palladium(II) dichloride (7.5 mol%), potassium carbonate (2 equiv.) and hydrazine monohydrate (0.4 equiv.). The reaction vial was sealed and heated to 135 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with diethyl ether (2 mL/mmol). The mixture was filtered through a pad of Celite® and concentrated *in vacuo*. The crude mixture was purified by silica gel flash chromatography, eluting with either diethyl ether in petroleum ether or ethyl acetate in petroleum ether to give the racemic 1-methyl-1-indanols.

1,3-Dimethylinden-1-ol (82a)[104] and 2,3-dihydro-1-methyl-3-(methylene)indan-1-ol (70a)[104]



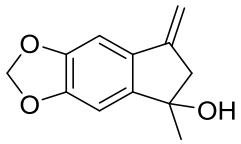
1,3-Dimethylinden-1-ol (**82a**) and 2,3-dihydro-1-methyl-3-(methylene)indan-1-ol (**70a**) were synthesised according to the general procedure using 2-(2'-bromophenyl)pent-4-en-2-ol (**76a**) (0.036 g, 0.150 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield first the *endo*-cyclic isomer **82a** (0.003 g, 13%), and then the *exo*-cyclic isomer **70a** (0.016 g, 65%) as colourless oils. Both compounds solidified upon standing to give white solids. Their melting point were as for **(*S*)-82a** and **(*S*)-70a**. Their spectroscopic data were consistent with the literature.[104]

2,3-Dihydro-1,5-dimethyl-3-(methylene)indan-1-ol (70b)



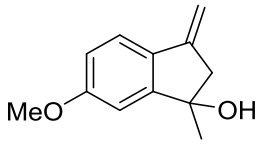
2,3-Dihydro-1,5-dimethyl-3-(methylene)indan-1-ol (**70b**) was synthesised according to the general procedure using 2-(2'-bromo-4'-methylphenyl)pent-4-en-2-ol (**76b**) (0.083 g, 0.330 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70b** (0.040 g, 71%) as a colourless oil. Spectroscopic data as for **(*S*)-70b**.

2,3-Dihydro-5,6-methylenedioxy-1-methyl-3-(methylene)indan-1-ol (70c)



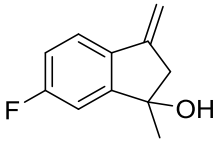
2,3-Dihydro-5,6-methylenedioxy-1-methyl-3-(methylene)indan-1-ol (**70c**) was synthesised according to the general procedure using 2-(2'-bromo-4',5'-methylenedioxyphenyl)pent-4-en-2-ol (**76g**) (0.080 g, 0.280 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70c** (0.021 g, 37%) as a colourless oil. Spectroscopic data as for **(*S*)-70c**.

2,3-Dihydro-6-methoxy-1-methyl-3-(methylene)indan-1-ol (70d)[104]



2,3-Dihydro-6-methoxy-1-methyl-3-(methylene)indan-1-ol (**70d**) was synthesised according to the general procedure using 2-(2'-bromo-5'-methoxyphenyl)pent-4-en-2-ol (**76h**) (0.085 g, 0.320 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70d** (0.031 g, 51%) as a yellow oil. Spectroscopic data for were consistent with the literature.[104]

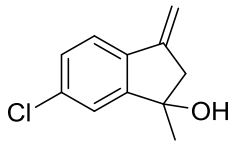
2,3-Dihydro-6-fluoro-1-methyl-3-(methylene)indan-1-ol (70e)



2,3-Dihydro-6-fluoro-1-methyl-3-(methylene)indan-1-ol (**70e**) was synthesised according to the general procedure using 2-(2'-bromo-5'-fluorophenyl)pent-4-en-2-ol (**76c**) (0.100 g, 0.390 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60)

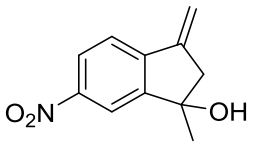
to yield the *exo*-cyclic isomer **70e** (0.040 g, 58%) as a colourless oil. Spectroscopic data as for **(*S*)-70e**.

2,3-Dihydro-6-chloro-1-methyl-3-(methylene)indan-1-ol (70f)



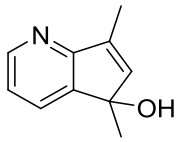
2,3-Dihydro-6-chloro-1-methyl-3-(methylene)indan-1-ol (**70f**) was synthesised according to the general procedure using 2-(2'-bromo-5'-chlorophenyl)pent-4-en-2-ol (**76d**) (0.090 g, 0.330 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% diethyl ether in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70f** (0.021 g, 33%) as a colourless oil. Spectroscopic data as for **(*S*)-70f**.

2,3-Dihydro-6-nitro-1-methyl-3-(methylene)indan-1-ol (70g)



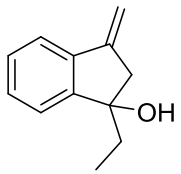
2,3-Dihydro-6-nitro-1-methyl-3-(methylene)indan-1-ol (**70g**) was synthesised according to the general procedure using 2-(2'-bromo-5'-nitrophenyl)pent-4-en-2-ol (**76i**) (0.029 g, 0.100 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 30% diethyl ether in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70g** (0.009 g, 41%) as a yellow oil. Spectroscopic data as for **(*S*)-70g**.

5,7-Dimethylcyclopenta[b]pyridin-5-ol (82h)



5,7-Dimethylcyclopenta[b]pyridin-5-ol (**82h**) was synthesised according to the general procedure using 2-(2'-bromo-3'-pyridyl)pent-4-en-2-ol (**76j**) (0.035 g, 0.140 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 10% ethyl acetate in petroleum ether (40–60) to yield the *endo*-cyclic isomer **70h** (0.004 g, 18%) as a yellow oil. Spectroscopic data as for **(*S*)-82h**.

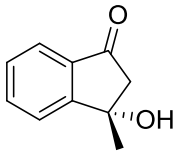
2,3-Dihydro-1-ethyl-3-(methylene)indan-1-ol (70i)



2,3-Dihydro-1-ethyl-3-(methylene)indan-1-ol (**70i**) was synthesised according to the general procedure using 3-(2'-bromophenyl)hex-5-en-3-ol (**76e**) (0.043 g, 0.170 mmol). The crude mixture was purified by silica gel flash chromatography, eluting with 7.5% ethyl acetate in petroleum ether (40–60) to yield the *exo*-cyclic isomer **70i** (0.010 g, 34%) as a yellow oil. Spectroscopic data as for **(*S*)-70i**.

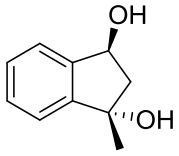
Functionalisation of (*S*)-70a

(3*S*)-2,3-Dihydro-3-hydroxy-3-methyl-1-indanone (83)



(3*S*)-2,3-Dihydro-1-methyl-3-(methylene)indan-1-ol [**(*S*)-70a**] (0.300 g, 1.87 mmol) was dissolved in a mixture of dichloromethane (60 mL) and methanol (60 mL) and cooled to −78 °C. The reaction mixture was purged with oxygen and then ozone was bubbled through until the clear solution turned to blue. The excess ozone was purged with oxygen and then with argon. Triphenylphosphine (1.47 g, 5.61 mmol) was added portionwise to the mixture with vigorous stirring. The reaction mixture was allowed to return to room temperature over 2 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to give (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.250 g, 81%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3393 (OH), 2972 (CH), 1701 (C=O), 1603 (C=C), 1464, 1288, 1242, 1080, 768; $[\alpha]_D^{31}$ +96.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73 (3H, s, 3-CH_3), 2.15 (1H, s, 3-OH), 2.91 (2H, s, 2-H_2), 7.45–7.53 (1H, m, ArH), 7.68–7.75 (3H, m, ArH); δ_c (101 MHz, $CDCl_3$) 29.3 (CH_3), 53.8 (CH_2), 74.5 (C), 123.2 (CH), 123.6 (CH), 129.4 (CH), 135.4 (C), 135.6 (CH), 158.6 (C), 203.2 (C); *m/z* (EI) 162.0680 (M^+. $C_{10}H_{10}O_2$ requires 162.0681), 147 (100%), 129 (53), 115 (43), 91 (22), 84 (38), 77 (19).

(1*S*,3*S*)-2,3-Dihydro-1-(methyl)indane-1,3-diol (84)



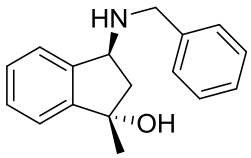
To a stirred solution of (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.020 g, 0.12 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (0.038 g, 0.18 mmol) and acetic acid (0.0070 mL, 0.12

mmol) at room temperature under an argon atmosphere. Sodium triacetoxyborohydride (0.038 g, 0.18 mmol) and acetic acid (0.0070 mL, 0.12 mmol) were then added after two days. The reaction mixture was stirred at room temperature for a total of 6 days and then quenched with 1 M sodium hydroxide solution (2 mL). After phase separation, the aqueous layer was extracted with dichloromethane (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash column chromatography, eluting with 5% methanol in dichloromethane gave (1*S*,3*S*)-2,3-dihydro-1-(methyl)indane-1,3-diol (**84**) (0.015 g, 75% yield) as a white solid. Mp 97–99 °C; ν_{max}/cm^{-1} (neat) 3331 (OH), 2967 (CH), 2361 (CH), 1373, 1200, 1092, 1053, 864, 752, 621; $[\alpha]_D^{31}$ +48.5 (*c* 0.6, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.70 (3H, s, 1-CH_3), 1.76 (1H, s, OH), 1.90 (1H, s, OH), 2.10 (1H, dd, *J* 13.7, 5.0 Hz, 2-*H*H), 2.63 (1H, dd, *J* 13.7, 6.7 Hz, 2-H*H*), 5.41 (1H, t, *J* 5.7 Hz, 3-H), 7.33–7.45 (4H, m, ArH); δ_c (101 MHz, $CDCl_3$) 28.7 (CH_3), 52.6 (CH_2), 73.6 (CH), 79.4 (C), 122.3 (CH), 124.5 (CH), 129.1 (CH), 129.1 (CH), 144.3 (C), 147.4 (C); *m/z* (ESI) 187.0730 (MNa^+. $C_{10}H_{12}NaO_2$ requires 187.0730).

General procedure for the reductive amination reactions

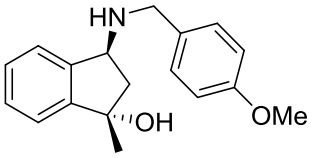
To a stirred solution of (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (1 equiv.) in 1,2-dichloroethane (2 mL/mmol) was added the amine (1.1–1.5 equiv.) and sodium triacetoxyborohydride (1.4–1.5 equiv) at room temperature under an argon atmosphere. The same amounts of amine and hydride source were added after two days. The reaction mixture was stirred at room temperature up to 6 days and then quenched with 1 M sodium hydroxide solution (2 mL/mmol). After phase separation, the aqueous layer was extracted with dichloromethane (2 × 5 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material using silica gel flash column chromatography, eluting with methanol in dichloromethane gave the 3-amino-substituted 2,3-dihydro-1-(methyl)indane-1-ols.

(1*S*,3*S*)-3-Benzylamino-2,3-dihydro-1-(methyl)indane-1-ol (85a)



The reaction was performed according to the general procedure using (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.032 g, 0.20 mmol) and benzylamine (0.024 mL, 0.22 mmol). The reaction mixture was stirred at room temperature for 3 days. Purification of the crude material using silica gel flash column chromatography, eluting with 5% methanol in dichloromethane gave (1*S*,3*S*)-3-benzylamino-2,3-dihydro-1-(methyl)indane-1-ol (**85a**) (0.042 g, 84%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3312 (NH and OH), 2965 (CH), 1452, 1113, 930, 766, 752, 734, 698; $[\alpha]_D^{31}$ +22.9 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.60–1.77 (5H, m, 1-CH_3, 1-OH and 3-NH), 1.98 (1H, dd, *J* 13.2, 6.5 Hz, 2-*H*H), 2.59 (1H, dd, *J* 13.2, 6.5 Hz, 2-H*H*), 3.88 (1H, d, *J* 13.0 Hz, N-C*H*H), 3.93 (1H, d, *J* 13.0 Hz, N-CH*H*), 4.48 (1H, t, *J* 6.5 Hz, 3-H), 7.22–7.44 (9H, m, ArH); δ_c (126 MHz, $CDCl_3$) 28.1 (CH_3), 50.4 (CH_2), 51.7 (CH_2), 59.8 (CH), 79.4 (C), 122.3 (CH), 124.5 (CH), 127.0 (CH), 128.2 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 128.7 (CH), 140.5 (C), 145.0 (C), 147.4 (C); *m*/*z* (ESI) 254.1534 (MH^+. $C_{17}H_{20}NO$ requires 254.1539).

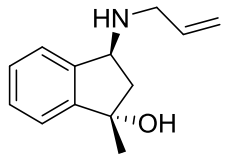
(1*S*,3*S*)-2,3-Dihydro-3-(4'-methoxybenzyl)amino-1-(methyl)indane-1-ol (85b)



The reaction was performed according to the general procedure using (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.020 g, 0.12 mmol) and 4-methoxybenzylamine (0.018 mL, 0.014 mmol). The reaction mixture was stirred at room temperature for 6 days. Purification of the crude material using silica gel flash column chromatography, eluting with 5% methanol in dichloromethane gave (1*S*,3*S*)-2,3-dihydro-3-(4'-methoxybenzyl)amino-1-(methyl)indane-1-ol (**85b**) (0.029 g, 84%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3360 (NH and OH), 2961 (CH), 2359 (CH), 1611 (C=C), 1512, 1246, 1034, 824, 768, 746; $[\alpha]_D^{31}$ +19.1 (*c*

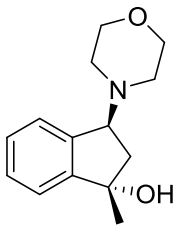
1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50–1.77 (5H, m, 1-CH_3, 1-OH and 3-NH), 1.99 (1H, dd, *J* 13.3, 6.5 Hz, 2-*H*H), 2.60 (1H, dd, *J* 13.3, 6.5 Hz, 2-H*H*), 3.80 (3H, s, 4'-OCH_3), 3.83 (1H, d, *J* 12.8 Hz, N-C*H*H), 3.88 (1H, d, *J* 12.8 Hz, N-CH*H*), 4.49 (1H, t, *J* 6.5 Hz, 3-H), 6.83–6.91 (2H, m, ArH), 7.27–7.43 (6H, m, ArH); δ_c (101 MHz, $CDCl_3$) 28.1 (CH_3), 50.4 (CH_2), 51.2 (CH_2), 55.3 (CH_3), 59.7 (CH), 79.4 (C), 113.8 (2 × CH), 122.2 (CH), 124.4 (CH), 128.2 (CH), 128.7 (CH), 129.3 (2 × CH), 132.6 (C), 145.1 (C), 147.3 (C), 158.7 (C); *m*/*z* (ESI) 284.1640 (MH^+. $C_{18}H_{22}NO_2$ requires 284.1645).

(1*S*,3*S*)-3-Allylamino-2,3-dihydro-1-(methyl)indane-1-ol (85c)



The reaction was performed according to the general procedure using (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.020 g, 0.12 mmol) and allylamine (0.013 mL, 0.18 mmol). The reaction mixture was stirred at room temperature for 6 days. Purification of the crude material using silica gel flash column chromatography, eluting with 5% methanol in dichloromethane gave (1*S*,3*S*)-3-allylamino-2,3-dihydro-1-(methyl)indane-1-ol (**85c**) (0.019 g, 78%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3329 (NH and OH), 2967 (CH), 2924 (CH), 1452, 1370, 1109, 924, 766, 752; $[\alpha]_D^{31}$ +30.3 (*c* 0.8, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.55–1.85 (5H, m, 1-CH_3, 1-OH and 3-NH), 1.93 (1H, dd, *J* 13.3, 6.7 Hz, 2-*H*H), 2.60 (1H, dd, *J* 13.3, 6.7 Hz, 2-H*H*), 3.37 (1H, dd, *J* 15.0, 5.0 Hz, 1'-*H*H), 3.42 (1H, dd, *J* 15.0, 5.0 Hz, 1'-H*H*), 4.49 (1H, t, *J* 6.7 Hz, 3-H), 5.13 (1H, dd, *J* 10.0, 1.0 Hz, 3'-*H*H), 5.25 (1H, dd, *J* 15.0, 1.0 Hz, 3'-H*H*), 5.98 (1H, ddt, *J* 15.0, 10.0, 5.0 Hz, 2'-H), 7.28–7.44 (4H, m, ArH); δ_c (126 MHz, $CDCl_3$) 28.0 (CH_3), 50.2 (CH_2), 50.4 (CH_2), 59.7 (CH), 79.3 (C), 116.2 (CH_2), 122.3 (CH), 124.4 (CH), 128.3 (CH), 128.8 (CH), 136.7 (CH), 144.8 (C), 147.3 (C); *m*/*z* (ESI) 204.1382 (MH^+. $C_{13}H_{18}NO$ requires 204.1383).

(1*S*,3*S*)-2,3-Dihydro-1-methy-3-(morpholino)indane-1-ol (85d)



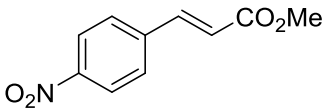
The reaction was performed according to the general procedure using (3*S*)-2,3-dihydro-3-hydroxy-3-methyl-1-indanone (**83**) (0.020 g, 0.12 mmol) and morpholine (0.016 mL, 0.18 mmol). The reaction mixture was stirred at room temperature for 6 days. Purification of the crude material using silica gel flash column chromatography, eluting with 8% methanol in dichloromethane gave (1*S*,3*S*)-2,3-dihydro-1-methy-3-(morpholino)indane-1-ol (**85d**) (0.022 g, 79%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3410 (NH and OH), 2961 (CH), 2855 (CH), 1452, 1350, 1138, 1115, 1009, 868, 766; $[\alpha]_D^{31}$ +74.8 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.65–1.77 (4H, m, 1-CH_3 and 1-OH), 2.20 (2H, d, *J* 7.2 Hz, 2-H_2), 2.48 (2H, dd, *J* 12.0, 8.0 Hz, 2 × NC*H*H), 2.53 (2H, dd, *J* 12.0, 8.0 Hz, 2 × NCH*H*), 3.71 (4H, t, *J* 8.0 Hz, 2 × OCH_2), 4.54 (1H, t, *J* 7.2 Hz, 3-H), 7.28–7.42 (4H, m, ArH); δ_c (101 MHz, $CDCl_3$) 27.5 (CH_3), 40.5 (CH_2), 49.2 (2 × CH_2), 67.2 (CH), 67.4 (2 × CH_2), 79.1 (C), 122.2 (CH), 125.5 (CH), 128.3 (CH), 128.5 (CH), 142.5 (C), 147.6 (C); *m*/*z* (ESI) 234.1490 (MH^+. $C_{14}H_{20}NO_2$ requires 234.1489).

3.3 Methyl Cinnamate and 3,4-Dihydroquinoline-2-one Experimental

General procedure for the preparation of the polymer-supported nitrite

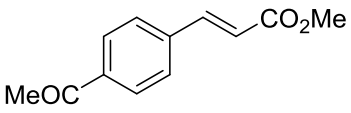
To a stirred solution of sodium nitrite (0.55 g, 8.00 mmol) in water (20 mL) was added Amberlyst® A26 hydroxide form resin (1.00 g, 4.00 mmol). The resulting mixture was stirred at room temperature for 0.5 h, and then polymer-supported resin was filtered and washed with water until the pH of filtrate became neutral. The content of prepared polymer-supported nitrite was 3.5 mmol of NO_2 per g of resin.[69]

Methyl (*E*)-3-(4'-nitrophenyl)acrylate (50a)[64]



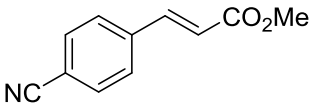
To a stirred solution of 4-nitroaniline (0.028 g, 0.20 mmol), polymer-supported nitrite (0.17 g, containing 0.60 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.10 g, 0.60 mmol) and palladium(II) acetate (0.0020 g, 0.010 mmol) in methanol (2 mL) was added methyl acrylate (0.090 mL, 1.0 mmol). The reaction mixture was heated to 60 °C and stirred for 1.5 h. The mixture was cooled to room temperature, filtered and the resin was washed with methanol (2 mL). The combined organic layers were concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) (0.028 g, 68%) as a pale yellow solid. Mp 159–161 °C (lit.[64] 160–162 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.56 (1H, d, *J* 16.1 Hz, 2-H), 7.67 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.71 (1H, d, *J* 16.1 Hz, 3-H), 8.24 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 122.1 (CH), 124.2 (2 × CH), 128.7 (2 × CH), 140.5 (C), 141.9 (CH), 148.6 (C), 166.5 (C); *m/z* (EI) 207 (M^+. 66%), 176 (100), 130 (24), 102 (26).

Methyl (*E*)-3-(4'-acetylphenyl)acrylate (98a)[204]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-aminoacetophenone (0.050 g, 0.37 mmol), polymer-supported nitrite (0.32 g, containing 1.1 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.19 g, 1.1 mmol), palladium(II) acetate (0.0040 g, 0.019 mmol) and methyl acrylate (0.17 mL, 1.9 mmol). Purification by silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-acetylphenyl)acrylate (**98a**) (0.050 g, 64%) as an orange oil. Spectroscopic data were consistent with the literature.[204] δ_H (400 MHz, $CDCl_3$) 2.62 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 6.53 (1H, d, *J* 16.1 Hz, 2-H), 7.61 (2H, d, *J* 8.3 Hz, 2'-H, and 6'-H), 7.71 (1H, d, *J* 16.1 Hz, 3-H), 7.97 (2H, d, *J* 8.3 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 26.6 (CH_3), 51.9 (CH_3), 120.3 (CH), 128.1 (2 × CH), 128.8 (2 × CH), 138.1 (C), 138.7 (C), 143.3 (CH), 166.9 (C), 197.2 (C); *m*/*z* (ESI) 205 (MH^+. 100%).

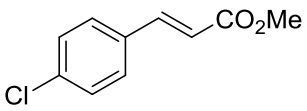
Methyl (*E*)-3-(4'-cyanophenyl)acrylate (98b)[205]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-aminobenzonitrile (0.050 g, 0.42 mmol), polymer-supported nitrite (0.36 g, containing 1.3 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.22 g, 1.3 mmol), palladium(II) acetate (0.005 g, 0.02 mmol) and methyl acrylate (0.19 mL, 2.1 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-cyanophenyl)acrylate (**98b**) (0.046 g, 59%) as a yellow solid. Mp 120–122 °C (lit.[205] 121–122 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.52 (1H, d, *J* 16.0 Hz, 2-H), 7.61 (2H, d, *J* 8.3 Hz, 2'-H and 6'-H), 7.64–7.71 (3H, m, 3-H, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 113.5 (C), 118.4 (C), 121.4 (CH), 128.4 (2

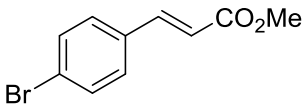
× CH), 132.7 (2 × CH), 138.7 (C), 142.4 (CH), 166.6 (C); *m*/*z* (EI) 187 (M^+. 50%), 156 (100), 128 (42), 84 (27).

Methyl (*E*)-3-(4'-chlorophenyl)acrylate (98c)[65]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-chloroaniline (0.050 g, 0.39 mmol), polymer-supported nitrite (0.33 g, containing 1.2 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.20 g, 1.2 mmol), palladium(II) acetate (0.0040 g, 0.020 mmol) and methyl acrylate (0.18 mL, 2.0 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-chlorophenyl)acrylate (**98c**) (0.040 g, 53%) as a yellow solid. Mp 73–75 °C (lit.[65] 74–75 °C); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 6.41 (1H, d, *J* 16.0 Hz, 2-H), 7.35 (2H, d, *J* 8.5 Hz, 3'-H and 5'-H), 7.45 (2H, d, *J* 8.5 Hz, 2'-H and 6'-H), 7.63 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.8 (CH_3), 118.4 (CH), 129.2 (2 × CH), 129.2 (2 × CH), 132.9 (C), 136.2 (C), 143.4 (CH), 167.2 (C); *m*/*z* (EI) 196 (M^+. 68%), 165 (100), 137 (27), 101 (24), 78 (22), 63 (25).

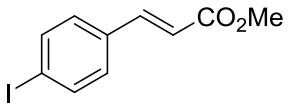
Methyl (*E*)-3-(4'-bromophenyl)acrylate (98d)[205]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-bromoaniline (0.050 g, 0.29 mmol), polymer-supported nitrite (0.25 g, containing 0.87 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.15 g, 0.87 mmol), palladium(II) acetate (0.0030 g, 0.015 mmol) and methyl acrylate (0.13 mL, 1.5 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.050 g, 72%) as a yellow solid. Mp 86–88 °C (lit.[205] 87–88 °C); δ_H (400 MHz,

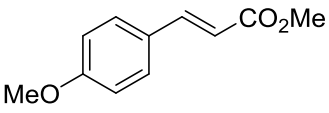
$CDCl_3$) 3.81 (3H, s, OCH_3), 6.43 (1H, d, *J* 16.0 Hz, 2-H), 7.38 (2H, d, *J* 8.5 Hz, 3'-H and 5'-H), 7.52 (2H, d, *J* 8.5 Hz, 2'-H and 6'-H), 7.62 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.8 (CH_3), 118.5 (CH), 124.6 (C), 129.5 (2 × CH), 132.2 (2 × CH), 133.3 (C), 143.5 (CH), 167.2 (C); *m*/*z* (EI) 242 (M^+. 95%), 240 (96), 211 (99), 209 (100), 102 (87), 84 (55).

Methyl (*E*)-3-(4'-iodophenyl)acrylate (98e)[205]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-iodoaniline (0.050 g, 0.23 mmol), polymer-supported nitrite (0.20 g, containing 0.69 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.12 g, 0.69 mmol), palladium(II) acetate (0.0030 g, 0.012 mmol) and methyl acrylate (0.10 mL, 1.2 mmol). Purification by alumina flash column chromatography, eluting with 2% diethyl ether in hexane gave methyl (*E*)-3-(4'-iodophenyl)acrylate (**98e**) (0.036 g, 55%) as a white solid. Mp 117–119 °C (lit.[205] 119–124 °C); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 6.44 (1H, d, *J* 16.0 Hz, 2-H), 7.24 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.60 (1H, d, *J* 16.0 Hz, 3-H), 7.73 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 51.8 (CH_3), 96.5 (C), 118.6 (CH), 129.5 (2 × CH), 133.9 (C), 138.1 (2 × CH), 143.7 (CH), 167.2 (C); *m*/*z* (EI) 288 (M^+. 96%), 257 (40), 130 (27), 102 (20), 84 (100).

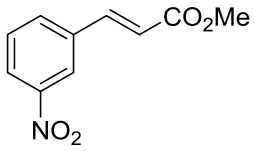
Methyl (*E*)-3-(4'-methoxyphenyl)acrylate (98f)[206]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-methoxyaniline (0.050 g, 0.41 mmol), polymer-supported nitrite (0.35 g, containing 1.2 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.2 mmol), palladium(II) acetate (0.0050 g, 0.021 mmol) and methyl acrylate (0.18 mL, 2.1 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with

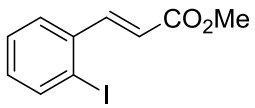
20% diethyl ether in hexane gave methyl (*E*)-3-(4'-methoxyphenyl)acrylate (**98f**) (0.052 g, 66%) as a white solid. Mp 85–87 °C (lit.[206] 86 °C); δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.31 (1H, d, *J* 16.0 Hz, 2-H), 6.90 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.47 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.65 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.6 (CH_3), 55.4 (CH_3), 114.3 (2 × CH), 115.3 (CH), 127.2 (C), 129.7 (2 × CH), 144.5 (CH), 161.4 (C), 167.8 (C); *m*/*z* (ESI) 193 (MH^+. 100%).

Methyl (*E*)-3-(3'-nitrophenyl)acrylate (98g)[207]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 3-nitroaniline (0.050 g, 0.36 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.19 g, 1.1 mmol), palladium(II) acetate (0.0040 g, 0.018 mmol) and methyl acrylate (0.16 mL, 1.8 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 5% diethyl ether in hexane gave methyl (*E*)-3-(3'-nitrophenyl)acrylate (**98g**) (0.040 g, 54%) as a pale yellow solid. Mp 120–122 °C (lit.[6] 122–123 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.56 (1H, d, *J* 16.0 Hz, 2-H), 7.58 (1H, t, *J* 8.0 Hz, 5'-H), 7.72 (1H, d, *J* 16.0 Hz, 3-H), 7.82 (1H, br d, *J* 8.0 Hz, 6'-H), 8.22 (1H, ddd, *J* 8.0, 2.0, 0.8 Hz, 4'-H), 8.37 (1H, t, *J* 2.0 Hz, 2'-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 121.0 (CH), 122.5 (CH), 124.6 (CH), 130.0 (CH), 133.6 (CH), 136.1 (C), 142.0 (CH), 148.7 (C), 166.6 (C); *m*/*z* (ESI) 230 (MNa^+. 100%).

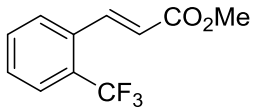
Methyl (*E*)-3-(2'-iodophenyl)acrylate (98h)[208]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-iodoaniline (0.050 g, 0.23

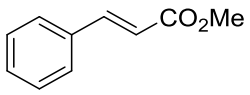
mmol), polymer-supported nitrite (0.20 g, containing 0.69 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.12 g, 0.69 mmol), palladium(II) acetate (0.0030 g, 0.011 mmol) and methyl acrylate (0.10 mL, 1.2 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 2% diethyl ether in hexane gave methyl (*E*)-3-(2'-iodophenyl)acrylate (**98h**) (0.042 g, 63%) as a yellow oil. Spectroscopic data were consistent with the literature.[208] δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 6.31 (1H, d, *J* 15.8 Hz, 2-H), 7.05 (1H, td, *J* 8.0, 1.6 Hz, 4'-H), 7.35 (1H, td, *J* 8.0, 1.2 Hz, 5'-H), 7.55 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 7.89 (1H, dd, *J* 8.0, 1.2 Hz, 3'-H), 7.90 (1H, d, *J* 15.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.9 (CH_3), 101.2 (C), 120.8 (CH), 127.4 (CH), 128.6 (CH), 131.3 (CH), 137.8 (C), 140.0 (CH), 147.9 (CH), 166.7 (C); *m/z* (ESI) 311 (MNa^+. 100%).

Methyl (*E*)-3-[2'-(trifluoromethyl)phenyl]acrylate (98i)[209]



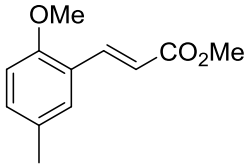
The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-trifluoromethylaniline (0.040 mL, 0.31 mmol), polymer-supported nitrite (0.27 g, containing 0.93 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.93 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.14 mL, 1.6 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-[2'-(trifluoromethyl)phenyl]acrylate (**98i**) (0.059 g, 83%) as a yellow oil. Spectroscopic data were consistent with the literature.[209] δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.41 (1H, d, *J* 16.0 Hz, 2-H), 7.48 (1H, t, *J* 8.0 Hz, 4'-H), 7.57 (1H, t, *J* 8.0 Hz, 5'-H), 7.70 (2H, br d, *J* 8.0 Hz, 3'-H and 6'-H), 8.06 (1H, dq, *J* 16.0, 2.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.9 (CH_3), 122.2 (CH), 123.9 (q, $^1J_{C\text{-}F}$ 274.0 Hz, C), 126.2 (q, $^3J_{C\text{-}F}$ 5.6 Hz, CH), 127.9 (CH), 128.9 (q, $^2J_{C\text{-}F}$ 30.4 Hz, C), 129.6 (CH), 132.1 (q, $^4J_{C\text{-}F}$ 1.0 Hz, CH), 133.4 (q, $^3J_{C\text{-}F}$ 1.3 Hz, C), 140.3 (q, $^4J_{C\text{-}F}$ 1.9 Hz, CH), 166.5 (C); *m/z* (ESI) 231 (MH^+. 100%).

Methyl (*E*)-3-phenylacrylate (98j)[205]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using aniline (0.050 mL, 0.54 mmol), polymer-supported nitrite (0.46 g, containing 1.6 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.28 g, 1.6 mmol), palladium(II) acetate (0.012 g, 0.054 mmol) and methyl acrylate (0.24 mL, 2.7 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-phenylacrylate (**98j**) (0.039 g, 45%) as a yellow oil. Spectroscopic data were consistent with the literature.[205] δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.45 (1H, d, *J* 16.0 Hz, 2-H), 7.35–7.42 (3H, m, 3'-H, 4'-H and 5'-H), 7.49–7.56 (2H, m, 2'-H and 6'-H), 7.70 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.7 (CH_3), 117.8 (CH), 128.1 (2 × CH), 128.9 (2 × CH), 130.3 (CH), 134.4 (C), 144.9 (CH), 167.4 (C); *m/z* (EI) 162 (M^+. 67%), 131 (100), 103 (49), 77 (39).

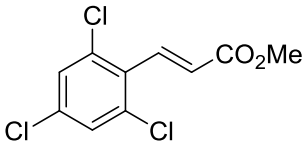
Methyl (*E*)-3-(2'-methoxy-5'-methylphenyl)acrylate (98k)[210]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-methoxy-5-methylaniline (0.050 g, 0.36 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.19 g, 1.1 mmol), palladium(II) acetate (0.0040 g, 0.018 mmol) and methyl acrylate (0.16 mL, 1.8 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(2'-methoxy-5'-methylphenyl)acrylate (**98k**) (0.045 g, 60%) as a yellow oil. Spectroscopic data were consistent with the literature.[210] δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, 5'-CH_3), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.52 (1H, d, *J* 16.0

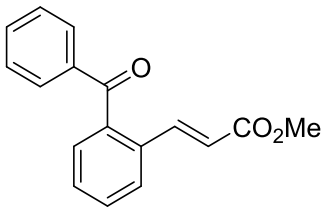
Hz, 2-H), 6.81 (1H, d, *J* 8.4 Hz, 3'-H), 7.14 (1H, dd, *J* 8.4, 2.0 Hz, 4'-H), 7.31 (1H, d, *J* 2.0 Hz, 6'-H), 7.97 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 51.6 (CH_3), 55.6 (CH_3), 111.1 (CH), 118.1 (CH), 123.0 (C), 129.4 (CH), 129.9 (C), 132.0 (CH), 140.4 (CH), 156.4 (C), 168.0 (C); *m*/*z* (ESI) 229 (MNa^+. 100%).

Methyl (*E*)-3-(2',4',6'-trichlorophenyl)acrylate (98l)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2,4,6-trichloroaniline (0.050 g, 0.25 mmol), polymer-supported nitrite (0.21 g, containing 0.75 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.13 g, 0.75 mmol), palladium(II) acetate (0.0030 g, 0.010 mmol) and methyl acrylate (0.11 mL, 1.3 mmol). Purification by silica gel flash column chromatography, eluting with 2% diethyl ether in hexane gave methyl (*E*)-3-(2',4',6'-trichlorophenyl)acrylate (**98l**) (0.045 g, 68%) as a pale yellow solid. Mp 64–66 °C; ν_{max}/cm^{-1} (neat) 2926 (CH), 1726 (C=O), 1651 (C=C), 1314, 1292, 1202, 1173, 970; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.57 (1H, d, *J* 16.4 Hz, 2-H), 7.37 (2H, s, 3'-H and 5'-H), 7.70 (1H, d, *J* 16.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 126.8 (CH), 128.8 (2 × CH), 130.6 (C), 134.9 (C), 135.5 (2 × C), 137.3 (CH), 166.4 (C); *m*/*z* (EI) 228.9821 ($[M\text{-}Cl]^-$. $C_{10}H_7{}^{35}Cl_2O_2$ requires 228.9823), 207 (13%), 170 (17), 84 (39).

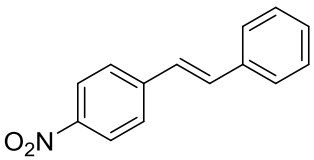
Methyl (*E*)-3-(2'-benzoylphenyl)acrylate (98m)[211]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-aminobenzophenone (0.050

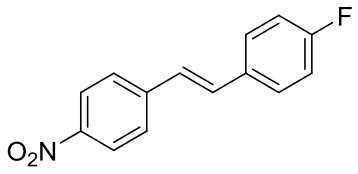
g, 0.25 mmol), polymer-supported nitrite (0.21 g, 0.75 mmol), *p*-toluenesulfonic acid monohydrate (0.13 g, 0.75 mmol), palladium(II) acetate (0.0030, 0.013 mmol) and methyl acrylate (0.11 mL, 1.3 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 5% diethyl ether in hexane gave methyl (*E*)-3-(2'-benzoylphenyl)acrylate (**98m**) as a yellow oil (0.047 g, 71%). Spectroscopic data were consistent with the literature.[211] δ_H (400 MHz, $CDCl_3$) 3.72 (3H, s, OCH_3), 6.38 (1H, d, *J* 16.0 Hz, 2-H), 7.39–7.49 (4H, m, 4 × ArH), 7.53 (1H, td, *J* 7.6, 2.4 Hz, ArH), 7.60 (1H, ddt, *J* 7.6, 7.2, 1.2 Hz, ArH), 7.71–7.82 (4H, m, 3-H and 3 × ArH); δ_C (101 MHz, $CDCl_3$) 51.7 (CH_3), 120.5 (CH), 127.3 (CH), 128.6 (2 × CH), 129.2 (CH), 129.2 (CH), 130.4 (2 × CH), 130.8 (CH), 133.6 (CH), 133.9 (C), 137.3 (C), 139.4 (C), 142.0 (CH), 166.8 (C), 197.2 (C); *m*/*z* (ESI) 289 (MNa^+. 100%).

(*E*)-1-Nitro-4-styrylbenzene (52a)[212]



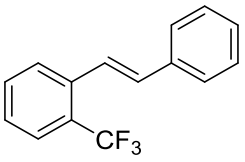
The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-nitroaniline (0.050 g, 0.36 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.19 g, 1.1 mmol), palladium(II) acetate (0.0080 g, 0.036 mmol) and styrene (0.21 mL, 1.8 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with, 10% diethyl ether in hexane gave (*E*)-1-nitro-4-styrylbenzene (**52a**) (0.060 g, 74%) as a yellow solid. Mp 154–156 °C (lit.[212] 155–158 °C); δ_H (400 MHz, $CDCl_3$) 7.14 (1H, d, *J* 16.4 Hz, 1'-H), 7.27 (1H, d, *J* 16.4 Hz, 2'-H), 7.31–7.44 (3H, m, 3 × ArH), 7.53–7.58 (2H, m, 2 × ArH), 7.63 (2H, d, *J* 8.8 Hz, 3-H and 5-H), 8.22 (2H, d, *J* 8.8 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 124.2 (2 × CH), 126.3 (CH), 126.9 (2 × CH), 127.0 (2 × CH), 128.9 (CH), 128.9 (2 × CH), 133.3 (CH), 136.2 (C), 143.9 (C), 146.8 (C); *m*/*z* (EI) 225 (M^+. 100%), 178 (84), 152 (21), 84 (35).

(*E*)-4-Fluoro-1-(4''-nitrostyryl)benzene (104a)[213]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-nitroaniline (0.050 g, 0.36 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 1.1 mmol), palladium(II) acetate (0.0040 g, 0.018 mmol) and 4-fluorostyrene (0.22 mL, 1.8 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave (*E*)-4-fluoro-1-(4''-nitrostyryl)benzene (**104a**) (0.040 g, 46%) as a yellow solid. Mp 110–113 °C (lit.[213] 110–114 °C); δ_H (400 MHz, $CDCl_3$) 7.03–7.13 (3H, m, 2 × ArH and 2'-H), 7.22 (1H, d, *J* 16.0 Hz, 1'-H), 7.49–7.56 (2H, m, 2 × ArH), 7.61 (2H, d, *J* 8.4 Hz, 2''-H and 6''-H), 8.21 (2H, d, *J* 8.4 Hz, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 116.0 (d, $^2J_{C\text{-}F}$ 21.9 Hz, 2 × CH), 124.2 (2 × CH), 126.1 (d, $^5J_{C\text{-}F}$ 2.4 Hz, CH), 126.8 (2 × CH), 128.7 (d, $^3J_{C\text{-}F}$ 8.1 Hz, 2 × CH), 132.0 (d, $^6J_{C\text{-}F}$ 0.8 Hz, CH), 132.4 (d, $^4J_{C\text{-}F}$ 3.3 Hz, C), 143.7 (C), 146.8 (C), 163.0 (d, $^1J_{C\text{-}F}$ 250.3 Hz, C); *m/z* (EI) 243 (M^+. 72%), 196 (62), 179 (32), 84 (100), 51 (42).

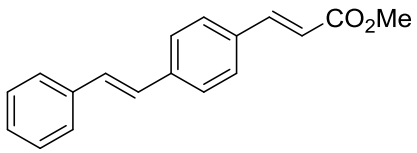
(*E*)-2-Styryl-1-(trifluoromethyl)benzene (104b)[214]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-trifluoromethyaniline (0.040 mL, 0.31 mmol), polymer-supported nitrite (0.27 g, containing 0.93 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.93 mmol), palladium(II) acetate (0.0080 g, 0.031 mmol) and styrene (0.18 mL, 1.6 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave (*E*)-2-styryl-1-(trifluoromethyl)benzene (**104b**)

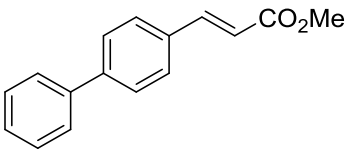
(0.070 g, 46%) as a yellow oil. Spectroscopic data were consistent with the literature.[214] δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* 16.0 Hz, 1'-H), 7.28–7.43 (4H, m, 3 × ArH and 2'-H), 7.46–7.58 (4H, m, 4 × ArH), 7.68 (1H, d, *J* 7.6 Hz, ArH), 7.80 (1H, d, *J* 7.6 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 124.4 (q, $^4J_{C\text{-}F}$ 1.8 Hz, CH), 124.5 (q, $^1J_{C\text{-}F}$ 273.2 Hz, C), 126.0 (q, $^3J_{C\text{-}F}$ 5.6 Hz, CH), 126.9 (2 × CH), 127.0 (CH), 127.2 (CH), 127.6 (q, $^2J_{C\text{-}F}$ 26.2 Hz, C), 128.3 (CH), 128.8 (2 × CH), 131.9 (CH), 132.7 (CH), 136.5 (C), 136.9 (C); *m/z* (EI) 248 (M^+. 100%), 179 (60), 78 (23), 63 (28).

Methyl (2*E*)-3-(4'-(1''*E*)-styrylphenyl)acrylate (105)[215]



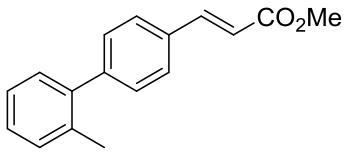
To a mixture of methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.50 g, 0.21 mmol), potassium carbonate (0.058 g, 0.42 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.0070 g, 0.011 mmol) in acetonitrile (2.5 mL) was added styrene (0.036 mL, 0.31 mmol). The reaction mixture was then heated to 90 °C and stirred for 24 h. On cooling to room temperature, the mixture was filtered through Celite®, washed with diethyl ether (20 mL) and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave methyl (2*E*)-3-(4'-(1''*E*)-styrylphenyl)acrylate (**105**) (0.040 g, 72%) as a white solid. Mp 179–181 °C (lit.[215] 183–184 °C); δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 6.45 (1H, d, *J* 16.0 Hz, 2-H), 7.10 (1H, d, *J* 16.3 Hz, 1''-H), 7.18 (1H, d, *J* 16.3 Hz, 2''-H), 7.29 (1H, t, *J* 7.4 Hz, 4'''-H), 7.38 (2H, t, *J* 7.4 Hz, 3'''-H and 5'''-H), 7.50–7.58 (6H, m, 6 × ArH), 7.69 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.7 (CH_3), 117.4 (CH), 126.7 (2 × CH), 126.9 (2 × CH), 127.8 (CH), 128.0 (CH), 128.5 (2 × CH), 128.8 (2 × CH), 130.1 (CH), 133.6 (C), 137.0 (C), 139.4 (C), 144.4 (CH), 167.5 (C); *m/z* (EI) 264 (M^+. 100%), 233 (10), 203 (12), 189 (6), 178 (8), 83 (22).

Methyl (*E*)-3-([1',1''-biphenyl]-4'-yl)acrylate (106a)[216]



To a mixture of methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.50 g, 0.21 mmol), phenylboronic acid (0.26 g, 0.21 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.0090 g, 0.011 mmol) in 1,4-dioxane (4 mL) was added cesium fluoride (0.064 g, 0.42 mmol). The reaction mixture was degassed with argon under sonication for 0.5 h and then heated to 80 °C for 24 h. On cooling to room temperature, the mixture was filtered through Celite®, washed with diethyl ether (20 mL) and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-([1',1''-biphenyl]-4'-yl)acrylate (**106a**) (0.044 g, 88%) as a pale yellow solid. Mp 146–148 °C (lit.[216] 147–148 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.49 (1H, d, *J* 16.0 Hz, 2-H), 7.35–7.41 (1H, m, ArH), 7.43–7.50 (2H, m, 2 × ArH), 7.57–7.66 (6H, m, 6 × ArH), 7.75 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.7 (CH_3), 117.7 (CH), 127.1 (2 × CH), 127.6 (2 × CH), 127.9 (CH), 128.6 (2 × CH), 128.9 (2 × CH), 133.4 (C), 140.2 (C), 143.1 (C), 144.4 (CH), 167.5 (C); *m/z* (ESI) 261 (MNa^+. 100%).

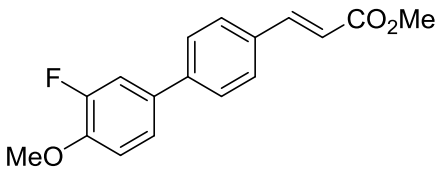
Methyl (*E*)-3-(2''-methyl-[1',1''-biphenyl]-4'-yl)acrylate (106b)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-([1',1''-biphenyl]-4'-yl)acrylate (**106a**) using methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.50 g, 0.21 mmol), 2-methylphenylboronic acid (0.44 g, 0.21 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.0090 g, 0.011 mmol) and cesium fluoride (0.064 g, 0.42 mmol). Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-(2''-methyl-[1',1''-biphenyl]-4'-yl)acrylate

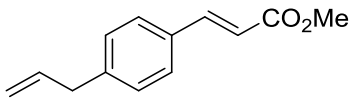
(**106b**) (0.044 g, 83%) as a white solid. Mp 51–53 °C; ν_{max}/cm^{-1} (neat) 2949 (CH), 1708 (C=O), 1632 (C=C), 1313, 1169, 998, 935, 765; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 2''-CH_3), 3.81 (3H, s, OCH_3), 6.47 (1H, d, *J* 16.0 Hz, 2-H), 7.19–7.29 (4H, m, 3''-H, 4''-H, 5''-H and 6''-H), 7.34 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 7.56 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H), 7.74 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 51.7 (CH_3), 117.6 (CH), 125.9 (CH), 127.7 (CH), 127.9 (2 × CH), 129.6 (CH), 129.8 (2 × CH), 130.5 (CH), 132.9 (C), 135.2 (C), 141.0 (C), 144.1 (C), 144.6 (CH), 167.5 (C); *m/z* (EI) 252.1142 (M^+. $C_{17}H_{16}O_2$ requires 252.1150), 221 (28%), 178 (21), 111 (6), 84 (14).

Methyl (*E*)-3-(3''-fluoro-4''-methoxy-[1',1''-biphenyl]-4'-yl)acrylate (106c)



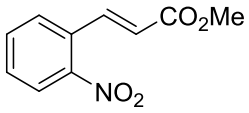
The reaction was carried out according to the previously described procedure for methyl (*E*)-3-([1',1''-biphenyl]-4'-yl)acrylate (**106a**) using methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.50 g, 0.21 mmol), 3-fluoro-4-methoxyphenylboronic acid (0.36 g, 0.21 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.0090 g, 0.011 mmol) and cesium fluoride (0.064 g, 0.42 mmol). Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-(3''-fluoro-4''-methoxy-[1',1''-biphenyl]-4'-yl)acrylate (**106c**) (0.045 g, 75%) as a white solid. Mp 118–121 °C; ν_{max}/cm^{-1} (neat) 2954 (CH), 1723 (C=O), 1316, 1173, 1135, 806; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 3.93 (3H, s, 4''-OCH_3), 6.46 (1H, d, *J* 16.0 Hz, 2-H), 7.03 (1H, t, *J* 8.8 Hz, ArH), 7.30–7.38 (2H, m, 2 × ArH), 7.54 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 7.58 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H), 7.71 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.7 (CH_3), 56.4 (CH_3), 113.7 (d, $^4J_{C\text{-}F}$ 2.2 Hz, CH), 114.7 (d, $^2J_{C\text{-}F}$ 19.2 Hz, CH), 117.7 (CH), 122.7 (d, $^3J_{C\text{-}F}$ 3.3 Hz, CH), 127.0 (2 × CH), 128.6 (2 × CH), 133.2 (C), 133.3 (C), 141.5 (d, $^3J_{C\text{-}F}$ 1.9 Hz, C), 144.2 (CH), 147.6 (d, $^2J_{C\text{-}F}$ 10.2 Hz, C), 152.6 (d, $^1J_{C\text{-}F}$ 246.9 Hz, C), 167.4 (C); *m/z* (ESI) 309.0899 (MNa^+. $C_{17}H_{15}FNaO_3$ requires 309.0897).

Methyl (*E*)-3-(4'-allylphenyl)acrylate (107)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-([1',1''-biphenyl]-4'-yl)acrylate (**106a**) using methyl (*E*)-3-(4'-bromophenyl)acrylate (**98d**) (0.50 g, 0.21 mmol), allylboronic acid pinacol ester (0.060 mL, 0.32 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.0017 g, 0.021 mmol) and cesium fluoride (0.064 g, 0.42 mmol). Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-(4'-allylphenyl)acrylate (**107**) (0.027 g, 64%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2950 (CH), 1717 (C=O), 1635 (C=C), 1317, 1271, 1204, 1166, 983, 826; δ_H (400 MHz, $CDCl_3$) 3.41 (2H, d, *J* 6.8 Hz, 1''-H_2), 3.80 (3H, s, OCH_3), 5.06–5.13 (2H, m, 3''-H_2), 5.95 (1H, ddt, *J* 17.2, 9.6, 6.8 Hz, 2''-H), 6.41 (1H, d, *J* 16.0 Hz, 2-H), 7.21 (2H, d, *J* 8.1 Hz, 3'-H and 5'-H), 7.46 (2H, d, *J* 8.1 Hz, 2'-H and 6'-H), 7.68 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 40.1 (CH_2), 51.7 (CH_3), 116.4 (CH_2), 117.1 (CH), 128.2 (2 × CH), 129.2 (2 × CH), 132.4 (C), 136.7 (CH), 142.7 (C), 144.7 (CH), 167.6 (C); *m/z* (ESI) 427.1886 ($[2MNa]^+$. $C_{26}H_{28}NaO_4$ requires 427.1880).

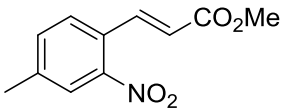
Methyl (*E*)-3-(2'-nitrophenyl)acrylate (50b)[65]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 2-nitroaniline (0.055 g, 0.40 mmol), polymer-supported nitrite (0.34 g, containing 1.2 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.2 mmol), palladium(II) acetate (0.0040 g, 0.020 mmol) and methyl acrylate (0.18 mL, 2.0 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(2'-nitrophenyl)acrylate (**50b**) (0.070 g, 84%) as a yellow solid. Mp 68–70 °C (lit.[65] 71–72 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.37 (1H, d, *J* 16.0 Hz, 2-H), 7.51–7.58 (1H, m, ArH),

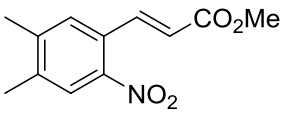
7.60–7.69 (2H, m, 2 × ArH), 8.04 (1H, d, *J* 8.7 Hz, 3'-H), 8.12 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 122.9 (CH), 124.9 (CH), 129.1 (CH), 130.3 (CH), 130.6 (C), 133.5 (CH), 140.2 (CH), 148.4 (C), 166.2 (C); *m*/*z* (EI) 207 (M^+. 28%), 175 (78), 143 (100), 115 (59), 89 (53).

Methyl (*E*)-3-(4'-methyl-2'-nitrophenyl)acrylate (109a)[65]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-methyl-2-nitroaniline (0.050 g, 0.33 mmol), polymer-supported nitrite (0.28 g, containing 0.99 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.99 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.15 mL, 1.6 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-methyl-2'-nitrophenyl)acrylate (**109a**) (0.056 g, 77%) as a pale yellow solid. Mp 72–74 °C (lit.[65] 73–75 °C); δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, 4'-CH_3), 3.81 (3H, s, OCH_3), 6.33 (1H, d, *J* 15.6 Hz, 2-H), 7.41–7.46 (1H, m, 5'-H), 7.52 (1H, d, *J* 8.0 Hz, 6'-H), 7.82 (1H, d, *J* 0.4 Hz, 3'-H), 8.06 (1H, d, *J* 15.6 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 51.9 (CH_3), 122.0 (CH), 125.2 (CH), 127.6 (C), 128.8 (CH), 134.2 (CH), 140.0 (CH), 141.4 (C), 148.3 (C), 166.4 (C); *m*/*z* (ESI) 244 (MNa^+. 100%).

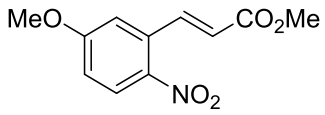
Methyl (*E*)-3-(4',5'-dimethyl-2'-nitrophenyl)acrylate (109c)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4,5-dimethyl-2-nitroaniline (0.050 g, 0.30 mmol), polymer-supported nitrite (0.26 g, containing 0.90 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.90 mmol), palladium(II) acetate (0.0030 g, 0.015 mmol) and methyl acrylate (0.14 mL, 1.5 mmol). Purification by neutral alumina (Brockmann V grade) flash column

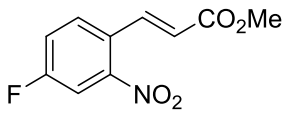
chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-(4',5'-dimethyl-2'-nitrophenyl)acrylate (**109c**) (0.050 g, 71%) as an orange solid. Mp 85–87 °C; ν_{max}/cm^{-1} (neat) 2922 (CH), 1729 (C=O), 1514 (N=O), 1335, 1165, 1024, 839; δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.31 (1H, d, *J* 16.0 Hz, 2-H), 7.36 (1H, s, 6'-H), 7.84 (1H, s, 3'-H), 8.11 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 19.6 (CH_3), 19.9 (CH_3), 51.9 (CH_3), 121.8 (CH), 125.8 (CH), 128.1 (C), 129.9 (CH), 139.8 (C), 140.6 (CH), 143.5 (C), 146.0 (C), 166.5 (C); *m/z* (ESI) 258.0743 (MNa^+. $C_{12}H_{13}NNaO_4$ requires 258.0737).

Methyl (*E*)-3-(5'-methoxy-2'-nitrophenyl)acrylate (109e)



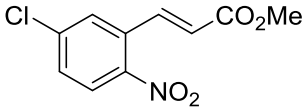
The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 5-methoxy-2-nitroaniline (0.050 g, 0.30 mmol), polymer-supported nitrite (0.26 g, containing 0.90 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.90 mmol), palladium(II) acetate (0.0030 g, 0.015 mmol) and methyl acrylate (0.13 mL, 1.5 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 20% diethyl ether in hexane gave methyl (*E*)-3-(5'-methoxy-2'-nitrophenyl)acrylate (**109e**) (0.054 g, 77%) as an orange solid. Mp 98–100 °C; ν_{max}/cm^{-1} (neat) 2922 (CH), 1717 (C=O), 1508 (N=O), 1341, 1234, 1028, 847; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 3.92 (3H, s, 5'-OCH_3), 6.29 (1H, d, *J* 15.8 Hz, 2-H), 6.95–7.00 (2H, m, 4'-H and 6'-H), 8.10–8.15 (1H, m, 3'-H), 8.20 (1H, d, *J* 15.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 56.1 (CH_3), 114.2 (CH), 114.9 (CH), 122.7 (CH), 127.7 (CH), 133.8 (C), 141.1 (C), 141.5 (CH), 163.5 (C), 166.3 (C); *m/z* (ESI) 260.0526 (MNa^+. $C_{11}H_{11}NNaO_5$ requires 260.0529).

Methyl (*E*)-3-(4'-fluoro-2'-nitrophenyl)acrylate (109f)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-fluoro-2-nitroaniline (0.05 g, 0.32 mmol), polymer-supported nitrite (0.27 g, containing 0.96 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.96 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.14 mL, 1.6 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-fluoro-2'-nitrophenyl)acrylate (**109f**) (0.056 g, 78%) as a pale yellow solid. Mp 87–89 °C; ν_{max}/cm^{-1} (neat) 2960 (CH), 1721 (C=O), 1526 (N=O), 1242, 1200, 1038, 797; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.33 (1H, d, *J* 16.0 Hz, 2-H), 7.39 (1H, dddd, *J* 8.8, 7.2, 2.6, 0.4 Hz, 5'-H), 7.64 (1H, dd, *J* 8.8, 5.9 Hz, 6'-H), 7.78 (1H, dd, *J* 8.0, 2.6 Hz, 3'-H), 8.06 (1H, dd, *J* 16.0, 0.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 112.7 (d, $^2J_{C\text{-}F}$ 26.8 Hz, CH), 121.1 (d, $^2J_{C\text{-}F}$ 21.5 Hz, CH), 123.1 (d, $^5J_{C\text{-}F}$ 0.5 Hz, CH), 126.9 (d, $^3J_{C\text{-}F}$ 4.0 Hz, C), 130.9 (d, $^3J_{C\text{-}F}$ 8.2 Hz, CH), 139.1 (CH), 148.8 (C), 162.6 (d, $^1J_{C\text{-}F}$ 255.1 Hz, C), 166.1 (C); *m/z* (ESI) 248.0327 (MNa^+. $C_{10}H_8FNNaO_4$ requires 248.0330).

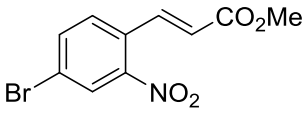
Methyl (*E*)-3-(5'-chloro-2'-nitrophenyl)acrylate (109g)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 5-chloro-2-nitroaniline (0.070 g, 0.40 mmol), polymer-supported nitrite (0.34 g, containing 1.2 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.2 mmol), palladium(II) acetate (0.0040 g, 0.020 mmol) and methyl acrylate (0.18 mL, 2.0 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(5'-chloro-2'-nitrophenyl)acrylate (**109g**) (0.066 g, 68%) as a yellow solid. Mp 110–

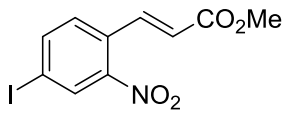
113 °C; ν_{max}/cm^{-1} (neat) 2961 (CH), 1715 (C=O), 1516 (N=O), 1343, 1279, 1250, 1034, 976, 829; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.35 (1H, d, *J* 15.8 Hz, 2-H), 7.50 (1H, dd, *J* 8.8, 2.5 Hz, 4'-H), 7.59 (1H, d, *J* 2.5 Hz, 6'H), 8.03 (1H, d, *J* 8.8 Hz, 3'-H), 8.08 (1H, d, *J* 15.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.2 (CH_3), 124.0 (CH), 126.5 (CH), 129.1 (CH), 130.2 (CH), 132.5 (C), 139.1 (CH), 140.1 (C), 146.4 (C), 165.8 (C); *m/z* (ESI) 264.0036 (MNa^+. $C_{10}H_8{}^{35}ClNNaO_4$ requires 264.0034).

Methyl (*E*)-3-(4'-bromo-2'-nitrophenyl)acrylate (109h)[65]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-bromo-2-nitroaniline (0.050 g, 0.23 mmol), polymer-supported nitrite (0.20 g, containing 0.69 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.12 g, 0.69 mmol), palladium(II) acetate (0.0030 g, 0.012 mmol) and methyl acrylate (0.10 mL, 1.2 mmol). Purification by neutral alumina (Brockmann V grade) and then silica gel flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4'-bromo-2'-nitrophenyl)acrylate (**109h**) (0.050 g, 76%) as a yellow solid. Mp 84–86 °C (lit.[65] 84–85 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.37 (1H, d, *J* 16.0 Hz, 2-H), 7.51 (1H, d, *J* 8.5 Hz, 6'-H), 7.77 (1H, d, *J* 8.5, 2.0 Hz, 5'-H), 8.03 (1H, d, *J* 16.0 Hz, 3-H), 8.18 (1H, d, *J* 2.0 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 123.4 (CH), 123.8 (C), 128.0 (CH), 129.4 (C), 130.3 (CH), 136.6 (CH), 139.0 (CH), 148.5 (C), 166.0 (C); *m/z* (ESI) 309 (MNa^+. 98%), 307 (100).

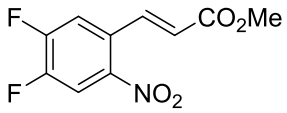
Methyl (*E*)-3-(4'-iodo-2'-nitrophenyl)acrylate (109i)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-iodo-2-nitroaniline (0.050 g, 0.19 mmol), polymer-supported nitrite (0.16 g, containing 0.57 mmol of NO_2), *p*-

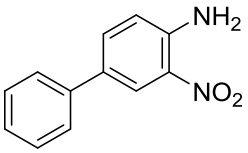
toluenesulfonic acid monohydrate (0.098 g, 0.57 mmol), palladium(II) acetate (0.0030 g, 0.014 mmol) and methyl acrylate (0.085 mL, 0.95 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 5% diethyl ether in hexane gave methyl (*E*)-3-(4'-iodo-2'-nitrophenyl)acrylate (**109i**) (0.046 g, 73%) as a yellow solid. Mp 83–85 °C; ν_{max}/cm^{-1} (neat) 2951 (CH), 1699 (C=O), 1524 (N=O), 1356, 1271, 1034, 824; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.37 (1H, d, *J* 16.0 Hz, 2-H), 7.35 (1H, d, *J* 8.2, Hz, 6'-H), 7.97 (1H, dd, *J* 8.2, 0.8 Hz, 5'-H), 8.01 (1H, d, *J* 16.0 Hz, 3-H), 8.35 (1H, d, *J* 0.8 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 94.5 (C), 123.4 (CH), 129.9 (C), 130.2 (CH), 133.6 (CH), 139.1 (CH), 142.5 (CH), 148.4 (C), 166.0 (C); *m/z* (ESI) 355.9391 (MNa^+. $C_{10}H_8INNaO_4$ requires 355.9390).

Methyl (*E*)-3-(4',5'-difluoro-2'-nitrophenyl)acrylate (109k)



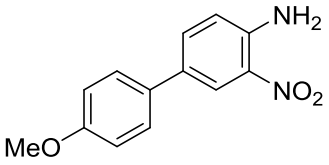
The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4,5-difluoro-2-nitroaniline (0.050 g, 0.29 mmol), polymer-supported nitrite (0.25 g, containing 0.86 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.15 g, 0.86 mmol), palladium(II) acetate (0.0050 g, 0.022 mmol) and methyl acrylate (0.13 mL, 1.5 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4',5'-difluoro-2'-nitrophenyl)acrylate (**109k**) (0.020 g, 29%) as a pale yellow solid. Mp 88–90 °C; ν_{max}/cm^{-1} (neat) 2950 (CH), 1713 (C=O), 1529 (N=O), 1497, 1333, 1275, 1177, 802; δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 6.31 (1H, d, *J* 15.9 Hz, 2-H), 7.44 (1H, dd, *J* 10.4, 7.6 Hz, 6'-H), 8.00 (1H, dd, *J* 9.6, 7.2 Hz, 3'-H), 8.09 (1H, d, *J* 15.9 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 52.2 (CH_3), 115.5 (dd, $^2J_{C-F}$ 22.1 Hz, $^3J_{C-F}$ 2.2 Hz, CH), 117.8 (d, $^2J_{C-F}$ 20.2 Hz, CH), 124.1 (CH), 128.9 (dd, $^3J_{C-F}$ 7.1 Hz, $^4J_{C-F}$ 4.3 Hz, C), 138.4 (CH), 143.6 (C), 150.0 (dd, $^1J_{C-F}$ 259.0 Hz, $^2J_{C-F}$ 13.9 Hz, C), 153.2 (dd, $^1J_{C-F}$ 261.4 Hz, $^2J_{C-F}$ 12.6 Hz, C), 165.7 (C); *m/z* (ESI) 266.0229 (MNa^+. $C_{10}H_7F_2NNaO_4$ requires 266.0235).

4-Phenyl-2-nitroaniline (110a)[217]



To a mixture of 4-iodo-2-nitroaniline (**108j**) (0.20 g, 0.75 mmol), phenylboronic acid (0.10 g, 0.83 mmol) and palladium(II) chloride (0.0030 g, 0.019 mmol) in methanol (3 mL) was added a solution of sodium hydroxide (0.12 g, 3.0 mmol) in water (1.5 mL) at room temperature. The reaction mixture was degassed with argon under sonication for 0.5 h, stirred for 24 h and then heated under reflux for a further 2 h. After cooling to room temperature, the solvent was evaporated and the residue was washed with a 5% aqueous solution of hydrochloric acid (5 mL) until the pH of the solution became neutral. The mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with brine (2 × 15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 4-phenyl-2-nitroaniline (**110a**) (0.13 g, 83%) as an orange solid. Mp 166–169 °C (lit.[217] 168–172 °C); δ_H (400 MHz, $CDCl_3$) 6.11 (2H, br s, NH_2), 6.90 (1H, d, *J* 8.6 Hz, 6-H), 7.31–7.37 (1H, m, 4'-H), 7.44 (2H, t, *J* 7.2 Hz, 3'-H and 5'-H), 7.53–7.59 (2H, m, 2'-H and 6'-H), 7.65 (1H, dd, *J* 8.6, 2.0 Hz, 5-H), 8.38 (1H, d, *J* 2.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 119.3 (CH), 123.9 (CH), 126.3 (2 × CH), 127.3 (CH), 129.0 (2 × CH), 130.4 (C), 132.5 (C), 134.5 (CH), 138.8 (C), 143.8 (C); *m/z* (ESI) 237 (MNa^+. 100%).

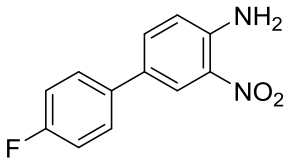
4-(4'-Methoxyphenyl)-2-nitroaniline (110b)[218]



The reaction was carried out according to the previously described procedure for 4-phenyl-2-nitroaniline (**110a**) using 4-iodo-2-nitroaniline (**108j**) (0.20 g, 0.75 mmol), 4-methoxyphenylboronic acid (0.13 g, 0.83 mmol), palladium(II) chloride (0.0030 g, 0.019 mmol) and sodium hydroxide (0.12 g, 3.0 mmol). Purification by

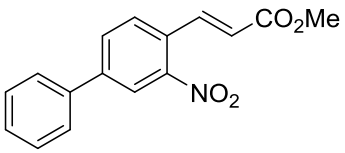
silica gel flash column chromatography, eluting with 50% diethyl ether in hexane gave 4-(4'-methoxyphenyl)-2-nitroaniline (**110b**) (0.14 g, 77%) as an orange solid. Mp 168–169 °C (lit.[218] 170–171 °C); δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, 4'-OCH_3), 6.07 (2H, br s, NH_2), 6.87 (1H, d, *J* 8.6 Hz, 6-H), 6.96 (2H, d, *J* 8.7 Hz, 3'-H and 5'-H), 7.47 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 7.59 (1H, dd, *J* 8.6, 2.1 Hz, 5-H), 8.31 (1H, dd, *J* 2.1 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 114.4 (2 × CH), 119.3 (CH), 123.2 (CH), 127.4 (2 × CH), 130.2 (C), 131.4 (C), 132.5 (C), 134.3 (CH), 143.4 (C), 159.2 (C); *m*/*z* (ESI) 267 (MNa^+. 100%).

4-(4'-Fluorophenyl)-2-nitroaniline (110c)[219]



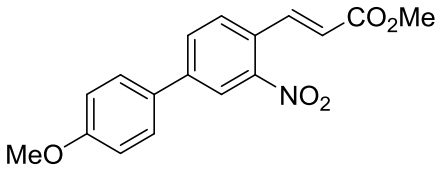
The reaction was carried out according to the previously described procedure for 4-phenyl-2-nitroaniline (**110a**) using 4-iodo-2-nitroaniline (**108j**) (0.20 g, 0.75 mmol), 4-fluorophenylboronic acid (0.12 g, 0.83 mmol), palladium(II) chloride (0.0030 g, 0.019 mmol) and sodium hydroxide (0.12 g, 3.0 mmol). Purification by silica gel flash column chromatography, eluting with 50% diethyl ether in hexane gave 4-(4'-fluorophenyl)-2-nitroaniline (**110c**) (0.15 g, 83%) as an orange solid. Spectroscopic data were consistent with the literature.[219] Mp 136–138 °C; δ_H (400 MHz, $CDCl_3$) 6.13 (2H, br s, NH_2), 6.89 (1H, d, *J* 8.8 Hz, 6-H), 7.12 (2H, t, *J* 8.8 Hz, 3'-H and 5'-H), 7.50 (2H, dd, *J* 8.8, 5.2 Hz, 2'-H and 6'-H), 7.58 (1H, dd, *J* 8.8, 2.2 Hz, 5-H), 8.31 (1H, d, *J* 2.2 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 115.9 (d, $^2J_{C\text{-}F}$ 21.7 Hz, 2 × CH), 119.4 (CH), 123.8 (CH), 127.9 (d, $^3J_{C\text{-}F}$ 8.1 Hz, 2 × CH), 129.4 (C), 132.4 (C), 134.4 (CH), 135.0 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 143.8 (C), 162.4 (d, $^1J_{C\text{-}F}$ 247.8 Hz, C); *m*/*z* (ESI) 255 (MNa^+. 100%).

Methyl (*E*)-3-(3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (111a)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-phenyl-2-nitroaniline (**110a**) (0.026 g, 0.12 mmol), polymer-supported nitrite (0.10 g, containing 0.36 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.062 g, 0.36 mmol), palladium(II) acetate (0.0010 g, 0.0060 mmol) and methyl acrylate (0.054 mL, 0.60 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (**111a**) (0.023 g, 68%) as a yellow solid. Mp 89–91 °C; ν_{max}/cm^{-1} (neat) 2920 (CH), 1701 (C=O), 1528 (N=O), 1350, 1287, 1225, 1032, 760; δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 6.42 (1H, d, *J* 15.8 Hz, 2-H), 7.42–7.53 (3H, m, 3''-H, 4''-H and 5''-H), 7.60–7.65 (2H, m, 2''-H and 6''-H), 7.71 (1H, d, *J* 8.2 Hz, 5'-H), 7.86 (1H, ddd, *J* 8.2, 1.8, 0.4 Hz, 6'-H), 8.14 (1H, d, *J* 15.8 Hz, 3-H), 8.24 (1H, d, *J* 1.8 Hz, 2'-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 122.6 (CH), 123.2 (CH), 127.0 (2 × CH), 128.8 (C), 129.0 (CH), 129.3 (2 × CH), 129.5 (CH), 131.6 (CH), 137.8 (C), 139.7 (CH), 143.7 (C), 148.9 (C), 166.3 (C); *m/z* (ESI) 306.0742 (MNa^+. $C_{16}H_{13}NNaO_4$ requires 306.0737).

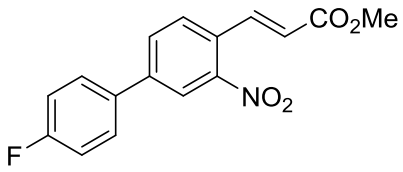
Methyl (*E*)-3-(4''-methoxy-3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (111b)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-(4'-methoxyphenyl)-2-nitroaniline (**110b**) (0.040 g, 0.16 mmol), polymer-supported nitrite (0.14 g, containing 0.48 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.083 g, 0.48 mmol), palladium(II) acetate (0.0020 g, 0.0080 mmol) and methyl acrylate (0.072 mL, 0.80 mmol). Purification by neutral alumina (Brockmann V grade) and

then silica gel flash column chromatography, eluting with 25% diethyl ether in hexane gave methyl (*E*)-3-(4''-methoxy-3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (**111b**) (0.038 g, 60%) as a yellow solid. Mp 90–92 °C; ν_{max}/cm^{-1} (neat) 2955 (CH), 1690 (C=O), 1605 (C=C), 1512 (N=O), 1350, 1250, 1173, 825; δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.41 (1H, d, *J* 15.8 Hz, 2-H), 7.01 (2H, d, *J* 8.8 Hz, 3''-H and 5''-H), 7.57 (2H, d, *J* 8.8 Hz, 2''-H and 6''-H), 7.68 (1H, d, *J* 8.2 Hz, 5'-H), 7.81 (1H, dd, *J* 8.2, 1.8 Hz, 6'-H), 8.12 (1H, d, *J* 15.8 Hz, 3-H), 8.18 (1H, d, *J* 1.8 Hz, 2'-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 55.4 (CH_3), 114.7 (2 × CH), 122.3 (CH), 122.5 (CH), 128.0 (C), 128.2 (2 × CH), 129.3 (CH), 130.1 (C), 130.9 (CH), 139.7 (CH), 143.3 (C), 148.9 (C), 160.5 (C), 166.3 (C); m/z (ESI) 336.0833 (MNa^+. $C_{17}H_{15}NNaO_5$ requires 336.0842).

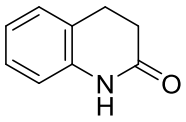
Methyl (*E*)-3-(4''-fluoro-3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (111c)



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(4'-nitrophenyl)acrylate (**50a**) using 4-(4'-fluorophenyl)-2-nitroaniline (**110c**) (0.050 g, 0.17 mmol), polymer-supported nitrite (0.15 g, containing 0.51 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.088 g, 0.51 mmol), palladium(II) acetate (0.0020 g, 0.0090 mmol) and methyl acrylate (0.076 mL, 0.85 mmol). Purification by neutral alumina (Brockmann V grade) flash column chromatography, eluting with 10% diethyl ether in hexane gave methyl (*E*)-3-(4''-fluoro-3'-nitro-[1',1''-biphenyl]-4'-yl)acrylate (**111c**) (0.043 g, 84%) as an orange solid. Mp 124–126 °C; ν_{max}/cm^{-1} (neat) 2922 (CH), 1730 (C=O), 1514 (N=O), 1435, 1350, 1165, 1030, 839; δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 6.42 (1H, d, *J* 15.6 Hz, 2-H), 7.19 (2H, t, *J* 8.8 Hz, 3''-H and 5''-H), 7.60 (2H, dd, *J* 8.8, 5.2, 2''-H and 6''-H), 7.71 (1H, d, *J* 8.0 Hz, 5'-H), 7.82 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 8.13 (1H, d, *J* 15.6 Hz, 3-H), 8.20 (1H, d, *J* 1.6 Hz, 2'-H); δ_C (101 MHz, $CDCl_3$) 52.0 (CH_3), 116.3 (d, $^2J_{C\text{-}F}$ 22.9 Hz, 2 × CH), 122.8 (CH), 123.0 (CH), 128.8 (d, $^3J_{C\text{-}F}$ 9.7 Hz, 2 × CH), 128.9 (C), 129.6 (CH), 131.4 (CH), 134.0 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 139.5 (CH), 142.7 (C), 148.9 (C), 163.4 (d, $^1J_{C\text{-}F}$ 250.5 Hz, C),

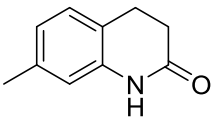
166.2 (C); *m/z* (EI) 301.0759 (M^+. $C_{16}H_{12}FNO_4$ requires 301.0750), 255 (15%), 214 (19), 183 (12), 105 (7), 84 (100).

3,4-Dihydro-1*H*-quinoline-2-one (112a)[62]



The reaction was carried out according to the previously described procedure for methyl (*E*)-3-(2'-nitrophenyl)acrylate (**50b**) except that after the first two steps, the mixture was purged with hydrogen gas and then hydrogenated at atmospheric pressure for a further 24 h at 40 °C. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite®, washed with methanol (20 mL) and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave 3,4-dihydro-1*H*-quinoline-2-one (**112a**) (0.043 g, 73%) as a white solid. Mp 162–164 °C (lit.[62] 164 °C); δ_H (400 MHz, $CDCl_3$) 2.65 (2H, dd, *J* 8.8, 8.0 Hz, 3-H_2), 2.97 (2H, dd, *J* 8.0, 7.2 Hz, 4-H_2), 6.82 (1H, d, *J* 7.6 Hz, 5-H), 6.99 (1H, td, *J* 7.6, 1.1 Hz, 6-H), 7.13–7.20 (2H, m, 7-H and 8-H), 8.87 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.4 (CH_2), 30.7 (CH_2), 115.5 (CH), 123.1 (CH), 123.7 (C), 127.5 (CH), 127.9 (CH), 137.3 (C), 172.0 (C); *m/z* (ESI) 170 (MNa^+. 100%).

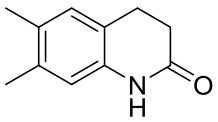
7-Methyl-3,4-dihydro-1*H*-quinoline-2-one (112b)[220]



The reaction was carried out according to the previously described procedure for 3,4-dihydro-1*H*-quinoline-2-one (**112a**) using 4-methyl-2-nitroaniline (0.050 g, 0.33 mmol), polymer-supported nitrite (0.28 g, containing 0.99 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.99 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.15 mL, 1.6 mmol). Purification by silica gel flash column chromatography, eluting with 40% ethyl acetate in hexane gave 7-methyl-3,4-dihydro-1*H*-quinoline-2-one (**112b**) (0.042 g, 79%) as a pale yellow solid. Mp 133–135 °C (lit.[220] 135–137 °C); δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s,

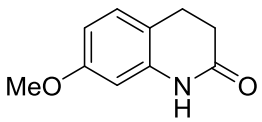
7-CH_3), 2.63 (2H, dd, *J* 8.4, 7.6 Hz, 3-H_2), 2.92 (2H, dd, *J* 7.6, 7.2 Hz, 4-H_2), 6.68 (1H, s, 8-H), 6.79 (1H, d, *J* 7.4 Hz, 6-H), 7.03 (1H, d, *J* 7.4 Hz, 5-H), 9.41 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 25.0 (CH_2), 30.9 (CH_2), 116.2 (CH), 120.6 (C), 123.8 (CH), 127.7 (CH), 137.2 (C), 137.5 (C), 172.6 (C); *m*/*z* (EI) 161 (M^+. 100%), 133 (55), 106 (20), 86 (46), 84 (59).

6,7-Dimethyl-3,4-dihydro-1*H*-quinoline-2-one (112d)[62]



The reaction was carried out according to the previously described procedure for 3,4-dihydro-1*H*-quinoline-2-one (**112a**) using 4,5-dimethyl-2-nitroaniline (0.050 g, 0.32 mmol), polymer-supported nitrite (0.27 g, containing 0.96 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.96 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.14 mL, 1.6 mmol). Purification by silica gel flash column chromatography, eluting with 10% ethyl acetate in hexane gave 6,7-dimethyl-3,4-dihydro-1*H*-quinoline-2-one (**112d**) (0.041 g, 77%) as a pale yellow solid. Mp 196–198 °C (lit.[62] 200 °C); δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.61 (2H, dd, *J* 9.2, 8.0 Hz, 3-H_2), 2.90 (2H, dd, *J* 8.0, 7.2 Hz, 4-H_2), 6.61 (1H, s, 5-H), 6.92 (1H, s, 8-H), 8.76 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 19.0 (CH_3), 19.4 (CH_3), 24.9 (CH_2), 31.0 (CH_2), 116.7 (CH), 120.8 (C), 129.0 (CH), 131.1 (C), 135.0 (C), 135.8 (C), 172.0 (C); *m*/*z* (EI) 175 (M^+. 100%), 147 (29), 133 (16), 83 (21).

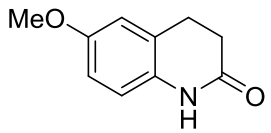
7-Methoxy-3,4-dihydro-1*H*-quinoline-2-one (112e)[64]



The reaction was carried out according to the previously described procedure for 3,4-dihydro-1*H*-quinoline-2-one (**112a**) using 4-methoxy-2-nitroaniline (0.500 g, 2.97 mmol), polymer-supported nitrite (2.55 g, containing 8.92 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (1.54 g, 8.92 mmol), palladium(II) acetate (0.0330 g, 0.149 mmol) and methyl acrylate (1.33 mL, 14.9 mmol). After the

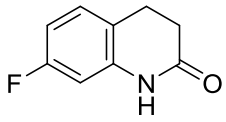
first two steps were complete (2 h), the vessel was transferred to a Parr Shaker Hydrogenation apparatus and hydrogenated at 2.5 bar pressure for 24 hours. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) (0.416 g, 79%) as a white solid. Mp 141–144 °C (lit.[64] 145–146 °C); δ_H (400 MHz, $CDCl_3$) 2.62 (2H, dd, *J* 7.6, 6.0 Hz, 3-H_2), 2.86 (2H, t, *J* 7.6 Hz, 4-H_2), 3.77 (3H, s, 7-OCH_3), 6.41 (1H, d, *J* 2.5 Hz, 8-H), 6.52 (1H, dd, *J* 8.3, 2.5 Hz, 6-H), 7.04 (1H, d, *J* 8.3 Hz, 5-H), 9.24 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 24.5 (CH_2), 31.1 (CH_2), 55.5 (CH_3), 101.7 (CH), 108.3 (CH), 115.8 (C), 128.6 (CH), 138.3 (C), 159.3 (C), 172.5 (C); *m*/*z* (ESI) 200 (MNa^+. 100%).

6-Methoxy-3,4-dihydro-1*H*-quinoline-2-one (112f)[221]



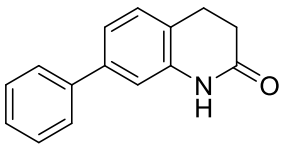
The reaction was carried out according to the previously described procedure for 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) using 5-methoxy-2-nitroaniline (0.050 g, 0.30 mmol), polymer-supported nitrite (0.26 g, containing 0.90 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.90 mmol), palladium(II) acetate (0.0030 g, 0.015 mmol) and methyl acrylate (0.13 mL, 1.5 mmol). Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 6-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112f**) (0.028 g, 54%) as a white solid. Mp 140–142 °C (lit.[221] 146–148°C); δ_H (400 MHz, $CDCl_3$) 2.61 (2H, dd, *J* 8.0, 7.2 Hz, 3-H_2), 2.93 (2H, dd, *J* 8.0, 7.2 Hz, 4-H_2), 3.77 (3H, s, 6-OCH_3), 6.69 (1H, d, *J* 2.4 Hz, 5-H), 6.71 (1H, d, *J* 7.6 Hz, 8-H), 6.77 (1H, dd, *J* 7.6, 2.4 Hz, 7-H), 9.11 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.7 (CH_2), 30.6 (CH_2), 55.6 (CH_3), 112.4 (CH), 113.8 (CH), 116.3 (CH), 125.0 (C), 130.9 (C), 155.6 (C), 171.8 (C); *m*/*z* (ESI) 200 (MNa^+. 100%).

7-Fluoro-3,4-dihydro-1*H*-quinoline-2-one (112g)[222]



The reaction was carried out according to the previously described procedure for 3,4-dihydro-1*H*-quinoline-2-one (**112a**) using 4-fluoro-2-nitroaniline (0.050 g, 0.32 mmol), polymer-supported nitrite (0.27 g, containing 0.96 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.96 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.14 mL, 1.6 mmol). Purification by silica gel flash column chromatography, eluting with 10% ethyl acetate in hexane gave 7-fluoro-3,4-dihydro-1*H*-quinoline-2-one (**112g**) (0.037 g, 70%) as a pale yellow solid. Spectroscopic data were consistent with the literature.[222] Mp 176–178 °C; δ_H (400 MHz, $CDCl_3$) 2.64 (2H, dd, *J* 8.8, 8.0 Hz, 3-H_2), 2.94 (2H, dd, *J* 8.0, 7.2 Hz, 4-H_2), 6.59 (1H, dd, *J* 9.2, 2.4 Hz, 8-H), 6.68 (1H, td, *J* 8.2, 2.4 Hz, 6-H), 7.09 (1H, dd, *J* 8.2, 6.0 Hz, 5-H), 9.23 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 24.7 (CH_2), 30.7 (CH_2), 103.1 (d, $^2J_{C\text{-}F}$ 25.7 Hz, CH), 109.5 (d, $^2J_{C\text{-}F}$ 21.4 Hz, CH), 119.2 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 129.0 (d, $^3J_{C\text{-}F}$ 9.3 Hz, CH), 138.6 (d, $^3J_{C\text{-}F}$ 10.6 Hz, C), 162.1 (d, $^1J_{C\text{-}F}$ 245.3 Hz, C), 172.2 (C); *m*/*z* (ESI) 188 (MNa^+. 100%).

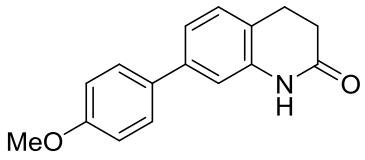
7-Phenyl-3,4-dihydro-1*H*-quinoline-2-one (113a)



The reaction was carried out according to the previously described procedure for 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) using 4-phenyl-2-nitroaniline (**110a**) (0.050 g, 0.32 mmol), polymer-supported nitrite (0.27 g, containing 0.96 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.96 mmol), palladium(II) acetate (0.0040 g, 0.016 mmol) and methyl acrylate (0.14 mL, 1.6 mmol). Purification by silica gel flash column chromatography, eluting with 60% ethyl acetate in hexane gave 7-phenyl-3,4-dihydro-1*H*-quinoline-2-one (**113a**) (0.030 g, 71%) as a white solid. Mp 178–181 °C; ν_{max}/cm^{-1} (neat) 2976 (CH), 1674 (C=O), 1483, 1391, 820, 760; δ_H (400 MHz, $CDCl_3$) 2.68 (2H, t, *J* 7.6 Hz, 3-H_2),

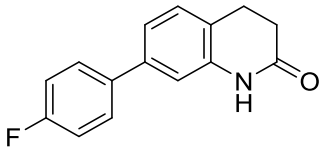
3.01 (2H, t, *J* 7.6 Hz, 4-H_2), 7.02 (1H, s, 8-H), 7.19–7.25 (2H, m, 5-H and 6-H), 7.35 (1H, t, *J* 7.6 Hz, 4'-H), 7.43 (2H, t, *J* 7.6 Hz, 3'-H and 5'-H), 7.56 (2H, d, *J* 7.6 Hz, 2'-H and 6'-H), 8.86 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.1 (CH_2), 30.8 (CH_2), 114.2 (CH), 121.9 (CH), 122.7 (C), 127.0 (2 × CH), 127.5 (CH), 128.3 (CH), 128.8 (2 × CH), 137.8 (C), 140.4 (C), 141.0 (C), 172.0 (C); *m/z* (EI) 223.0989 (M^+. $C_{15}H_{13}NO$ requires 223.0997), 195 (38%), 168 (14), 152 (10), 83 (51), 75 (30).

7-(4'-Methoxyphenyl)-3,4-dihydro-1*H*-quinolin-2-one (113b)



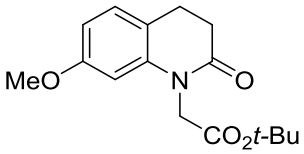
The reaction was carried out according to the previously described procedure for 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) using 4-(4'-methoxyphenyl)-2-nitroaniline (**110b**) (0.040 g, 0.16 mmol), polymer-supported nitrite (0.14 g, containing 0.48 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.083 g, 0.48 mmol), palladium(II) acetate (0.0020 g, 0.0080 mmol) and methyl acrylate (0.072 mL, 0.80 mmol). Purification by silica gel flash column chromatography, eluting with 60% ethyl acetate in hexane gave 7-(4'-methoxyphenyl)-3,4-dihydro-1*H*-quinolin-2-one (**113b**) (0.023 g, 57%) as a white solid. Mp 145–150 °C; ν_{max}/cm^{-1} (neat) 2963 (CH), 1671 (C=O), 1589, 1183, 1023, 807; δ_H (400 MHz, $CDCl_3$) 2.67 (2H, t, *J* 7.2 Hz, 3-H_2), 2.99 (2H, t, *J* 7.2 Hz, 4-H_2), 3.84 (3H, s, 4'-OCH_3), 6.93–6.99 (3H, m, 8-H, 3'-H and 5'-H), 7.16 (1H, dd, *J* 7.8, 1.6 Hz, 6-H), 7.19 (1H, d, *J* 7.8 Hz, 5-H), 7.48 (2H, d, *J* 8.7 Hz, 2'-H and 6'-H), 8.83 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.1 (CH_2), 30.9 (CH_2), 55.4 (CH_3), 113.7 (CH), 114.3 (2 × CH), 121.5 (CH), 122.1 (C), 128.1 (2 × CH), 128.3 (CH), 132.9 (C), 137.7 (C), 140.6 (C), 159.3 (C), 172.0 (C); *m/z* (ESI) 276.0982 (MNa^+. $C_{16}H_{15}NNaO_2$ requires 276.0995).

7-(4'-Fluorophenyl)-3,4-dihydro-1*H*-quinolin-2-one (113c)



The reaction was carried out according to the previously described procedure for 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) using 4-(4'-fluorophenyl)-2-nitroaniline (**110c**) (0.050 g, 0.17 mmol), polymer-supported nitrite (0.15 g, containing 0.51 mmol of NO_2), *p*-toluenesulfonic acid monohydrate (0.088 g, 0.51 mmol), palladium(II) acetate (0.0020 g, 0.0090 mmol) and methyl acrylate (0.076 mL, 0.85 mmol). Purification by silica gel flash column chromatography, eluting with 40% ethyl acetate in hexane gave 7-(4'-fluorophenyl)-3,4-dihydro-1*H*-quinolin-2-one (**113c**) (0.030 g, 73%) as a white solid. Mp 141–143 °C; ν_{max}/cm^{-1} (neat) 2924 (CH), 1674 (C=O), 1487, 1395, 1219, 812; δ_H (400 MHz, $CDCl_3$) 2.68 (2H, dd, *J* 9.2, 8.0 Hz, 3-H_2), 3.01 (2H, dd, *J* 8.0, 7.2 Hz, 4-H_2), 6.96 (1H, d, *J* 1.8 Hz, 8-H), 7.08–7.14 (2H, m, 3'-H and 5'-H), 7.16 (1H, dd, *J* 7.8, 1.8 Hz, 6-H), 7.22 (1H, d, *J* 7.8 Hz, 5-H), 7.47–7.54 (2H, m, 2'-H and 6'-H), 8.76 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 25.1 (CH_2), 30.8 (CH_2), 113.9 (CH), 115.7 (d, $^2J_{C\text{-}F}$ 21.5 Hz, 2 × CH), 121.8 (CH), 122.7 (C), 128.4 (CH), 128.6 (d, $^3J_{C\text{-}F}$ 8.1 Hz, 2 × CH), 136.5 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 137.8 (C), 140.0 (C), 162.6 (d, $^1J_{C\text{-}F}$ 247.8 Hz, C), 171.9 (C); *m/z* (EI) 241.0909 (M^+. $C_{15}H_{12}FNO$ requires 241.0903), 213 (38%), 186 (16), 170 (8), 133 (5), 83 (12).

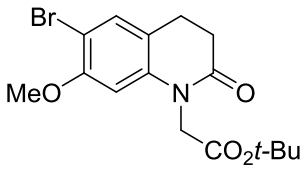
***tert*-Butyl 2-(7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl)acetate (118)**



To a stirred solution of 7-methoxy-3,4-dihydro-1*H*-quinoline-2-one (**112e**) (0.050 g, 0.23 mmol) in dry *N*,*N*'-dimethylformamide (7 mL) was added a 60% dispersion of sodium hydride in mineral oil (0.043 mg, 1.1 mmol) and the resulting mixture was stirred for 0.25 h at room temperature. *tert*-Butyl chloroacetate (0.20 mL,

1.4 mmol) was added dropwise and the reaction mixture was then stirred for 2 h. Methanol (6 mL) was added and the mixture was concentrated *in vacuo*. The reaction mixture was diluted with ethyl acetate (20 mL), washed with a 5% aqueous solution of lithium chloride (3 × 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by silica gel flash chromatography, eluting with 20% ethyl acetate in hexane gave *tert*-butyl 2-(7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl)acetate (**118**) (0.067 g, 100%) as a yellow solid. Mp 57–59 °C; ν_{max}/cm^{-1} (neat) 2978 (CH), 1743 (C=O), 1677 (C=O), 1616, 1367, 1168, 1153, 747; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 2.66 (2H, dd, *J* 9.2, 8.0 Hz, 3'-H_2), 2.85 (2H, dd, *J* 9.2, 8.0 Hz, 4'-H_2), 3.76 (3H, s, 7'-OCH_3), 4.53 (2H, s, 2-H_2), 6.31 (1H, d, *J* 2.4 Hz, 8'-H), 6.52 (1H, dd, *J* 8.4, 2.4 Hz, 6'-H), 7.05 (1H, d, *J* 8.4 Hz, 5'-H); δ_C (101 MHz, $CDCl_3$) 24.6 (CH_2), 28.0 (3 × CH_3), 31.8 (CH_2), 45.0 (CH_2), 55.4 (CH_3), 82.1 (C), 102.0 (CH), 107.0 (CH), 118.4 (C), 128.5 (CH), 140.6 (C), 159.2 (C), 167.7 (C), 170.6 (C); *m/z* (EI) 291.1484 (M^+. $C_{16}H_{21}NO_4$ requires 291.1471), 235 (80%), 218 (35), 190 (98), 162 (100), 148 (47), 121 (18), 57 (58).

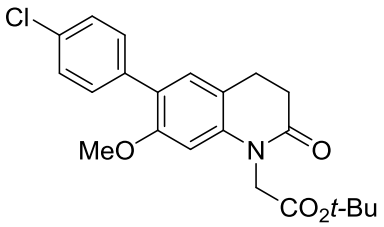
tert-Butyl 2-(6'-bromo-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl) acetate (115)



Iron(III) chloride (0.60 mg, 0.0038 mmol) and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM]NTf_2) (3.3 μL, 0.011 mmol) were stirred for 0.5 h at room temperature. This was added to a solution of *tert*-butyl 2-(7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl)acetate (**118**) (0.045 g, 0.15 mmol) and *N*-bromosuccinimide (0.027 g, 0.15 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 40 °C for 24 h, cooled to room temperature and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 30% ethyl acetate in hexane gave *tert*-butyl 2-(6'-bromo-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl)acetate (**115**) (0.045 g, 81%) as a pale yellow solid. Mp 70–72 °C; ν_{max}/cm^{-1} (neat) 2977 (CH), 1740 (C=O), 1678 (C=O), 1605, 1413, 1354, 1152, 748; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 2.68

(2H, dd, *J* 9.4, 8.0 Hz, 3'-H_2), 2.86 (2H, dd, *J* 9.4, 8.0 Hz, 4'-H_2), 3.85 (3H, s, 7'-OCH_3), 4.58 (2H, s, 2-H_2), 6.30 (1H, s, 8'-H), 7.33 (1H, s, 5'-H); δ_C (101 MHz, $CDCl_3$) 24.3 (CH_2), 28.0 (3 × CH_3), 31.5 (CH_2), 45.1 (CH_2), 56.4 (CH_3), 82.4 (C), 99.8 (CH), 104.8 (C), 119.7 (C), 132.1 (CH), 140.0 (C), 155.1 (C), 167.6 (C), 170.2 (C); *m/z* (EI) 369.0569 (M^+. $C_{16}H_{20}{}^{79}BrNO_4$ requires 369.0576), 315 (100%), 313 (99), 270 (52), 268 (52), 242 (39), 240 (41), 160 (38), 147 (26), 57 (74).

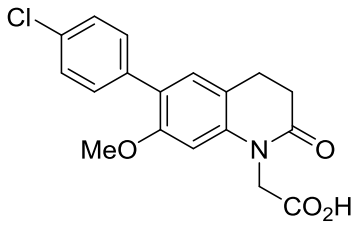
tert-Butyl 2-[6'-(4''-chlorophenyl)-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl]acetate (119)



To a stirred solution of *tert*-butyl 2-(6'-bromo-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl)acetate (**115**) (0.080 g, 0.22 mmol) in *N,N'*-dimethylformamide (5 mL) was added 4-chlorophenylboronic acid (0.041 g, 0.26 mmol), a solution of sodium bicarbonate (0.074 g, 0.88 mmol) in water (1 mL) and tetrakis(triphenylphospine)palladium(0) (0.013 g, 0.011 mmol). The mixture was degassed with argon under sonication for 0.5 h and then heated to 120 °C for 24 h. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite®, which was washed with ethyl acetate (20 mL). The filtrate was washed with a 5% aqueous solution of lithium chloride (3 × 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 30% ethyl acetate in hexane gave *tert*-butyl 2-[6'-(4''-chlorophenyl)-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl]acetate (**119**) (0.066 g, 75%) as a white solid. Mp 114–116 °C; ν_{max}/cm^{-1} (neat) 2980 (CH), 1734 (C=O), 1678 (C=O), 1614, 1489, 1352, 1155, 833, 748; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, O^{t}Bu), 2.73 (2H, dd, *J* 9.2, 7.6 Hz, 3'-H_2), 2.91 (2H, dd, *J* 9.2, 7.6 Hz, 4'-H_2), 3.76 (3H, s, 7'-OCH_3), 4.63 (2H, s, 2-H_2), 6.37 (1H, s, 8'-H), 7.09 (1H, s, 5'-H), 7.35 (2H, d, *J* 8.8 Hz, 2''-H and 6''-H), 7.43 (2H, d, *J* 8.8 Hz, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 24.5 (CH_2), 28.0 (3 × CH_3), 31.8 (CH_2), 45.0 (CH_2), 55.8 (CH_3), 82.3 (C), 99.0 (CH), 118.3 (C), 123.9 (C), 128.2 (2 × CH), 129.9 (CH), 130.7 (2 × CH), 132.8 (C),

136.1 (C), 140.1 (C), 155.7 (C), 167.8 (C), 170.4 (C); *m/z* (EI) 401.1378 (M^+. $C_{22}H_{24}{}^{35}ClNO_4$ requires 401.1394), 345 (100%), 272 (34), 258 (11), 84 (12), 57 (18).

2-[6'-(4''-Chlorophenyl)-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl]acetic acid (114)[150]



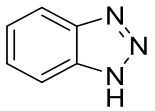
Trifluoroacetic acid (0.050 mL, 0.65 mmol) was added dropwise to a solution of *tert*-butyl 2-[6'-(4''-chlorophenyl)-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl]acetate (**119**) (0.065 g, 0.16 mmol) in dry dichloromethane (3 mL) and stirred at room temperature for 5 days. The reaction mixture was then concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 1% acetic acid and 3% methanol in dichloromethane gave 2-[6'-(4''-chlorophenyl)-7'-methoxy-3',4'-dihydro-1*H*-quinolin-2'-one-1'-yl]acetic acid (**114**) (0.052 g, 92%) as a white solid. Spectroscopic data were consistent with the literature.[150] Mp 218–220 °C; δ_H (400 MHz, $CDCl_3$ + 10% TFA) 2.82–2.90 (2H, m, 3'-H_2), 2.93–3.02 (2H, m, 4'-H_2), 3.80 (3H, s, 7'-OCH_3), 4.85 (2H, s, 2-H_2), 6.49 (1H, s, 8'-H), 7.18 (1H, s, 5'-H), 7.38 (2H, d, *J* 8.4 Hz, 2''-H and 6''-H), 7.43 (2H, d, *J* 8.4 Hz, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 23.9 (CH_2), 31.2 (CH_2), 45.2 (CH_2), 56.5 (CH_3), 100.1 (CH), 118.9 (C), 126.5 (C), 128.6 (2 × CH), 130.6 (CH), 130.8 (2 × CH), 133.6 (C), 135.6 (C), 138.4 (C), 156.2 (C), 174.7 (C), 174.8 (C); *m/z* (EI) 345 (M^+. 100%), 272 (33), 248 (18), 165 (10), 109 (17), 97 (22), 69 (23), 55 (49).

3.4 1*H*-Benzotriazole Experimental

General Procedure for Synthesis of 1*H*-Benzotriazoles

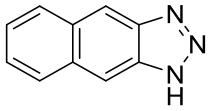
To a stirred solution of the corresponding 1,2-phenylenediamines (1.0 equiv.) in methanol (**127a–m** and **134 and 153a–c**) or acetonitrile (all other substrates) (10 mL/mmol) at 0 °C was added polymer-supported nitrite (containing 3.0 equiv. of NO_2) and *p*-toluenesulfonic acid monohydrate (3.0 equiv.). The reaction mixture was stirred for 1 h at 0 °C (**127a–m** and **134 and 153a–c**) or 0.5 h at 0 °C (all other substrates). The reaction mixture was then warmed to room temperature and stirred until completion (1–6 h). The resin was filtered and washed with ethyl acetate (20 mL/mmol). The reaction mixture was concentrated *in vacuo*. Purification by silica gel flash column chromatography eluting with ethyl acetate in hexane, diethyl ether in hexane or methanol in dichloromethane gave the 1*H*-benzotriazoles.

1*H*-Benzo[*d*][1.2.3]triazole (127a)[223]



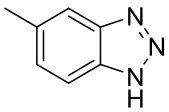
The reaction was carried out as described in the general procedure using 1,2-phenylenediamine (**126a**) (0.0500 g, 0.463 mmol), polymer-supported nitrite (0.396 g, containing 1.39 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.239 g, 1.39 mmol). The reaction was complete after 6 h. Purification by silica gel flash column chromatography, eluting with 40% ethyl acetate in hexane gave 1*H*-benzo[*d*][1.2.3]triazole (**127a**) (0.036 g, 66%) as a white solid. Mp 94–96 °C (lit.[223] 97 °C); δ_H (400 MHz, $CDCl_3$) 7.36–7.43 (2H, m, 5-H and 6-H), 7.94 (2H, dd, *J* 6.2, 3.0 Hz, 4-H and 7-H), 14.54 (1H, br s, 1-H); δ_C (101 MHz, $CDCl_3$) 115.0 (2 × CH), 126.1 (2 × CH), 138.9 (2 × C); *m*/*z* (ESI) 142 (MNa^+. 100%).

1*H*-Naphtho-(2,3-*d*)[1.2.3]triazole (127b)[224]



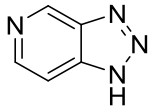
The reaction was carried out as described in the general procedure using 2,3-diaminonaphthalene (**126b**) (0.158 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 1*H*-naphtho-(2,3-*d*)-benzo[1.2.3]triazole (**127b**) (0.114 g, 67%) as a pale yellow solid. Mp 178–180 °C (lit.[224] 186 °C); δ_H (400 MHz, DMSO-d_6 + TFA) 7.45–7.52 (2H, m, 6-H and 7-H), 8.12 (2H, dd, *J* 6.5, 3.3 Hz, 5-H and 8-H), 8.53 (2H, s, 4-H and 9-H), 11.85 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6 + TFA) 111.4 (2 × CH), 125.2 (2 × CH), 128.6 (2 × CH), 131.3 (2 × C), 137.8 (2 × C); *m*/*z* (ESI) 170 (MH^+. 100%).

5-Methyl-1*H*-benzo[*d*][1.2.3]triazole (127c)[225]



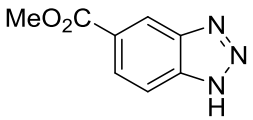
The reaction was carried out as described in the general procedure using 3,4-diaminotoluene (**126c**) (0.122 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 40% ethyl acetate in hexane gave 5-methyl-1*H*-benzo[*d*][1.2.3]triazole (**127c**) (0.097 g, 73%) as an orange solid. Mp 78–80 °C (lit.[225] 80–83 °C); δ_H (400 MHz, DMSO-d_6 + TFA) 2.46 (3H, s, 5-CH_3), 7.23 (1H, dd, *J* 8.4, 1.2 Hz, 6-H), 7.62 (1H, d, *J* 1.2 Hz, 4-H), 7.80 (1H, d, *J* 8.4 Hz, 7-H), 11.07 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6 + TFA) 21.2 (CH_3), 112.9 (CH), 115.4 (CH), 127.1 (CH), 135.6 (C), 138.0 (C), 138.7 (C); *m*/*z* (ESI) 156 (MNa^+. 100%).

1*H*-[1.2.3]Triazolo-(4,5-*c*)pyridine (127d)[226]



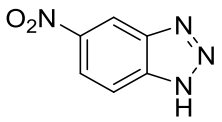
The reaction was carried out as described in the general procedure using 3,4-diaminopyridine (**126d**) (0.109 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 2 h. Purification by silica gel flash column chromatography, eluting with 5% methanol in dichloromethane gave 1*H*-[1.2.3]triazolo-(4,5-*c*)pyridine (**127d**) (0.072 g, 60%) as a white solid. Spectroscopic data were consistent with the literature.[226] Mp 171–174 °C; δ_H (400 MHz, DMSO-d_6) 7.86 (1H, dd, *J* 5.8, 0.6 Hz, 6-H), 8.45 (1H, d, *J* 5.8 Hz, 7-H), 9.45 (1H, br s, 4-H); δ_C (101 MHz, DMSO-d_6) 108.1 (CH), 139.7 (C), 140.6 (C), 142.1 (CH), 142.7 (CH); *m*/*z* (EI) 120 (M^+. 100%), 92 (65), 66 (79).

Methyl 1*H*-benzo[*d*][1.2.3]triazole-5-carboxylate (127e)[227]



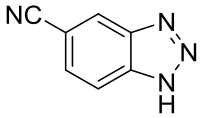
The reaction was carried out as described in the general procedure using methyl-3,4-diaminobenzoate (**126e**) (0.0500 g, 0.301 mmol), polymer-supported nitrite (0.258 g, containing 0.903 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.155 g, 0.903 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave methyl 1*H*-benzo[*d*][1.2.3]triazole-5-carboxylate (**127e**) (0.046 g, 86%) as a white solid. Mp 166–168 °C (lit.[227] 169–170 °C); δ_H (400 MHz, $CDCl_3$ + TFA) 4.04 (3H, s, OCH_3), 8.09 (1H, d, *J* 8.8 Hz, 7-H), 8.37 (1H, dd, *J* 8.8, 1.2 Hz, 6-H), 8.79 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$ + TFA) 53.5 (CH_3), 114.1 (CH), 117.4 (CH), 130.3 (CH), 131.1 (C), 135.8 (C), 136.9 (C), 166.3 (C); *m*/*z* (ESI) 178 (MH^+. 100%).

5-Nitro-1*H*-benzo[*d*][1.2.3]triazole (127f)[223]



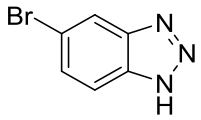
The reaction was carried out as described in the general procedure using 4-nitro-1,2-phenylenediamine (**126f**) (0.0500 g, 0.326 mmol), polymer-supported nitrite (0.280 g, containing 0.979 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.169 g, 0.979 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 5-nitro-1*H*-benzo[*d*][1.2.3]triazole (**127f**) (0.035 g, 66%) as a white solid. Spectroscopic data were consistent with the literature.[223] Mp 188–190 °C; δ_H (400 MHz, $CDCl_3$ + TFA) 8.14 (1H, d, *J* 5.2 Hz, 7-H), 8.54 (1H, dd, *J* 5.2, 1.6 Hz, 6-H), 9.03 (1H, d, *J* 1.6 Hz, 4-H); δ_C (101 MHz, $CDCl_3$ + TFA) 113.3 (CH), 114.9 (CH), 123.6 (CH), 138.1 (2 × C), 147.0 (C); *m*/*z* (EI) 164 (M^+. 95%), 106 (42), 90 (25), 79 (26), 63 (100).

1*H*-Benzo[*d*][1.2.3]triazole-5-carbonitrile (127g)[228]



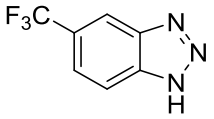
The reaction was carried out as described in the general procedure using 3,4-diaminobenzonitrile (**126g**) (0.0500 g, 0.376 mmol), polymer-supported nitrite (0.322 g, containing 1.13 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.194 g, 1.13 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 1*H*-benzo[*d*][1.2.3]triazole-5-carbonitrile (**127g**) (0.047 g, 86%) as an off-white solid. Spectroscopic data were consistent with the literature.[228] Mp 72–74 °C; δ_H (400 MHz, DMSO-d_6 + TFA) 7.68 (1H, dd, *J* 8.6, 1.4 Hz, 6-H), 7.96 (1H, d, *J* 8.6 Hz, 7-H), 8.12 (1H, br s, 4-H), 8.49 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6 + TFA) 107.7 (C), 115.7 (CH), 119.3 (C), 123.5 (CH), 128.6 (CH), 138.6 (C), 140.6 (C); *m*/*z* (EI) 144 (M^+. 100%), 116 (78), 69 (55), 57 (94).

5-Bromo-1*H*-benzo[*d*][1.2.3]triazole (127h)[225]



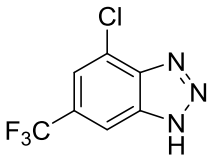
The reaction was carried out as described in the general procedure using 4-bromo-1,2-phenylenediamine (**126h**) (0.0500 g, 0.267 mmol), polymer-supported nitrite (0.229 g, containing 0.802 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.138 g, 0.802 mmol). The reaction was complete after 6 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave 5-bromo-1*H*-benzo[*d*][1.2.3]triazole (**127h**) (0.044 g, 82%) as a red solid. Mp 126–128 °C (lit.[225] 127–129 °C); δ_H (400 MHz, $CDCl_3$ + TFA) 7.88 (1H, dd, *J* 9.0, 1.2 Hz, 6-H), 7.96 (1H, d, *J* 9.0 Hz, 7-H), 8.24 (1H, d, *J* 1.2 Hz, 4-H); δ_C (101 MHz, $CDCl_3$ + TFA) 115.5 (CH), 116.9 (CH), 123.7 (C), 133.1 (CH), 134.9 (C), 136.7 (C); *m*/*z* (EI) 199 (M^+. 72%), 197 (73), 171 (50), 169 (52), 90 (50), 63 (100).

5-Trifluoromethyl-1*H*-benzo[*d*][1.2.3]triazole (127i)[225]



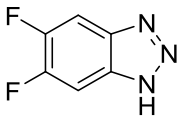
The reaction was carried out as described in the general procedure using 4-trifluoromethyl-1,2-phenylenediamine (**126i**) (0.0500 g, 0.284 mmol), polymer-supported nitrite (0.243 g, containing 0.852 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.147 g, 0.852 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave 5-trifluoromethyl-1*H*-benzo[*d*][1.2.3]triazole (**127i**) (0.046 g, 88%) as a yellow solid. Spectroscopic data were consistent with the literature.[225] Mp 94–96 °C; δ_H (400 MHz, DMSO-d_6) 7.73 (1H, dd, *J* 8.8, 1.2 Hz, 6-H), 8.09 (1H, d, *J* 8.8 Hz, 7-H), 8.41 (1H, br s, 4-H); δ_C (101 MHz, DMSO-d_6) 115.2 (CH), 115.8 (CH), 122.7 (CH), 124.8 (q, $^1J_{C\text{-}F}$ 272.2 Hz, C), 126.0 (q, $^2J_{C\text{-}F}$ 33.5 Hz, C), 138.8 (C), 140.3 (C); *m*/*z* (EI) 187 (M^+. 55%), 84 (81), 66 (100).

4-Chloro-6-(trifluoromethyl)-1*H*-benzo[*d*][1.2.3]triazole (127j)



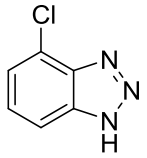
The reaction was carried out as described in the general procedure using 3-chloro-5-trifluoromethyl-1,2-phenylenediamine (**126j**) (0.0500 g, 0.237 mmol), polymer-supported nitrite (0.204 g, containing 0.712 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.23 g, 0.712 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave 4-chloro-6-(trifluoromethyl)-1*H*-benzo[*d*][1.2.3]triazole (**127j**) (0.0390 g, 72%) as a white solid. Mp 166–169 °C; ν_{max}/cm^{-1} (neat) 2711 (CH), 1593, 1341, 1242, 1167, 1130, 1069, 874; δ_H (400 MHz, DMSO-d_6) 7.90 (1H, s, 7-H), 8.40 (1H, s, 5-H), 16.75 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6) 113.2 (CH), 121.7 (CH), 123.9 (q, $^1J_{C\text{-}F}$ 275.6 Hz, C), 126.8 (C), 127.6 (q, $^2J_{C\text{-}F}$ 32.8 Hz, C), 139.4 (C), 139.4 (C); *m*/*z* (EI) 220.9971 (M^+. $C_7H_3{}^{35}ClF_3N_3$ requires 220.9968), 193 (79%), 174 (45), 84 (47), 66 (53).

5,6-Difluoro-1*H*-benzo[*d*][1.2.3]triazole (127k)[229]



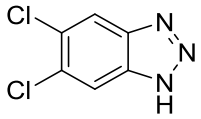
The reaction was carried out as described in the general procedure using 4,5-difluoro-1,2-phenylenediamine (**126k**) (0.144 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 4 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave 5,6-difluoro-1*H*-benzo[*d*][1.2.3]triazole (**127k**) (0.095 g, 61%) as an off-white solid. Mp 176–178 °C (lit.[229] 183–184 °C); δ_H (400 MHz, DMSO-d_6) 8.03 (2H, dd, *J* 8.8, 8.0 Hz, 4-H and 7-H), 15.97 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6) 102.2 (2 × CH), 134.6 (2 × C), 149.2 (dd, $^1J_{C\text{-}F}$ 248.1, $^2J_{C\text{-}F}$ 17.7 Hz, 2 × C); *m*/*z* (EI) 155 (M^+. 100%), 127 (47), 100 (58), 84 (32), 66 (40).

4-Chloro-1*H*-benzo[*d*][1.2.3]triazole (127l)[225]



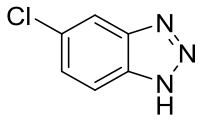
The reaction was carried out as described in the general procedure using 3-chloro-1,2-phenylenediamine (**126l**) (0.143 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave 4-chloro-1*H*-benzo[*d*][1.2.3]triazole (**127l**) (0.090 g, 59%) as a white solid. Mp 160–162 °C (lit.[225] 168–170 °C); δ_H (400 MHz, DMSO-d_6) 7.36–7.53 (2H, m, 6-H and 7-H), 7.76–7.90 (1H, m, 5-H), 16.13 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6) 113.1 (CH), 121.5 (C), 124.9 (CH), 127.4 (CH), 136.5 (C), 139.2 (C); *m*/*z* (ESI) 154 (MH^+. 100%).

5,6-Dichloro-1*H*-benzo[*d*][1.2.3]triazole (127m)[223]



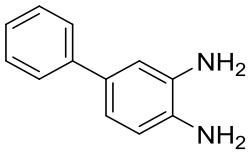
The reaction was carried out as described in the general procedure using 4,5-dichloro-1,2-phenylenediamine (**126m**) (0.177 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave 5,6-dichloro-1*H*-benzo[*d*][1.2.3]triazole (**127m**) (0.139 g, 74%) as a white solid. Mp 249–252 °C (lit.[223] 267 °C); δ_H (400 MHz, DMSO-d_6) 8.22 (2H, s, 4-H and 7-H), 15.99 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6) 116.9 (2 × CH), 128.9 (2 × C), 138.5 (2 × C); *m*/*z* (EI) 189 (M^+. 65%), 187 (100), 161 (48), 159 (78), 97 (77), 66 (41).

5-Chloro-1*H*-benzo[*d*][1.2.3]triazole (134)[225]



The reaction was carried out as described in the general procedure using 4-chloro-1,2-phenylenediamine (**126n**) (0.143 g, 1.00 mmol), polymer-supported nitrite (0.857 g, containing 3.00 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.517 g, 3.00 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave 5-chloro-1*H*-benzo[*d*][1.2.3]triazole (**134**) (0.110 g, 72%) as a white solid. Mp 125–128 °C (lit.[225] 129–131 °C); δ_H (400 MHz, DMSO-d_6) 7.39 (1H, dd, *J* 8.8, 1.4 Hz, 6-H), 7.92 (1H, d, *J* 8.8 Hz, 7-H), 7.98 (1H, d, *J* 1.4 Hz, 4-H), 15.87 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6) 114.7 (CH), 117.2 (CH), 126.4 (CH), 130.7 (C), 138.3 (C), 139.0 (C); *m/z* (EI) 153 (M^+. 100%), 125 (74), 90 (39), 63 (88).

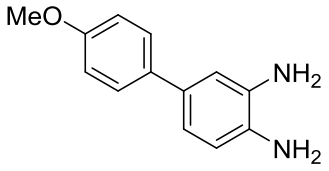
[1,1'-Biphenyl]-3,4-diamine (152a)[230]



To a stirred solution of 4-phenyl-2-nitroaniline (**110a**) (0.240 g, 1.12 mmol) in methanol (5.0 mL) was added 10% palladium on carbon (0.060 g, 0.0560 mmol) under an atmosphere of argon. To this mixture was then added sodium borohydride (0.128 g, 3.36 mmol) and the reaction was stirred at room temperature for 27 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate (20 mL) and concentrated *in vacuo*. This gave [1,1'-biphenyl]-3,4-diamine (**152a**) (0.192 g, 94%) as a white solid. Mp 99–102 °C (lit.[230] 102 °C); δ_H (400 MHz, $CDCl_3$) 3.45 (4H, br s, 3-NH_2 and 4-NH_2), 6.77 (1H, d, *J* 8.4 Hz, 5-H), 6.96–7.00 (2H, m, 2-H and 6-H), 7.27 (1H, tt, *J* 7.5, 1.2 Hz, 4'-H), 7.39 (2H, dd, *J* 8.2, 7.5 Hz, 3'-H and 5'-H), 7.53 (2H, dd, *J* 8.2, 1.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 115.5 (CH), 117.0 (CH), 119.1 (CH), 126.4 (CH),

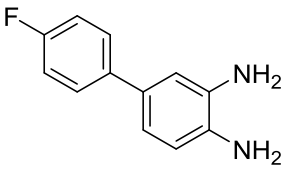
126.6 (2 × CH), 128.6 (2 × CH), 133.5 (C), 134.3 (C), 134.9 (C), 141.3 (C); *m/z* (ESI) 207 (MNa^+. 100%).

4'-Methoxy-[1,1'-biphenyl]-3,4-diamine (152b)



The reaction was carried out according to the previously described procedure for [1,1'biphenyl]-3,4-diamine (**152a**) using 4-(4'-methoxyphenyl)-2-nitroaniline (**110b**) (0.160 g, 0.655 mmol), 10% palladium on carbon (0.0348 g, 0.0327 mmol) and sodium borohydride (0.0748 g, 1.96 mmol). This gave 4'-methoxy-[1,1'-biphenyl]-3,4-diamine (**152b**) (0.118 g, 85%) as a white solid. Mp 155–158 °C; ν_{max}/cm^{-1} (neat) 3383 (NH), 2835 (CH), 1607, 1503, 1242, 810; δ_H (400 MHz, $CDCl_3$) 3.43 (2H, br s, NH_2), 3.47 (2H, br s, NH_2), 3.84 (3H, s, 4'-OCH_3), 6.75 (1H, d, *J* 7.6 Hz, 5-H), 6.90–6.98 (4H, m, 2-H, 6-H, 3'-H and 5'-H), 7.47 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.3 (CH_3), 114.1 (2 × CH), 115.1 (CH), 117.0 (CH), 118.6 (CH), 127.5 (2 × CH), 133.2 (C), 133.7 (C), 134.0 (C), 135.0 (C), 158.5 (C); *m/z* (ESI) 215.1171 (MH^+. $C_{13}H_{15}N_2O$ requires 215.1179).

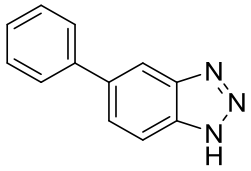
4'-Fluoro-[1,1'-biphenyl]-3,4-diamine (152c)[231]



The reaction was carried out according to the previously described procedure for [1,1'-biphenyl]-3,4-diamine (**152a**) using 4-(4'-fluorophenyl)-2-nitroaniline (**110c**) (0.160 g, 0.689 mmol), 10% palladium on carbon (0.0363 g, 0.0345 mmol) and sodium borohydride (0.0786 g, 2.07 mmol). This gave 4'-fluoro-[1,1'-biphenyl]-3,4-diamine (**152c**) (0.120 g, 86%) as a light purple solid. Spectroscopic data were consistent with the literature.[231] Mp 117–120 °C; δ_H (400 MHz, $CDCl_3$) 3.45 (4H, br s, 3-NH_2 and 4-NH_2), 6.76 (1H, d, *J* 8.0 Hz, 5-H), 6.89–6.94 (2H, m, 2-H and 6-H), 7.07 (2H, t, *J* 8.8 Hz, 3'-H and 5'-H), 7.47 (2H,

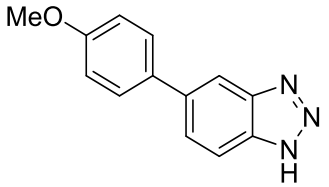
dd, *J* 8.8, 5.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 115.3 (CH), 115.4 (d, $^2J_{C-F}$ 21.3 Hz, 2 × CH), 117.0 (CH), 118.9 (CH), 128.0 (d, $^3J_{C-F}$ 8.1 Hz, 2 × CH), 132.6 (C), 134.3 (C), 135.0 (C), 137.5 (d, $^4J_{C-F}$ 3.0 Hz, C), 161.9 (d, $^1J_{C-F}$ 246.9 Hz, C); *m*/*z* (ESI) 203 (MH^+. 100%).

5-Phenyl-1*H*-benzo[*d*][1.2.3]triazole (153a)[232]



The reaction was carried out as described in the general procedure using [1,1'-biphenyl]-3,4-diamine (**152a**) (0.100 g, 0.543 mmol), polymer-supported nitrite (0.465 g, containing 1.63 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.281 g, 1.63 mmol). The reaction was complete after 1 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave 5-phenyl-1*H*-benzo[*d*][1.2.3]triazole (**153a**) (0.069 g, 65%) as a pale yellow solid. Mp 152–155 °C (lit.[232] 156 °C); δ_H (400 MHz, DMSO-d_6 + TFA) 7.38 (1H, t, *J* 7.4 Hz, 4'-H), 7.48 (2H, t, *J* 7.4 Hz, 3'-H and 5'-H), 7.70–7.77 (3H, m, 2'-H, 6'-H and 6-H), 7.98 (1H, d, *J* 8.8 Hz, 7-H), 8.12 (1H, br s, 4-H); δ_C (101 MHz, DMSO-d_6 + TFA) 112.6 (CH), 116.0 (CH), 125.6 (CH), 127.8 (2 × CH), 128.0 (CH), 129.4 (2 × CH), 138.5 (C), 139.0 (C), 139.7 (C), 140.4 (C); *m*/*z* (ESI) 218 (MNa^+. 100%).

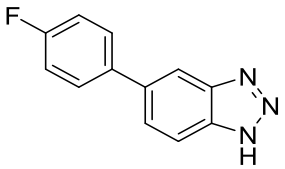
5-(4'-Methoxyphenyl)-(1*H*)-benzo[*d*][1.2.3]triazole (153b)[233]



The reaction was carried out as described in the general procedure using 4'-methoxy-[1,1'-biphenyl]-3,4-diamine (**152b**) (0.118 g, 0.551 mmol), polymer-supported nitrite (0.472 g, containing 1.65 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.284 g, 1.65 mmol). The reaction was complete after 2 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl

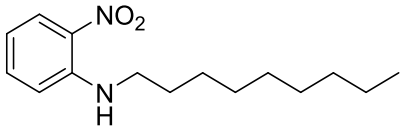
acetate in hexane gave 5-(4'-methoxyphenyl)-1*H*-benzo[*d*][1.2.3]triazole (**153b**) (0.063 g, 51%) as a white solid. Spectroscopic data were consistent with literature.[233] Mp 181–183 °C; δ_H (400 MHz, DMSO-d_6 + TFA) 3.80 (3H, s, 4'-OCH_3), 7.02–7.07 (2H, m, 3'-H and 5'-H), 7.67–7.73 (3H, m, 2'-H, 6'-H and 6-H), 7.95 (1H, d, *J* 8.8 Hz, 7-H), 8.03 (1H, br s, 4-H); δ_C (101 MHz, DMSO-d_6 + TFA) 55.6 (CH_3), 111.5 (CH), 114.9 (2 × CH), 116.1 (CH), 125.3 (CH), 128.9 (2 × CH), 132.7 (C), 138.3 (C), 139.0 (C), 139.4 (C), 159.5 (C); *m*/*z* (ESI) 226 (MH^+. 100%).

5-(4'-Fluorophenyl)-1*H*-benzo[*d*][1.2.3]triazole (153c)



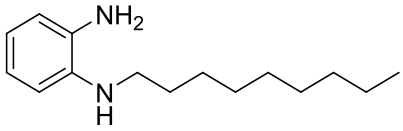
The reaction was carried out as described in the general procedure using 4'-fluoro-[1,1'-biphenyl]-3,4-diamine (**152c**) (0.120 g, 0.593 mmol), polymer-supported nitrite (0.509 g, containing 1.78 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.307 g, 1.78 mmol). The reaction was complete after 6 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave 5-(4'-fluorophenyl)-1*H*-benzo[*d*][1.2.3]triazole (**153c**) (0.053 g, 43%) as a pale yellow solid. Mp 176–179 °C; ν_{max}/cm^{-1} (neat) 3460 (NH), 2250 (CH), 1053, 1024, 1005, 758; δ_H (400 MHz, DMSO-d_6 + TFA) 7.28–7.35 (2H, m, 3'-H and 5'-H), 7.72 (1H, dd, *J* 8.6, 2.2 Hz, 6-H), 7.77–7.84 (2H, m, 2'-H and 6'-H), 7.98 (1H, dd, *J* 8.6, 0.6 Hz, 7-H), 8.11 (1H, br s, 4-H), 8.90 (1H, br s, 1-H); δ_C (101 MHz, DMSO-d_6 + TFA) 112.7 (CH), 116.0 (CH), 116.2 (d, $^2J_{C\text{-}F}$ 21.4 Hz, 2 × CH), 125.6 (CH), 129.8 (d, $^3J_{C\text{-}F}$ 8.2 Hz, 2 × CH), 136.9 (d, $^4J_{C\text{-}F}$ 3.1 Hz, C), 137.4 (C), 138.9 (C), 139.6 (C), 162.5 (d, $^1J_{C\text{-}F}$ 244.7 Hz, C); *m*/*z* (ESI) 214.0776 (MH^+. $C_{12}H_9FN_3$ requires 214.0775).

***N*-Nonyl-2-nitroaniline (154a)**



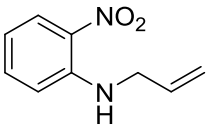
To a stirred solution of 2-nitroaniline (**108a**) (0.400 g, 2.89 mmol) and nonanal (0.498 mL, 2.89 mmol) in 1,2-dichloroethane (20 mL) were added sodium triacetoxyborohydride (1.23 g, 5.79 mmol) and acetic acid (0.331 mL, 5.79 mmol) at room temperature. The reaction was stirred for 18 h then nonanal (0.249 mL, 1.45 mmol), triacetoxyborohydride (0.613 g, 2.89 mmol) and acetic acid (0.165 mL, 2.89 mmol) were added. The reaction mixture was stirred for a further 48 h and then nonanal (0.149 mL, 0.868 mmol), triacetoxyborohydride (0.368 g, 1.74 mmol) and acetic acid (0.099 mL, 1.74 mmol) were added. The reaction was complete after 4 days. The reaction was quenched with a 1 M aqueous solution of sodium hydroxide (20 mL) and extracted with 1,2-dichloroethane (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 2% diethyl ether in hexane gave *N*-nonyl-2-nitroaniline (**154a**) (0.615 g, 80%) as an orange oil. ν_{max}/cm^{-1} (neat) 3379 (NH), 2924 (CH), 1618, 1512, 1263, 743; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 9'-H_3), 1.20–1.49 (12H, m, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2, 7'-H_2 and 8'-H_2), 1.72 (2H, pent, *J* 7.3 Hz, 2'-H_2), 3.28 (2H, td, *J* 7.3, 5.2 Hz, 1'-H_2), 6.61 (1H, ddd, *J* 8.4, 7.0, 1.1 Hz, 4-H), 6.84 (1H, dd, *J* 8.4, 1.1 Hz, 6-H), 7.42 (1H, dddd, *J* 8.4, 7.0, 1.6, 0.6 Hz, 5-H), 8.05 (1H, br s, NH), 8.16 (1H, dd, *J* 8.4, 1.6 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 27.1 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 43.1 (CH_2), 113.8 (CH), 115.0 (CH), 126.9 (CH), 131.7 (C), 136.2 (CH), 145.7 (C); *m/z* (ESI) 287.1733 (MNa^+. $C_{15}H_{24}N_2NaO_2$ requires 287.1730).

***N*-Nonyl-1,2-phenylenediamine (155a)**



To a stirred solution of *N*-nonyl-2-nitroaniline (**154a**) (0.440 g, 1.66 mmol) in ethyl acetate (20 mL) was added tin(II) chloride dihydrate (1.88 g, 8.32 mmol). The reaction mixture was heated to 70 °C for 24 h. The reaction mixture was quenched with a saturated aqueous solution of sodium hydrogen carbonate (20 mL). The resulting biphasic emulsion was filtered through Celite®, which washed with ethyl acetate (30 mL). After separation, the aqueous phase was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 5% ethyl acetate in hexane gave *N*-nonyl-1,2-phenylenediamine (**155a**) (0.312 g, 80%) as a white solid. Mp 36–38 °C; ν_{max}/cm^{-1} (neat) 3360 (NH), 3271 (NH), 1630, 1518, 1487, 1285, 905, 712; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz, 9'-H_3), 1.24–1.50 (12H, m, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2, 7'-H_2 and 8'-H_2), 1.68 (2H, pent, *J* 7.2 Hz, 2'-H_2), 3.11 (2H, t, *J* 7.2 Hz, 1'-H_2), 3.33 (3H, br s, NH and NH_2), 6.65–6.75 (3H, m, 3 × ArH), 6.84 (1H, ddd, *J* 8.0, 6.6, 1.8 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 27.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 44.3 (CH_2), 111.6 (CH), 116.5 (CH), 118.3 (CH), 120.8 (CH), 134.0 (C), 138.2 (C); *m/z* (ESI) 235.2160 (MH^+. $C_{15}H_{27}N_2$ requires 235.2169).

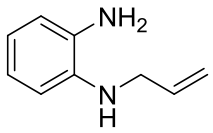
***N*-Allyl-2-nitroaniline (154b)**[234]



To a stirred solution of 2-nitroaniline (**108a**) (0.774 g, 5.60 mmol) and cesium carbonate (1.37 g, 4.20 mmol) in *N*,*N*'-dimethylformamide (40 mL) was added dropwise, a solution of allyl bromide (0.242 mL, 2.80 mmol) in *N*,*N*'-dimethylformamide (16 mL) at 0° C. After the addition was complete, the reaction mixture was stirred for 1 h at 0 °C and then warmed to room

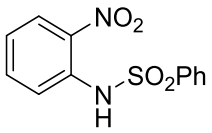
temperature and stirred for further 24 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with a 5% aqueous solution of lithium chloride (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave *N*-allyl-2-nitroaniline (**154b**) (0.373 g, 75%) as a yellow solid. Mp 50–52 °C (lit.[234] 52–54 °C); δ_H (400 MHz, $CDCl_3$) 3.99 (2H, tt, *J* 5.2, 1.2 Hz, 1'-H_2), 5.25 (1H, ddt, *J* 10.4, 3.0, 1.2 Hz, 3'-*H*H), 5.32 (1H, ddt, *J* 17.2, 3.0, 1.2 Hz, 3'-H*H*), 5.96 (1H, ddt, *J* 17.2, 10.4, 5.2 Hz, 2'-H), 6.66 (1H, ddd, *J* 8.8, 6.8, 1.2 Hz, 4-H), 6.83 (1H, dd, *J* 8.4, 1.2 Hz, 6-H), 7.42 (1H, dddd, *J* 8.4, 6.8, 1.6, 0.6 Hz, 5-H), 8.14–8.24 (2H, m, 3-H and NH); δ_C (101 MHz, $CDCl_3$) 45.3 (CH_2), 114.1 (CH), 115.5 (CH), 117.1 (CH_2), 126.9 (CH), 132.1 (C), 133.2 (CH), 136.1 (CH), 145.3 (C); *m*/*z* (ESI) 201 (MNa^+. 100%).

_N_-Allyl-1,2-phenylenediamine (155b)[235]



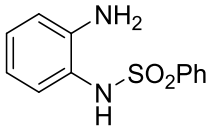
To a stirred solution of *N*-allyl-2-nitroaniline (**154b**) (0.480 g, 2.69 mmol) and zinc powder (0.880 g, 13.5 mmol) in methanol (10 mL) was added acetic acid (0.690 mL, 12.1 mmol) at room temperature. The reaction mixture was stirred for 24 h, filtered through Celite®, washed with ethyl acetate (30 mL) and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 25% diethyl ether in hexane gave *N*-allyl-1,2-phenylenediamine (**155b**) (0.209 g, 52%) as a pale yellow oil. Spectroscopic data were consistent with the literature.[235] δ_H (400 MHz, $CDCl_3$) 3.37 (3H, br s, NH and NH_2), 3.76 (2H, dt, *J* 5.6, 1.6 Hz, 1'-H_2), 5.18 (1H, ddt, *J* 10.4, 3.0, 1.6 Hz, 3'-*H*H), 5.30 (1H, ddt, *J* 17.2, 3.0, 1.6 Hz, 3'-H*H*), 6.01 (1H, ddt, *J* 17.2, 10.4, 5.6 Hz, 2'-H), 6.64–6.74 (3H, m, 3 × ArH), 6.81 (1H, ddd, *J* 9.2, 7.2, 2.0 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 46.9 (CH_2), 112.1 (CH), 116.3 (CH_2), 116.5 (CH), 118.8 (CH), 120.7 (CH), 134.3 (C), 135.6 (CH), 137.5 (C); *m*/*z* (EI) 148 (M^+. 74%), 119 (70), 107 (100), 80 (45).

***N*-(2'-Nitrophenyl)benzenesulfonamide (154c)[236]**



To a stirred solution of 2-nitroaniline (**108a**) (0.300 g, 2.17 mmol) and pyridine (0.525 mL, 6.51 mmol) in dichloromethane (5.5 mL) was added benzenesulfonyl chloride (0.833 mL, 6.51 mmol) at room temperature. The reaction mixture was stirred for 20 h, then pyridine (0.262 mL, 3.26 mmol) and benzenensulfonyl chloride (0.417 mL, 3.26 mmol) were added. The reaction was complete after 2 days. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave *N*-(2'-nitrophenyl)benzenesulfonamide (**154c**) (0.353 g, 58%) as a yellow solid. Mp 100–102 °C (lit.[236] 103–105 °C); δ_H (400 MHz, $CDCl_3$) 7.16 (1H, ddd, *J* 8.6, 7.6, 1.2 Hz, 4'-H), 7.44–7.50 (2H, m, 3-H and 5-H), 7.54–7.62 (2H, m, 5'-H and 6'-H), 7.82–7.87 (3H, m, 2-H, 4-H and 6-H), 8.09 (1H, dd, *J* 8.6, 1.6 Hz, 3'-H), 9.85 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 121.2 (CH), 124.0 (CH), 126.2 (CH), 127.2 (2 × CH), 129.4 (2 × CH), 133.7 (CH), 133.8 (C), 135.9 (CH), 137.2 (C), 138.7 (C); *m*/*z* (ESI) 301 (MNa^+. 100%).

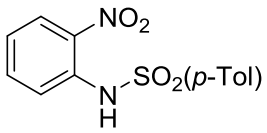
***N*-(2'-Aminophenyl)benzenesulfonamide (155c)[237]**



To a stirred solution of *N*-(2'-nitrophenyl)benzenesulfonamide (**154c**) (0.353 g, 1.27 mmol) and 10% palladium on carbon (0.0674 g, 0.0634 mmol) in methanol (13 mL) was added portionwise sodium borohydride (0.144 g, 3.81 mmol) under an argon atmosphere. The reaction was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite®, washed with ethyl acetate (20 mL) and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane, followed by

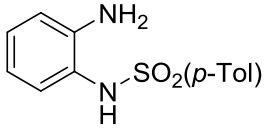
trituration with hexane gave *N*-(2'-aminophenyl)benzenesulfonamide (**155c**) (0.150 g, 48%) as a white solid. Mp 170–171 °C (lit.[237] 170–172 °C); δ_H (400 MHz, CD_3OD) 6.40–6.47 (2H, m, 3'-H and 4'-H), 6.75 (1H, dd, *J* 8.2, 1.2 Hz, 6'-H), 6.96 (1H, ddd, *J* 8.2, 6.4, 2.2 Hz, 5'-H), 7.46–7.53 (2H, m, 3-H and 5-H), 7.57–7.63 (1H, m, 4-H), 7.69–7.74 (2H, m, 2-H and 6-H); δ_C (101 MHz, CD_3OD) 116.5 (CH), 117.4 (CH), 121.6 (C), 127.1 (2 × CH), 127.8 (CH), 127.9 (CH), 128.6 (2 × CH), 132.5 (CH), 139.6 (C), 145.0 (C); *m*/*z* (ESI) 271 (MNa^+. 100%).

4-Methyl-*N*-(2'-nitrophenyl)benzenesulfonamide (154d)[238]



The reaction was carried out according to the previously described procedure for *N*-(2'-nitrophenyl)benzenesulfonamide (**154c**) using 2-nitroaniline (**108a**) (0.500 g, 3.62 mmol), *p*-tosyl chloride (2.08 g, 10.8 mmol) and pyridine (0.875 mL, 10.8 mmol) in dichloromethane (9 mL). The reaction was stirred at room temperature for 48 h. Purification by silica gel flash column chromatography, eluting with 10% ethyl acetate in hexane gave 4-methyl-*N*-(2'-nitrophenyl)benzenesulfonamide (**154d**) (0.953 g, 90%) as a yellow solid. Mp 110–112 °C (lit.[238] 110–113 °C); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4-CH_3), 7.15 (1H, ddd, *J* 8.4, 7.2, 1.2 Hz, 4'-H), 7.23–7.29 (2H, m, 3-H and 5-H), 7.58 (1H, ddd, *J* 8.4, 7.2, 1.2 Hz, 5'-H), 7.71–7.76 (2H, m, 2-H and 6-H), 7.84 (1H, dd, *J* 8.4, 1.2 Hz, 6'-H), 8.11 (1H, dd, *J* 8.4, 1.2 Hz, 3'-H), 9.85 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 121.0 (CH), 123.8 (CH), 126.2 (CH), 127.3 (2 × CH), 130.0 (2 × CH), 134.0 (C), 135.7 (C), 135.9 (CH), 137.1 (C), 144.8 (C); *m*/*z* (ESI) 315 (MNa^+. 100%).

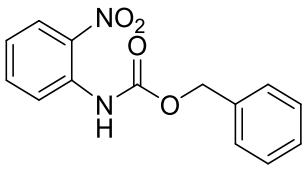
***N*-(2'-Aminophenyl)-4-methylbenzenesulfonamide (155d)**[239]



The reaction was carried out according to the previously described procedure for *N*-(2'-aminophenyl)benzenesulfonamide (**155c**) using 4-methyl-*N*-(2'-

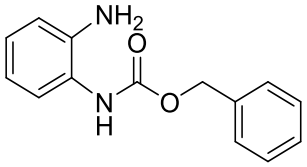
nitrophenyl)benzenesulfonamide (**154d**) (0.100 g, 0.342 mmol), 10% palladium on carbon (0.0182 g, 0.0171 mmol) and sodium borohydride (0.0388 g, 1.03 mmol) in methanol (3.4 mL). The reaction was stirred at room temperature for 24 h, then filtered through Celite®, washed with ethyl acetate (20 mL) and concentrated *in vacuo*. This gave *N*-(2'-aminophenyl)-4-methylbenzenesulfonamide (**155d**) (0.081 g, 91%) as a yellow solid. Mp 130–132 °C (lit.[239] 138 °C); δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, 4-CH_3), 4.05 (2H, br s, NH_2), 6.48–6.53 (2H, m, 3'-H and 5'-H), 6.71 (1H, d, *J* 8.0 Hz, 6'-H), 6.97–7.04 (1H, m, 4'-H), 7.21 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.62 (2H, d, *J* 8.0 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 117.1 (CH), 118.6 (CH), 121.3 (C), 127.6 (2 × CH), 128.5 (CH), 128.8 (CH), 129.6 (2 × CH), 136.0 (C), 143.9 (C), 144.4 (C); *m*/*z* (ESI) 285 (MNa^+. 100%).

_N_-Benzyloxycarbonyl-2-nitroaniline (154e)[240]



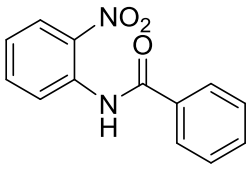
To a stirred solution of 2-nitroaniline (**108a**) (0.100 g, 0.723 mmol) in THF (0.880 mL) at 0 °C, was added a solution of sodium hydride (60% dispersion in mineral oil) (0.062 g, 1.56 mmol) in dry THF (0.750 mL). The mixture was stirred at 0 °C for 0.5 h, then was allowed to warm to room temperature. After 1 h, a solution of benzyl chloroformate (0.102 mL, 0.723 mmol) in toluene (0.290 mL) was added dropwise. The reaction mixture was stirred at toom temperature for 3 h. The mixture was diluted with ethyl acetate (15 mL) and washed with water (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave *N*-benzyloxycarbonyl-2-nitroaniline (**154e**) (0.150 g, 77%) as a yellow solid. Mp 65–66 °C (lit.[240] 64–66 °C); δ_H (400 MHz, $CDCl_3$) 5.25 (2H, s, 1'-H_2), 7.12 (1H, ddd, *J* 8.6, 7.4, 1.4 Hz, 4-H), 7.33–7.47 (5H, m, Ph), 7.63 (1H, ddd, *J* 8.6, 7.4, 1.4 Hz, 5-H), 8.20 (1H, dd, *J* 8.6, 1.4 Hz, 6-H), 8.59 (1H, dd, *J* 8.6, 1.4 Hz, 3-H), 9.92 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 67.6 (CH_2), 120.7 (CH), 122.4 (CH), 125.9 (CH), 128.5 (2 × CH), 128.6 (CH), 128.7 (2 × CH), 135.3 (C), 135.5 (C), 135.9 (CH), 136.1 (C), 153.0 (C); *m*/*z* (ESI) 295 (MNa^+. 100%).

***N*-Benzyloxycarbonyl-1,2-phenylenediamine (155e)**[241]



The reaction was carried out according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**154a**) using *N*-benzyloxycarbonyl-2-nitroaniline (**154e**)(0.350 g, 1.29 mmol) and tin(II) chloride dihydrate (1.45 g, 6.43 mmol) in ethyl acetate (13 mL). The reaction was stirred under reflux for 20 h. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane gave *N*-benzoyl-1,2-phenylenediamine (**155e**) (0.229 g, 73%) as a white solid. Spectroscopic data were consistent with the literature.[241] Mp 101–103 °C; δ_H (400 MHz, CD_3OD) 5.18 (2H, s, 1'-H_2), 6.69 (1H, ddd, *J* 8.0, 7.6, 1.4 Hz, 5-H), 6.81 (1H, dd, *J* 8.0, 1.4 Hz, 3-H), 6.97 (1H, ddd, *J* 8.0, 7.6, 1.4 Hz, 4-H), 7.12–7.20 (1H, m, 6-H), 7.28–7.48 (5H, m, Ph); δ_C (101 MHz, CD_3OD) 66.5 (CH_2), 116.7 (CH), 118.1 (CH), 123.8 (C), 125.1 (C), 125.3 (CH), 126.2 (CH), 127.6 (2 × CH), 127.7 (CH), 128.1 (2 × CH), 136.8 (C), 155.8 (C); *m*/*z* (ESI) 243 (MH^+. 100%).

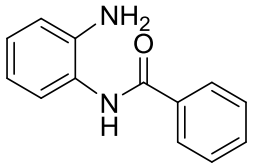
***N*-Benzoyl-2-nitroaniline (154f)**[238]



To a stirred solution of 2-nitroaniline (**108a**) (0.200 g, 1.45 mmol) and benzoyl chloride (0.336 mL, 2.89 mmol) in dichloromethane (10 mL) was added triethylamine (0.350 mL, 2.51 mmol) at 0 °C. The reaction was then allowed to slowly warm to room temperature and was stirred for 20 h. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid (10 mL) and extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave *N*-benzoyl-2-nitroaniline (**154f**) (0.287 g, 82%) as a yellow solid. Mp 76–78 °C (lit.[238] 76–78

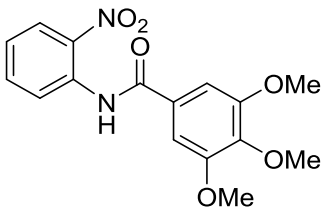
°C); δ_H (400 MHz, $CDCl_3$) 7.23 (1H, ddd, *J* 8.6, 7.4, 1.4 Hz, 4-H), 7.51–7.65 (3H, m, 3'-H, 4'-H and 5'-H), 7.72 (1H, ddd, *J* 8.6, 7.4, 1.4 Hz, 5-H), 7.98–8.05 (2H, m, 2'-H and 6'-H), 8.29 (1H, dd, *J* 8.6, 1.4 Hz, 6-H), 9.02 (1H, dd, *J* 8.6, 1.4 Hz, 3-H), 11.36 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 122.2 (CH), 123.3 (CH), 125.9 (CH), 127.4 (2 × CH), 129.1 (2 × CH), 132.7 (CH), 134.1 (C), 135.4 (C), 136.2 (CH), 136.5 (C), 165.8 (C); *m*/*z* (ESI) 265 (MNa^+. 100%).

_N_-Benzoyl-1,2-phenylenediamine (155f)[242]



The reaction was carried out according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**155a**) using *N*-benzoyl-2-nitroaniline (**154f**) (0.270 g, 1.11 mmol) and tin(II) chloride dihydrate (1.26 g, 5.55 mmol) in ethyl acetate (12 mL). The reaction was stirred under reflux for 20 h. Purification by silica gel flash column chromatography, eluting with 25% ethyl acetate in hexane gave *N*-benzoyl-1,2-phenylenediamine (**155f**) (0.120 g, 51%) as a white solid. Mp 150–154 °C (lit.[242] 154–155 °C); δ_H (400 MHz, $CDCl_3$) 3.87 (2H, br s, NH_2), 6.81–6.87 (2H, m, 3-H and 4-H), 7.09 (1H, ddd, *J* 8.0, 7.2, 1.4 Hz, 5-H), 7.32 (1H, d, *J* 8.0 Hz, 6-H), 7.44–7.59 (3H, m, 3'-H, 4'-H and 5'-H), 7.85–7.95 (3H, m, NH, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 118.4 (CH), 119.8 (CH), 124.6 (C), 125.2 (CH), 127.2 (CH), 127.3 (2 × CH), 128.8 (2 × CH), 131.9 (CH), 134.2 (C), 140.7 (C), 165.8 (C); *m*/*z* (ESI) 235 (MNa^+. 100%).

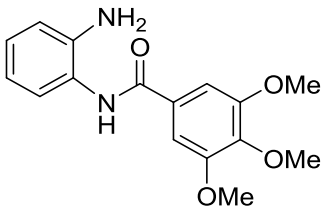
_N_-(3',4',5'-Trimethoxybenzoyl)-2-nitroaniline (154g)[243]



The reaction was carried out according to the previously described procedure for *N*-benzoyl-2-nitroaniline (**154f**) using 2-nitroaniline (**108a**) (0.200 g, 1.45 mmol),

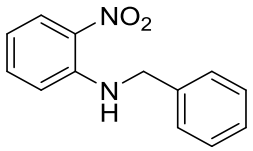
3,4,5-trimethoxybenzoyl chloride (0.667 g, 2.89 mmol) and triethylamine (0.343 mL, 2.46 mmol) in dichloromethane (15 mL). The reaction was stirred at room temperature for 24 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave *N*-(3',4',5'-trimethoxybenzoyl)-2-nitroaniline (**154g**) (0.240 g, 50%) as a yellow solid. Mp 144–145 °C (lit.[243] 145–147 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, 4'-OCH_3), 3.97 (6H, s, 3'-OCH_3 and 5'-OCH_3), 7.19–7.25 (3H, m, 4-H, 2'-H and 6'-H), 7.72 (1H, ddd, *J* 8.4, 7.4, 1.4 Hz, 5-H), 8.29 (1H, dd, *J* 8.4, 1.4 Hz, 6-H), 9.00 (1H, dd, *J* 8.6, 1.4 Hz, 3-H), 11.39 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.3 (2 × CH_3), 61.0 (CH_3), 104.6 (2 × CH), 121.9 (CH), 123.3 (CH), 126.0 (CH), 129.2 (C), 135.5 (C), 136.3 (C), 136.4 (CH), 141.9 (C), 153.5 (2 × C), 165.3 (C); *m/z* (ESI) 355 (MNa^+. 100%).

_N_-(3',4',5'-Trimethoxybenzoyl)-1,2-phenylenediamine (155g)



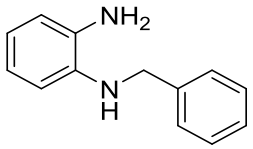
The reaction was carried out according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**155a**) using *N*-(3',4',5'-trimethoxybenzoyl)-2-nitroaniline (**154g**) (0.240 g, 0.722 mmol) and tin(II) chloride dihydrate (0.815 g, 3.61 mmol) in ethyl acetate (8 mL). The reaction was stirred under reflux for 24 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave *N*-(3',4',5'-trimethoxybenzoyl)-1,2-phenylenediamine (**155g**) (0.161 g, 74%) as a white solid. Mp 157–159 °C; ν_{max}/cm^{-1} (neat) 3360 (NH), 3271 (NH), 1630, 1578, 1497, 1335, 1229, 1125, 907, 712; NMR data showed a 9:1 mixture of rotamers. Data is presented for the major rotamer: δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, 4'-OCH_3), 3.87 (6H, s, 3'-OCH_3 and 5'-OCH_3), 3.90 (2H, br s, NH_2), 6.74–6.82 (2H, m, 2 × ArH), 7.02–7.10 (3H, m, 2'-H, 6'-H and ArH), 7.23 (1H, br d, *J* 7.7 Hz, 6-H), 8.12 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.3 (2 × CH_3), 60.9 (CH_3), 104.8 (2 × CH), 118.3 (CH), 119.6 (CH), 124.5 (C), 125.3 (CH), 127.3 (CH), 129.6 (C), 140.9 (C), 141.1 (C), 153.2 (2 × C), 165.9 (C); *m/z* (ESI) 325.1146 (MNa^+. $C_{16}H_{18}N_2NaO_4$ requires 325.1159).

***N*-Benzyl-2-nitroaniline (154h)**[234]



To a stirred solution of 1-fluoro-2-nitrobenzene (**158**) (0.150 mL, 1.42 mmol) in THF (5.7 mL) was added benzylamine (0.311 mL, 2.48 mmol) at room temperature. The reaction mixture was stirred for 18 h, filtered through Celite®, washed with ethyl acetate (20 mL) and concentrated *in vacuo*. Purification by silica gel flash chromatography, eluting with 5% diethyl ether in hexane gave *N*-benzyl-2-nitroaniline (**154h**) (0.128 g, 40%) as a yellow solid. Mp 90–92 °C (lit.[234] 91–93 °C); δ_H (400 MHz, $CDCl_3$) 4.56 (2H, d, *J* 5.6 Hz, 1'-H_2), 6.67 (1H, ddd, *J* 8.6, 6.8, 1.2 Hz, 4-H), 6.82 (1H, dd, *J* 8.6, 1.2 Hz, 6-H), 7.28–7.41 (6H, m, 5-H and Ph), 8.20 (1H, dd, *J* 8.6, 1.6 Hz, 3-H), 8.43 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 47.1 (CH_2), 114.2 (CH), 115.7 (CH), 126.9 (CH), 127.1 (2 × CH), 127.7 (CH), 128.9 (2 × CH), 132.3 (C), 136.2 (CH), 137.4 (C), 145.3 (C); *m/z* (ESI) 251 (MNa^+. 100%).

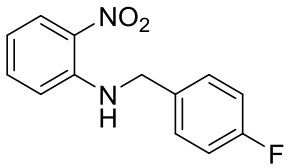
***N*-Benzyl-1,2-phenylenediamine (155h)**[244]



The reaction was carried out according to the previously described procedure for *N*-allyl-1,2-phenylenediamine (**155b**) using *N*-benzyl-2-nitroaniline (**154h**) (0.290 g, 1.27 mmol), zinc powder (0.416 g, 6.35 mmol) and acetic acid (0.363 mL, 6.35 mmol) in methanol (6.5 mL). The reaction mixture was stirred for 24 h at room temperature, Purification by silica gel flash chromatography, eluting with 20% ethyl acetate in hexane gave *N*-benzyl-1,2-phenylenediamine (**155h**) (0.132 g, 52%) as a yellow solid. Mp 60–62 °C (lit.[244] 60–63 °C); δ_H (400 MHz, $CDCl_3$) 3.20–3.85 (3H, m, NH and NH_2), 4.33 (2H, s, 1'-H_2), 6.68–6.86 (4H, m, 4 × ArH), 7.27–7.44 (5H, m, 5 × ArH); δ_C (101 MHz, $CDCl_3$) 48.7 (CH_2), 112.0 (CH), 116.5 (CH),

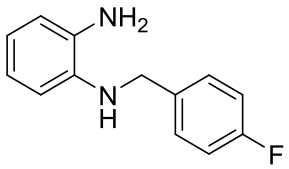
118.8 (CH), 120.7 (CH), 127.3 (CH), 127.8 (2 × CH), 128.6 (2 × CH), 134.2 (C), 137.7 (C), 139.4 (C); *m*/*z* (ESI) 199 (MH^+. 100%).

_N_-(4''-Fluorobenzyl)-2-nitroaniline (154i)[245]



The reaction was carried out according to the previously described procedure for *N*-benzyl-2-nitroaniline (**154h**) using 1-fluoro-2-nitrobenzene (**158**) (0.224 mL, 2.12 mmol) and 4-fluorobenzylamine (0.242 mL, 2.12 mmol) in THF (5.3 mL) except that triethylamine (0.588 mL, 4.24 mmol) was added and the reaction was heated to 70 °C for 18 h. Purification by silica gel flash column chromatography, eluting with 2% diethyl ether in hexane gave *N*-(4''-fluorobenzyl)-2-nitroaniline (**154i**) (0.333 g, 64%) as a yellow solid. Mp 72–74 °C (lit.[245] 74–76 °C); δ_H (400 MHz, $CDCl_3$) 4.52 (2H, d, *J* 5.6 Hz, 1'-H_2), 6.68 (1H, ddd, *J* 8.6, 6.8, 1.2 Hz, 4-H), 6.79 (1H, dd, *J* 8.6, 1.2 Hz, 6-H), 7.02–7.09 (2H, m, 2''-H and 6''-H), 7.29–7.35 (2H, m, 3''-H and 5''-H), 7.39 (1H, dddd, *J* 8.6, 6.8, 1.6, 0.6 Hz, 5-H), 8.20 (1H, dd, *J* 8.6, 1.6 Hz, 3-H), 8.39 (1H, br s, 1-H); δ_C (101 MHz, $CDCl_3$) 46.4 (CH_2), 114.1 (CH), 115.8 (d, $^2J_{C\text{-}F}$ 21.6 Hz, 2 × CH), 115.9 (CH), 126.9 (CH), 128.7 (d, $^3J_{C\text{-}F}$ 8.0 Hz, 2 × CH), 132.4 (C), 133.1 (d, $^4J_{C\text{-}F}$ 3.2 Hz, C), 136.3 (CH), 145.0 (C), 162.3 (d, $^1J_{C\text{-}F}$ 246.5 Hz, C); *m*/*z* (ESI) 269 (MNa^+. 100%).

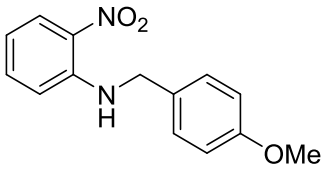
_N_-(4''-Fluorobenzyl)-1,2-phenylenediamine (155i)[246]



The reaction was carried out according to the previously described procedure for *N*-allyl-1,2-phenylenediamine (**155b**) using *N*-(4''-fluorobenzyl)-2-nitroaniline (**154i**) (0.500 g, 2.03 mmol), zinc powder (0.663 g, 10.2 mmol) and acetic acid (0.500 mL, 10.2 mmol) in methanol (10 mL). The reaction was stirred at room

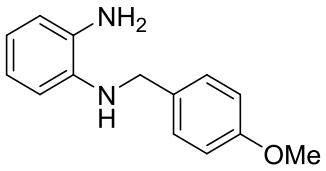
temperature for 24 h. Purification by silica gel flash chromatography, eluting with 20% ethyl acetate in hexane gave *N*-(4''-fluorobenzyl)-1,2-phenylenediamine (**155i**) (0.282 g, 64%) as a yellow solid. Mp 80–82 °C (lit.[246] 79–82 °C); δ_H (400 MHz, $CDCl_3$) 3.47 (3H, br s, NH and NH_2), 4.30 (2H, s, 1'-H_2), 6.67 (1H, br d, *J* 7.6 Hz, 6-H), 6.70–6.79 (2H, m, 3-H and 5-H), 6.80–6.87 (1H, m, 4-H), 7.06 (2H, td, *J* 8.4, 2.0 Hz, 2''-H and 6''-H), 7.38 (2H, dd, *J* 8.4, 6.0 Hz, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 48.0 (CH_2), 112.1 (CH), 115.5 (d, $^2J_{C\text{-}F}$ 21.3 Hz, 2 × CH), 116.7 (CH), 119.0 (CH), 120.8 (CH), 129.3 (d, $^3J_{C\text{-}F}$ 8.0 Hz, 2 × CH) 134.2 (C), 135.1 (d, $^4J_{C\text{-}F}$ 2.5 Hz, C), 137.6 (C), 162.1 (d, $^1J_{C\text{-}F}$ 245.0 Hz, C); *m*/*z* (ESI) 217 (MH^+. 100%).

_N_-(4''-Methoxybenzyl)-2-nitroaniline (154j)[247]



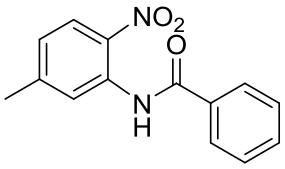
The reaction was carried out according to the previously described procedure for *N*-benzyl-2-nitroaniline (**154h**) using 1-fluoro-2-nitrobenzene (**158**) (0.0526 mL, 0.500 mmol) and 4-methoxybenzylamine (0.130 mL, 1.00 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 48 h. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave *N*-(4''-methoxybenzyl)-2-nitroaniline (**154j**) (0.121 g, 94%) as a yellow solid. Mp 94–96 °C (lit.[247] 94–95 °C); δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 4.48 (2H, d, *J* 5.2 Hz, 1'-H_2), 6.66 (1H, ddd, *J* 8.4, 7.0, 1.0 Hz, 4-H), 6.84 (1H, dd, *J* 8.4, 1.0 Hz, 6-H), 6.88–6.93 (2H, m, 3''-H and 5''-H), 7.25–7.30 (2H, m, 2''-H and 6''-H), 7.39 (1H, ddd, *J* 8.4, 7.0, 1.6 Hz, 5-H), 8.19 (1H, dd, *J* 8.4, 1.6 Hz, 3-H), 8.35 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 46.6 (CH_2), 55.3 (CH_3), 114.2 (CH), 114.3 (2 × CH), 115.6 (CH), 126.9 (CH), 128.4 (2 × CH), 129.3 (C), 132.2 (C), 136.2 (CH), 145.2 (C), 159.2 (C); *m*/*z* (ESI) 281 (MNa^+. 100%).

***N*-(4''-Methoxybenzyl)-1,2-phenylenediamine (155j)**[247]



The reaction was carried out according to the previously described procedure for *N*-allyl-1,2-phenylenediamine (**155b**) using *N*-(4''-methoxybenzyl)-2-nitroaniline (**154j**) (0.105 g, 0.407 mmol), zinc powder (0.133 g, 2.03 mmol) and acetic acid (0.105 mL, 1.83 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 24 h. Purification by silica gel flash chromatography, eluting with 20% ethyl acetate in hexane gave *N*-(4''-methoxybenzyl)-1,2-phenylenediamine (**155j**) (0.069 g, 74%) as a yellow solid. Mp 90–92 °C (lit.[247] 91–92 °C); δ_H (400 MHz, $CDCl_3$) 3.36 (2H, br s, NH_2), 3.63 (1H, br s, NH), 3.84 (3H, s, 4''-OCH_3), 4.27 (2H, s, 1'-H_2), 6.71–6.78 (3H, m, 3-H, 5-H and 6-H), 6.85 (1H, ddd, *J* 7.6, 6.4, 2.6 Hz, 4-H), 6.90–6.95 (2H, m, 3''-H and 5''-H), 7.33–7.37 (2H, m 2''-H and 6''-H); δ_C (101 MHz, $CDCl_3$) 48.1 (CH_2), 55.3 (CH_3), 111.9 (CH), 114.0 (2 × CH), 116.4 (CH), 118.7 (CH), 120.7 (CH), 129.0 (2 × CH), 131.4 (C), 134.2 (C), 137.7 (C), 158.8 (C); *m/z* (ESI) 251 (MNa^+. 100%).

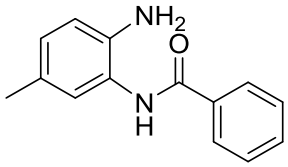
***N*-Benzoyl-5-methyl-2-nitroaniline (159a)**[238]



The reaction was carried out according to the previously described procedure for *N*-benzoyl-2-nitroaniline (**154f**) using 5-methyl-2-nitroaniline (0.200 g, 1.31 mmol), benzoyl chloride (0.304 mL, 2.62 mmol) and triethylamine (0.310 mL, 2.23 mmol) in dichloromethane (10 mL). The reaction was stirred at room temperature for 44 h, then benzoyl chloride (0.100 mL, 0.655 mmol) and triethylamine (0.106 mL, 0.655 mmol) were added. The reaction was complete after 3 days. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave *N*-benzoyl-5-methyl-2-nitroaniline (**159a**) (0.225 g, 67%) as a yellow solid. Mp 84–86 °C (lit.[238] 85–87 °C); NMR data

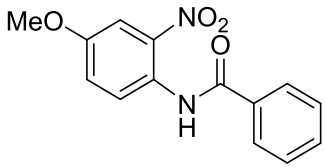
showed a 4:1 mixture of rotamers. Data is presented for the major rotamer: δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, 5-CH_3), 7.00 (1H, dd, *J* 8.6, 1.2 Hz, 4-H), 7.50–7.63 (2H, m, 3'-H, 4'-H and 5'-H), 7.97–8.02 (2H, m, 2'-H and 6'-H), 8.17 (1H, d, *J* 8.6 Hz, 3-H), 8.84 (1H, d, *J* 1.2 Hz, 6-H), 11.42 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 22.2 (CH_3), 122.0 (CH), 124.3 (CH), 125.9 (CH), 127.4 (2 × CH), 129.1 (2 × CH), 132.6 (CH), 134.2 (C), 134.4 (C), 135.4 (C), 148.3 (C), 165.8 (C); *m*/*z* (ESI) 279 (MNa^+. 100%).

_N_-Benzoyl-5-methyl-1,2-phenylenediamine (160a)[248]



The reaction was carried out according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**155a**) using *N*-benzoyl-5-methyl-2-nitroaniline (**159a**) (0.230 g, 0.897 mmol) and tin(II) chloride dihydrate (1.01 g, 4.49 mmol) in ethyl acetate (10 mL). The reaction was stirred under reflux for 20 h. Purification by silica gel flash column chromatography, eluting with 50% ethyl acetate in hexane gave *N*-benzoyl-5-methyl-1,2-phenylenediamine (**160a**) (0.130 g, 64%) as a white solid. Mp 155–156 °C (lit.[248] 158 °C); δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 5-CH_3), 3.70 (2H, br s, NH_2), 6.77 (1H, d, *J* 8.0 Hz, 3-H), 6.90 (1H, dd, *J* 8.0, 1.2 Hz, 4-H), 7.25 (1H, br s, 6-H), 7.46–7.59 (3H, m, 3'-H, 4'-H and 5'-H), 7.84–7.92 (3H, m, NH, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 118.8 (CH), 125.1 (C), 125.1 (CH), 127.3 (2 × CH), 127.6 (CH), 128.8 (2 × CH), 129.7 (C), 131.9 (CH), 134.4 (C), 137.5 (C), 165.7 (C); *m*/*z* (ESI) 249 (MNa^+. 100%).

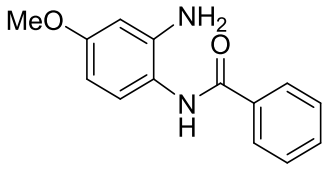
_N_-Benzoyl-4-methoxy-2-nitroaniline (159b)[249]



The reaction was carried out according to the previously described procedure for *N*-benzoyl-2-nitroaniline (**154f**) using 4-methoxy-2-nitroaniline (0.200 g, 1.19

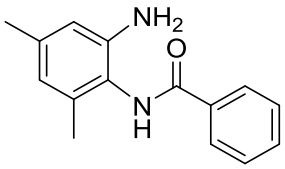
mmol), benzoyl chloride (0.288 mL, 2.38 mmol) and triethylamine (0.282 mL, 2.02 mmol) in dichloromethane (8.5 mL). The reaction was stirred at room temperature for 24 h. Purification by silica gel flash column chromatography, eluting with 5% diethyl ether in hexane gave *N*-benzoyl-4-methoxy-2-nitroaniline (**159b**) (0.300 g, 93%) as a yellow solid. Mp 138–140 °C (lit.[249] 139–141 °C); δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, 4-OCH_3), 7.31 (1H, dd, *J* 9.6, 3.2 Hz, 5-H), 7.51–7.63 (3H, m, 3'-H, 4'-H and 5'-H), 7.74 (1H, d, *J* 3.2 Hz, 3-H), 7.96–8.01 (2H, m, 2'-H and 6'-H), 8.90 (1H, d, *J* 9.6 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 108.7 (CH), 123.7 (CH), 123.8 (CH), 127.3 (2 × CH), 129.0 (2 × CH), 129.1 (C), 132.5 (CH), 134.2 (C), 137.2 (C), 155.1 (C), 165.6 (C); *m*/*z* (ESI) 295 (MNa^+. 100%).

_N_-Benzoyl-4-methoxy-1,2-phenylenediamine (160b)[250]



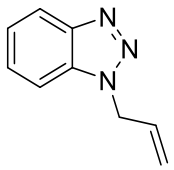
The reaction was carried out according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**155a**) using *N*-benzoyl-4-methoxy-2-nitroaniline (**159b**) (0.290 g, 1.07 mmol) and tin(II) chloride dihydrate (1.10 g, 5.33 mmol) in ethyl acetate (11 mL). The reaction was stirred under reflux for 24 h. Purification by silica gel flash column chromatography, eluting with 30% ethyl acetate in hexane gave *N*-benzoyl-4-methoxy-1,2-phenylenediamine (**160b**) (0.180 g, 69%) as a white solid. Mp 197–199 °C (lit.[250] 200–201 °C); δ_H (400 MHz, CD_3OD) 3.76 (3H, s, 4-OCH_3), 6.35 (1H, dd, *J* 8.6, 2.6 Hz, 5-H), 6.48 (1H, d, *J* 2.6 Hz, 3-H), 7.06 (1H, d, *J* 8.6 Hz, 6-H), 7.50 (2H, t, *J* 7.6 Hz, 3'-H and 5'-H), 7.58 (1H, t, *J* 7.6 Hz, 4'-H), 7.97 (2H, d, *J* 7.6 Hz, 2'-H and 6'-H); δ_C (101 MHz, CD_3OD) 54.3 (CH_3), 101.9 (CH), 103.9 (CH), 116.9 (C), 127.4 (2 × CH), 127.5 (CH), 128.2 (2 × CH), 131.5 (CH), 134.2 (C), 143.9 (C), 159.5 (C), 167.9 (C); *m*/*z* (ESI) 265 (MNa^+. 100%).

***N*-Benzoyl-4,6-dimethyl-1,2-phenylenediamine (160c)**



The reaction was carried out according to the previously described procedure for *N*-benzoyl-2-nitroaniline (**154f**) using 4,6-dimethyl-2-nitroaniline (0.300 g, 1.81 mmol), benzoyl chloride (0.437 mL, 3.61 mmol) and triethylamine (0.428 mL, 3.07 mmol) in dichloromethane (13 mL). The reaction was stirred at room temperature for 24 h. Without purification, the resulting residue was reduced according to the previously described procedure for *N*-nonyl-1,2-phenylenediamine (**155a**) using tin(II) chloride dihydrate (0.609 g, 2.70 mmol) in ethyl acetate (10 mL). The reaction was stirred under reflux for 20 h. Purification by silica gel flash column chromatography, eluting with 60% ethyl acetate in hexane gave *N*-benzoyl-4,6-dimethyl-1,2-phenylenediamine (**160c**) (0.046 g, 11% over two steps) as a white solid. Mp 239–241 °C; ν_{max}/cm^{-1} (neat) 3360 (NH), 3273 (NH), 2918 (CH), 1630 (C=O), 1520, 1404, 1285, 829, 712; δ_H (400 MHz, CD_3OD) 2.18 (3H, s, CH_3), 2.22 (3H, s, CH_3), 6.49 (1H, s, ArH), 6.56 (1H, s, ArH), 7.52 (2H, t, *J* 7.4 Hz, 3'-H and 5'-H), 7.59 (1H, t, *J* 7.4 Hz, 4'-H), 8.00 (2H, t, *J* 7.4 Hz, 2'-H and 6'-H); δ_C (101 MHz, CD_3OD) 16.9 (CH_3), 19.8 (CH_3), 114.8 (CH), 119.6 (C), 120.7 (CH), 127.3 (2 × CH), 128.2 (2 × CH), 131.5 (CH), 134.2 (C), 135.7 (C), 137.4 (C), 143.6 (C), 168.1 (C); *m/z* (EI) 240.1262 (M^+. $C_{15}H_{16}N_2O$ requires 240.1263), 222 (100%), 207 (25), 135 (16), 105 (24), 91 (11), 77 (22).

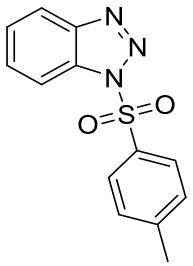
1-Allyl-1*H*-benzo[*d*][1.2.3]triazole (161a)[251]



The reaction was carried out as described in the general procedure using *N*-allyl-1,2-phenylenediamine (**155b**) (0.106 g, 0.715 mmol), polymer-supported nitrite (0.613 g, containing 2.15 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate

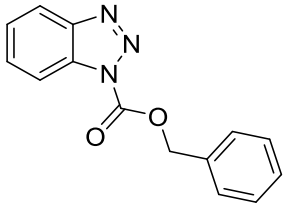
(0.370 g, 2.15 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 30% diethyl ether in hexane gave 1-allyl-1*H*-benzo[*d*][1.2.3]triazole (**161a**) (0.0790 g, 69%) as a yellow oil. Spectroscopic data were consistent with the literature.[251] δ_H (400 MHz, $CDCl_3$) 5.21–5.34 (4H, m, 1'-H_2 and 3'-H_2), 6.05 (1H, ddt, *J* 16.8, 10.4, 6.0 Hz, 2'-H), 7.35 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, ArH), 7.45 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, ArH), 7.50 (1H, dt, *J* 8.4, 1.2 Hz, ArH), 8.05 (1H, dt, *J* 8.4, 1.2 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 50.9 (CH_2), 109.7 (CH), 119.3 (CH_2), 120.1 (CH), 123.9 (CH), 127.3 (CH), 131.2 (CH), 132.9 (C), 146.2 (C); *m*/*z* (ESI) 182 (MNa^+. 100%).

1-(4'-Methylbenzenesulfonyl)-1*H*-benzo[*d*][1.2.3]triazole (161b)[252]



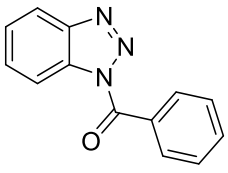
The reaction was carried out as described in the general procedure using *N*-(2'-aminophenyl)-4-methylbenzenesulfonamide (**155d**) (0.0500 g, 0.190 mmol), polymer-supported nitrite (0.163 g, containing 0.570 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.0980 g, 0.570 mmol). After 0.5 h, further polymer-supported nitrite (0.081 g, containing 0.285 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.0490 g, 0.285 mmol) were added and the reaction was stopped after 5 h. Purification by silica gel flash column chromatography, eluting with 50% diethyl ether in hexane gave 1-(4'-methylbenzenesulfonyl)-1*H*-benzo[*d*][1.2.3]triazole (**161b**) (0.0330 g, 64%) as a white solid. Mp 126–128 °C (lit.[252] 130–132 °C); δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, 4'-CH_3), 7.29–7.33 (2H, m, 3'-H and 5'-H), 7.47 (1H, ddd, *J* 8.4, 7.2, 1.2, ArH), 7.65 (1H, ddd, *J* 8.0, 7.2, 1.0, ArH), 7.97–8.02 (2H, m, 2'-H and 6'-H), 8.07 (1H, dt, *J* 8.4, 0.8 Hz, ArH), 8.10 (1H, dd, *J* 8.4, 0.8 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 112.1 (CH), 120.6 (CH), 125.8 (CH), 128.0 (2 × CH), 130.2 (CH), 130.3 (2 × CH), 131.6 (C), 134.1 (C), 145.5 (C), 146.8 (C); *m*/*z* (ESI) 296 (MNa^+. 100%).

1-Benzyloxycarbonyl-1*H*-benzo[*d*][1.2.3]triazole (161c)[253]



The reaction was carried out as described in the general procedure using *N*-benzyloxycarbonyl-1,2-phenylenediamine (**155e**) (0.148 g, 0.611 mmol), polymer-supported nitrite (0.524 g, containing 1.83 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.315 g, 1.83 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 1-benzyloxycarbonyl-1*H*-benzo[*d*][1.2.3]triazole (**161c**) (0.102 g, 66%) as a white solid. Mp 108–110 °C (lit.[253] 108–110 °C); δ_H (400 MHz, $CDCl_3$) 5.63 (2H, s, 1'-H_2), 7.36–7.45 (3H, m, 3 × ArH), 7.48 (1H, ddd, *J* 8.0, 7.2, 1.0 Hz, ArH), 7.53–7.58 (2H, m, 2 × ArH), 7.63 (1H, ddd, *J* 8.4, 7.2, 1.0 Hz, ArH), 8.08 (1H, dt, *J* 8.4, 1.2 Hz, ArH), 8.12 (1H, dt, *J* 8.0, 1.2 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 70.4 (CH_2), 113.5 (CH), 120.5 (CH), 125.8 (CH), 128.9 (2 × CH), 128.9 (2 × CH), 129.2 (CH), 130.2 (CH), 131.8 (C), 134.0 (C), 145.9 (C), 148.9 (C); *m*/*z* (ESI) 276 (MNa^+. 100%).

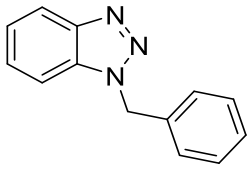
1-Benzoyl-1*H*-benzo[*d*][1.2.3]triazole (161d)[254]



The reaction was carried out as described in the general procedure using *N*-benzoyl-1,2-phenylenediamine (**155f**) (0.0900 g, 0.424 mmol), polymer-supported nitrite (0.364 g, containing 1.27 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.219 g, 1.27 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 1-benzoyl-1*H*-benzo[*d*][1.2.3]triazole (**161d**) (0.0700 g, 75%) as a white solid. Mp 110–112 °C (lit.[254] 113–114 °C); δ_H (400 MHz, $CDCl_3$) 7.52–7.62 (3H, m, 3 × ArH), 7.66–7.73 (2H, m, 2 × ArH), 8.15–8.24 (3H, m, 5-H,

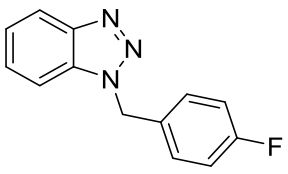
6-H and 7-H), 8.39 (1H, d, *J* 8.0 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 114.8 (CH), 120.2 (CH), 126.3 (CH), 128.4 (2 × CH), 130.4 (CH), 131.5 (C), 131.7 (2 × CH), 132.3 (C), 133.7 (CH), 145.8 (C), 166.7 (C); *m*/*z* (ESI) 246 (MNa^+. 100%).

1-Benzyl-1*H*-benzo[*d*][1.2.3]triazole (161e)[252]



The reaction was carried out as described in the general procedure using *N*-benzyl-1,2-phenylenediamine (**155h**) (0.112 g, 0.565 mmol), polymer-supported nitrite (0.484 g, containing 1.70 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.292 g, 1.70 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 1-benzyl-1*H*-benzo[*d*][1.2.3]triazole (**161e**) (0.0890 g, 75%) as a white solid. Mp 113–115 °C (lit.[252] 115–116 °C); δ_H (400 MHz, $CDCl_3$) 5.85 (2H, s, 1'-H_2), 7.25–7.44 (8H, m, 8 × ArH), 8.07 (1H, dt, 8.0, 1.2 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 52.3 (CH_2), 109.7 (CH), 120.1 (CH), 123.9 (CH), 127.4 (CH), 127.6 (2 × CH), 128.5 (CH), 129.0 (2 × CH), 132.8 (C), 134.8 (C), 146.4 (C); *m*/*z* (ESI) 232 (MNa^+. 100%).

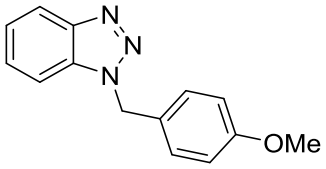
1-(4''-Fluorobenzyl)-1*H*-benzo[*d*][1.2.3]triazole (161f)[255]



The reaction was carried out as described in the general procedure using *N*-(4''-fluorobenzyl)-1,2-phenylenediamine (**155i**) (0.200 g, 0.925 mmol), polymer-supported nitrite (0.793 g, containing 2.78 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.478 g, 2.78 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 30% diethyl ether in hexane gave 1-(4''-fluorobenzyl)-1*H*-benzo[*d*][1.2.3]triazole (**161f**) (0.160 g, 77%) as a white solid. Mp 98–100 °C (lit.[255] 99–101 °C); δ_H (400 MHz,

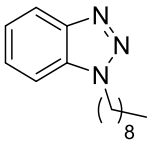
$CDCl_3$) 5.80 (2H, s, 1'-H_2), 6.97–7.04 (2H, m, 2''-H and 6''-H), 7.23–7.29 (2H, m, 3''-H and 5''-H), 7.31–7.37 (2H, m, 5-H and 7-H), 7.41 (1H, ddd, *J* 7.6, 5.6 0.8 Hz, 6-H), 8.04–8.07 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 51.5 (CH_2), 109.5 (CH), 116.0 (d, $^2J_{C\text{-}F}$ 21.8 Hz, 2 × CH), 120.1 (CH), 124.0 (CH), 127.5 (CH), 129.4 (d, $^3J_{C\text{-}F}$ 8.3 Hz, 2 × CH), 130.6 (d, $^4J_{C\text{-}F}$ 3.3 Hz, C), 132.7 (C), 146.4 (C), 162.7 (d, $^1J_{C\text{-}F}$ 247.6 Hz, C); *m*/*z* (ESI) 250 (MNa^+. 100%).

1-(4''-Methoxybenzyl)-1*H*-benzo[*d*][1.2.3]triazole (161g)[256]



The reaction was carried out as described in the general procedure using *N*-(4''-methoxybenzyl)-1,2-phenylenediamine (**155j**) (0.0630 g, 0.276 mmol), polymer-supported nitrite (0.237 g, containing 0.828 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.143 g, 0.828 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 30% diethyl ether in hexane gave 1-(4''-methoxybenzyl)-1*H*-benzo[*d*][1.2.3]triazole (**161g**) (0.0490 g, 75%) as a white solid. Mp 80–82 °C (lit.[256] 80–81 °C); δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 5.77 (2H, s, 1'-H_2), 6.82–6.87 (2H, m, 3''-H and 5''-H), 7.21–7.27 (2H, m, 2''-H and 6''-H), 7.32 (1H, ddd, *J* 8.2, 6.4, 1.6 Hz, 5-H), 7.34–7.36 (1H, m, 7-H), 7.39 (1H, ddd, *J* 8.4, 6.4, 1.2 Hz, 6-H), 8.02–8.06 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 51.9 (CH_2), 55.3 (CH_3), 109.8 (CH), 114.3 (2 × CH), 120.0 (CH), 123.9 (CH), 126.8 (C), 127.3 (CH), 129.1 (2 × CH), 132.7 (C), 146.4 (C), 159.7 (C); *m*/*z* (ESI) 262 (MNa^+. 100%).

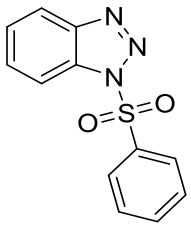
1-Nonyl-1*H*-benzo[*d*][1.2.3]triazole (133)[159]



The reaction was carried out as described in the general procedure using *N*-nonyl-1,2-phenylenediamine (**155a**) (0.100 g, 0.427 mmol), polymer-supported

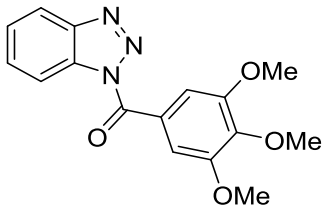
nitrite (0.366 g, containing 1.28 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.220 g, 1.28 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 35% diethyl ether in hexane gave 1-nonyl-1*H*-benzo[*d*][1.2.3]triazole (**133**) (0.0690 g, 66%) as a white solid. Mp 34–35 °C (lit.[159] 32–35 °C); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8 Hz, 9'-H_3), 1.19–1.39 (12H, m, 3'-H_2, 4'-H_2, 5'-H_2, 6'-H_2, 7'-H_2 and 8'-H_2), 1.95–2.05 (2H, m, 2'-H_2), 4.63 (2H, t, *J* 7.2 Hz, 1'-H_2), 7.36 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, 5-H), 7.47 (1H, ddd, *J* 8.4, 6.8, 1.0 Hz, 6-H), 7.50–7.55 (1H, m, 7-H), 8.06 (1H, br d, *J* 8.4 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 48.3 (CH_2), 109.3 (CH), 120.1 (CH), 123.7 (CH), 127.1 (CH), 133.0 (C), 146.0 (C); *m*/*z* (ESI) 268 (MNa^+. 100%).

1-Benzenesulfonyl-1*H*-benzo[*d*][1.2.3]triazole (135)[252]



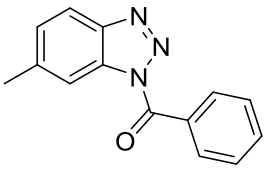
The reaction was carried out as described in the general procedure using *N*-benzenesulfonyl-1,2-phenylenediamine (**155c**) (0.130 g, 0.524 mmol), polymer-supported nitrite (0.448 g, containing 1.57 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.270 g, 1.57 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 1-benzenesulfonyl-1*H*-benzo[*d*][1.2.3]triazole (**135**) (0.103 g, 77%) as a white solid. Mp 106–109 °C (lit.[252] 108–110 °C); δ_H (400 MHz, $CDCl_3$) 7.48 (1H, ddd, *J* 8.0, 7.2, 0.8 Hz, ArH), 7.51–7.57 (2H, m, 2 × ArH), 7.62–7.69 (2H, m, 2 × ArH), 8.06–8.15 (4H, m, 4 × ArH); δ_C (101 MHz, $CDCl_3$) 112.0 (CH), 120.6 (CH), 125.9 (CH), 128.0 (2 × CH), 129.7 (2 × CH), 130.3 (CH), 131.7 (C), 135.2 (CH), 137.2 (C), 145.5 (C); *m*/*z* (ESI) 282 (MNa^+. 100%).

1-(3',4',5'-Trimethoxybenzoyl)-1*H*-benzo[*d*][1.2.3]triazole (140)[177]



The reaction was carried out as described in the general procedure using *N*-(3',4',5'-trimethoxybenzoyl)-1,2-phenylenediamine (**155g**) (0.120 g, 0.397 mmol), polymer-supported nitrite (0.340 g, containing 1.19 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.205 g, 1.19 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 60% diethyl ether in hexane gave 1-(3',4',5'-trimethoxybenzoyl)-1*H*-benzo[*d*][1.2.3]triazole (**140**) (0.088 g, 71%) as a white solid. Mp 124–126 °C (lit.[177] 126–128 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (6H, s, 3'-CH_3 and 5'-CH_3), 3.97 (3H, s, 4'-CH_3), 7.52 (1H, ddd, *J* 8.0, 7.2, 1.0 Hz, ArH), 7.55 (2H, s, 2'-H and 6'-H), 7.68 (1H, ddd, *J* 8.4, 7.2, 1.0 Hz, ArH), 8.13 (1H, d, *J* 8.4 Hz, ArH), 8.33 (1H, d, *J* 8.0 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 56.4 (2 × CH_3), 61.1 (CH_3), 109.6 (2 × CH), 114.8 (CH), 120.1 (CH), 125.9 (C), 126.3 (CH), 130.4 (CH), 132.6 (C), 143.2 (C), 145.6 (C), 152.9 (2 × C), 165.7 (C); *m*/*z* (ESI) 336 (MNa^+. 100%).

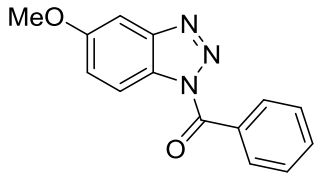
1-Benzoyl-6-methyl-1*H*-benzo[*d*][1.2.3]triazole (163a)[248]



The reaction was carried out as described in the general procedure using *N*-benzoyl-5-methyl-1,2-phenylenediamine (**160a**) (0.0900 g, 0.398 mmol), polymer-supported nitrite (0.524 g, containing 1.19 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.205 g, 1.19 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 20% diethyl ether in hexane gave 1-benzoyl-6-methyl-1*H*-benzo[*d*][1.2.3]triazole (**163a**) (0.0730 g, 77%) as a white solid. Mp 122–123 °C (lit.[248] 122–123 °C); δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, 6-CH_3), 7.36 (1H, dd, *J* 8.4,

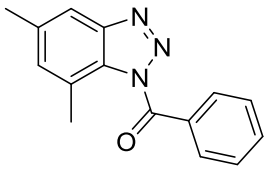
1.2 Hz, 5-H), 7.54–7.60 (2H, m, 3'-H and 5'-H), 7.68 (1H, tt, *J* 7.6, 1.2 Hz, 4'-H), 8.02 (1H, d, *J* 8.4 Hz, 4-H), 8.17–8.23 (3H, m, 7-H, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 22.1 (CH_3), 114.3 (CH), 119.6 (CH), 128.3 (CH), 128.4 (2 × CH), 131.6 (C), 131.7 (2 × CH), 132.8 (C), 133.6 (CH), 141.5 (C), 144.4 (C), 166.9 (C); *m*/*z* (ESI) 260 (MNa^+. 100%).

1-Benzoyl-5-methoxy-1*H*-benzo[*d*][1.2.3]triazole (163b)[250]



The reaction was carried out as described in the general procedure using *N*-benzoyl-4-methoxy-1,2-phenylenediamine (**160b**) (0.0380 g, 0.157 mmol), polymer-supported nitrite (0.134 g, containing 0.470 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.0810 g, 0.470 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 30% diethyl ether in hexane gave 1-benzoyl-6-methyl-1*H*-benzo[*d*][1.2.3]triazole (**163b**) (0.0300 g, 76%) as a white solid. Mp 114–116 °C (lit.[250] 116 °C); δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, 5-OCH_3), 7.32 (1H, dd, *J* 9.0, 2.2 Hz, 6-H), 7.49 (1H, d, *J* 2.2 Hz, 4-H), 7.57 (2H, t, *J* 7.5 Hz, 3'-H and 5'-H), 7.68 (1H, t, *J* 7.5 Hz, 4'-H), 8.19–8.23 (2H, m, 2'-H and 6'-H), 8.25 (1H, d, *J* 9.0 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 55.8 (CH_3), 99.8 (CH), 115.3 (CH), 121.9 (CH), 127.4 (C), 128.4 (2 × CH), 131.5 (C), 131.7 (2 × CH), 133.6 (CH), 147.0 (C), 158.6 (C), 166.5 (C); *m*/*z* (ESI) 276 (MNa^+. 100%).

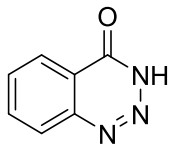
1-Benzoyl-5,7-dimethyl-1*H*-benzo[*d*][1.2.3]triazole (163c)[257]



The reaction was carried out as described in the general procedure using *N*-benzoyl-4,6-dimethyl-1,2-phenylenediamine (**160c**) (0.046 g, 0.19 mmol), polymer-supported nitrite (0.16 g, containing 0.57 mmol of NO_2) and *p*-

toluenesulfonic acid monohydrate (0.098 g, 0.57 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 25% diethyl ether in hexane gave 1-benzoyl-5,7-dimethyl-1*H*-benzo[*d*][1.2.3]triazole (**163c**) (0.033 g, 69%) as a white solid. Mp 109–111 °C (lit.[257] 111 °C); δ_H (400 MHz, $CDCl_3$) 2.53 (3H, s, CH_3), 2.66 (3H, s, CH_3), 7.30 (1H, br s, 6-H), 7.54–7.60 (2H, m, 3'-H and 5'-H), 7.71 (1H, tt, *J* 7.5, 1.4 Hz, 4'-H), 7.77 (1H, br s, 4-H), 8.08–8.13 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 20.9 (CH_3), 21.3 (CH_3), 117.0 (CH), 123.9 (C), 128.5 (2 × CH), 130.7 (C), 132.0 (2 × CH), 132.0 (C), 133.9 (CH), 134.1 (CH), 136.6 (C), 147.4 (C), 166.2 (C); *m*/*z* (ESI) 274 (MNa^+. 100%).

3*H*-1,2,3-Benzotriazin-4-one (165)[198]



The reaction was carried out as described in the general procedure using anthranilamide (**164**) (0.100 g, 0.734 mmol), polymer-supported nitrite (0.630 g, containing 2.20 mmol of NO_2) and *p*-toluenesulfonic acid monohydrate (0.379 g, 2.20 mmol). The reaction was complete after 1.5 h. Purification by silica gel flash column chromatography, eluting with 25% ethyl acetate in hexane gave 3*H*-1,2,3-benzotriazin-4-one (**165**) (0.094 g, 87%) as a white solid. Mp 214–216 °C (lit.[198] 215–217 °C); δ_H (400 MHz, DMSO-d_6) 7.90 (1H, ddd, *J* 8.8, 7.4, 1.2 Hz, ArH), 8.08 (1H, ddd, *J* 8.8, 7.4, 1.2 Hz, ArH), 8.17 (1H, br d, *J* 8.8 Hz, ArH), 8.22 (1H, dd, *J* 7.4, 1.2 Hz, ArH), 14.95 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 120.2 (C), 124.3 (CH), 127.9 (CH), 132.6 (CH), 135.5 (CH), 144.2 (C), 155.6 (C); *m*/*z* (EI) 147 (M^+. 20%), 92 (21), 84 (67), 76 (22), 66 (100).

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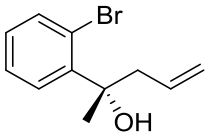
5.0 Appendices

Appendix 1. Chiral HPLC traces

(2*S*)-2-(2'-Bromophenyl)pent-4-en-2-ol [(S)-76a]



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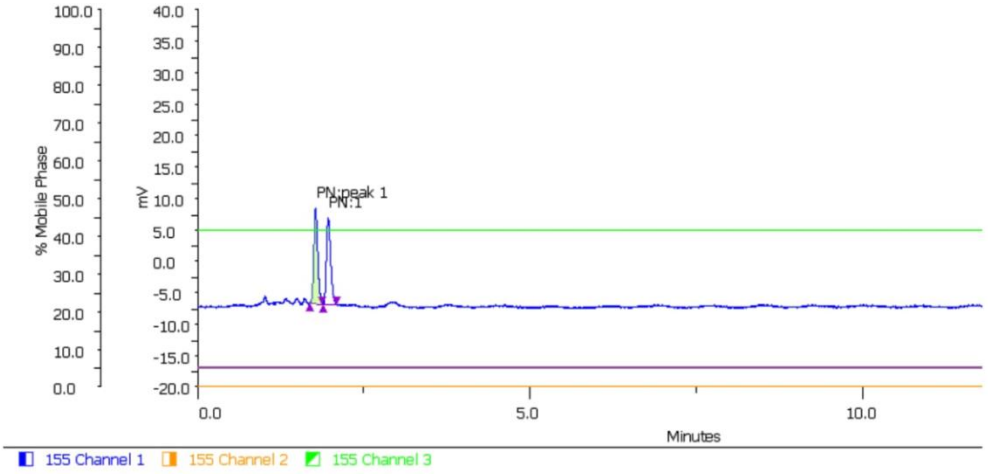
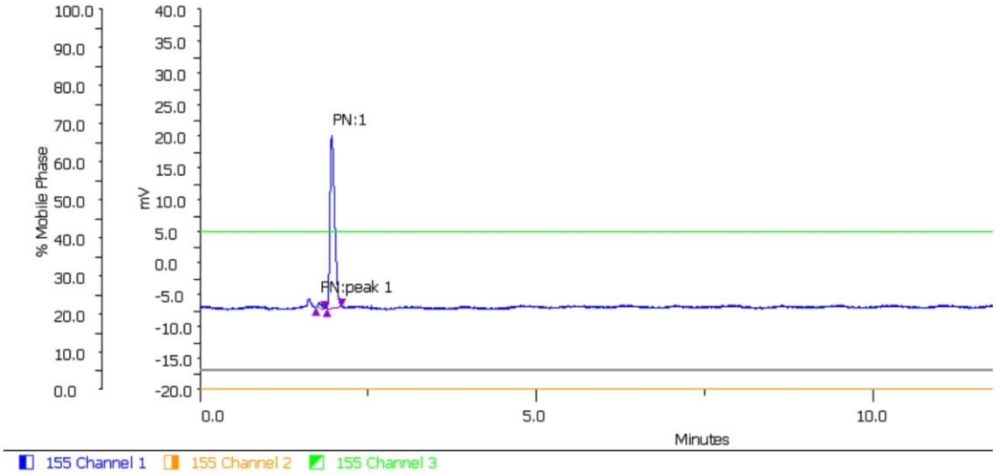


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Area %
2	peak 1	1.78	104794.1652	15.357	RF239	50.378
2	1	1.969	103223.3339	13.762	RF239	49.622

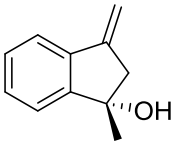
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Area %
3	peak 1	1.783	4644.168	0.802	RF240	2.051
3	1	1.963	221814.1655	27.129	RF240	97.949

(1*S*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70a]



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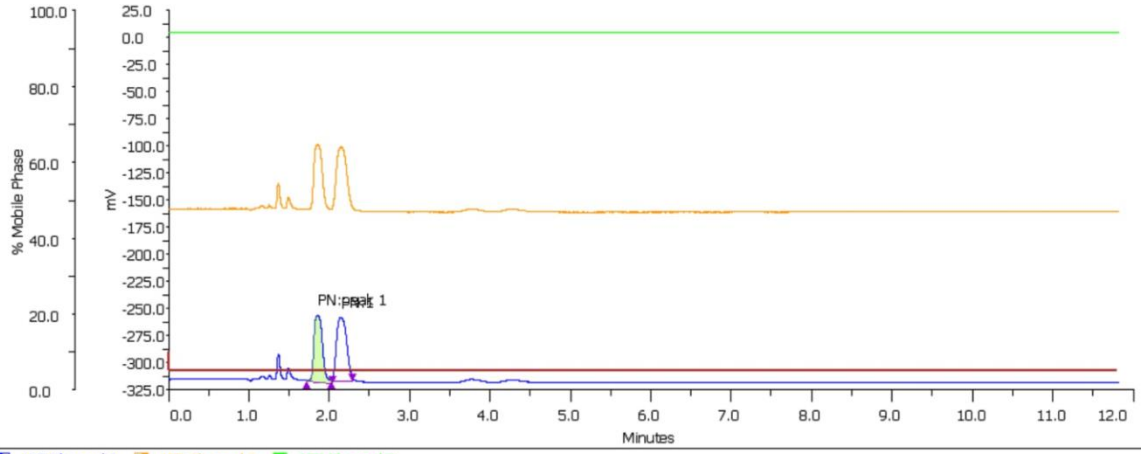
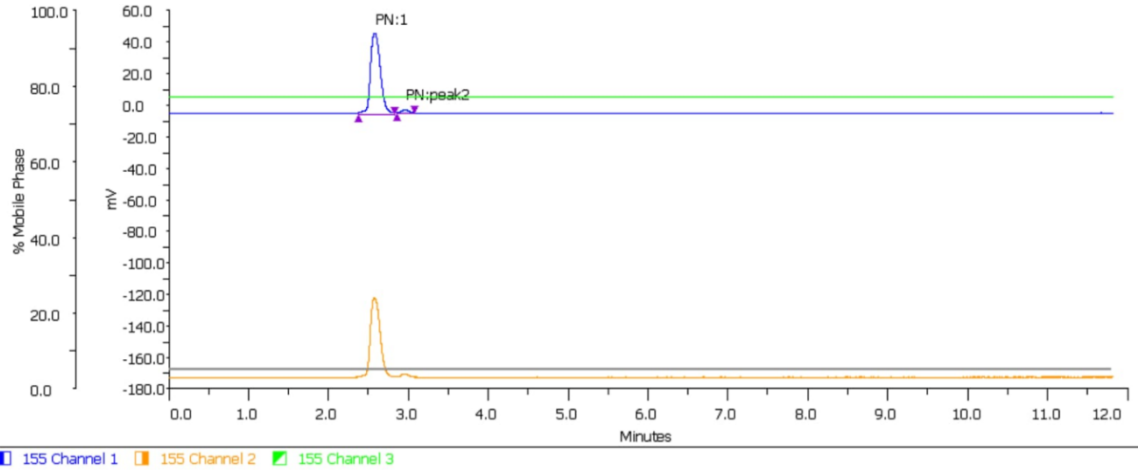


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Area %
1	peak 1	1.859	764408.1049	61.554	RF072 low 16/6	46.664
1	1	2.15	873716.7248	59.149	RF072 low 16/6	53.336

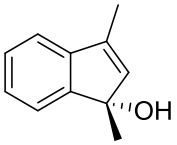
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %
1	1	2.583	741960.0554	51.097	96.028
1	peak2	2.962	30692.7001	2.469	3.972

(1*S*)-1,3-Dimethylinden-1-ol [(*S*)-82a)]



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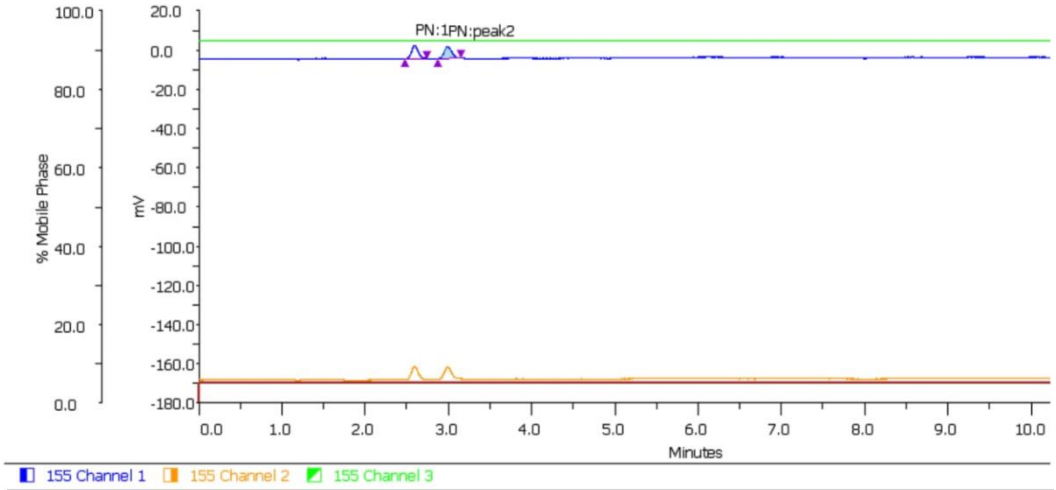
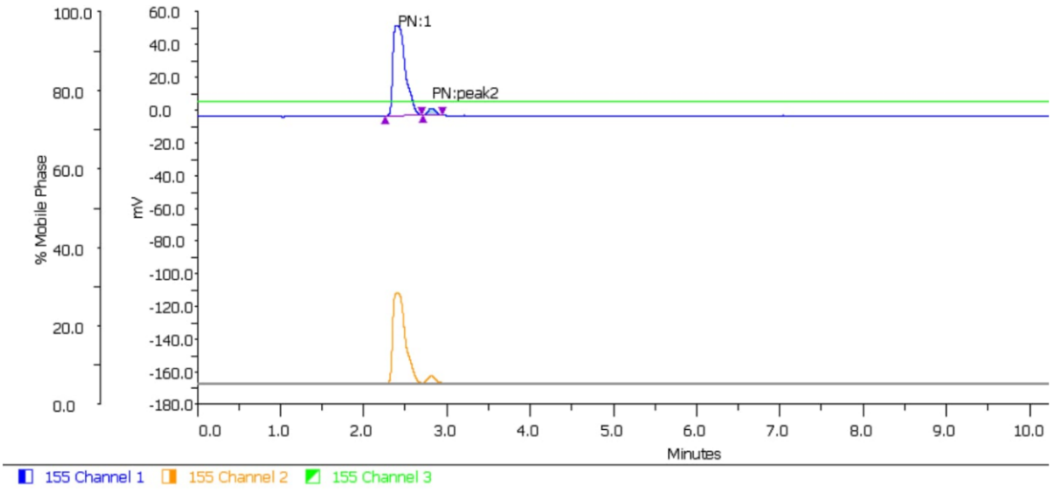


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %	
1	1	2.598	63741.6701	6.829	49.798	
1	peak2	2.996	64259.1672	6.09	50.202	

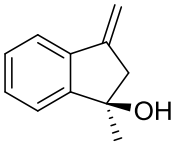
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %	
2	1	2.408	956577.5038	54.997	95.703	
2	peak2	2.82	42953.7516	4.195	4.297	

(1*R*)-2,3-dihydro-1-methyl-3-(methylene)indan-1-ol [(*R*)-70a]



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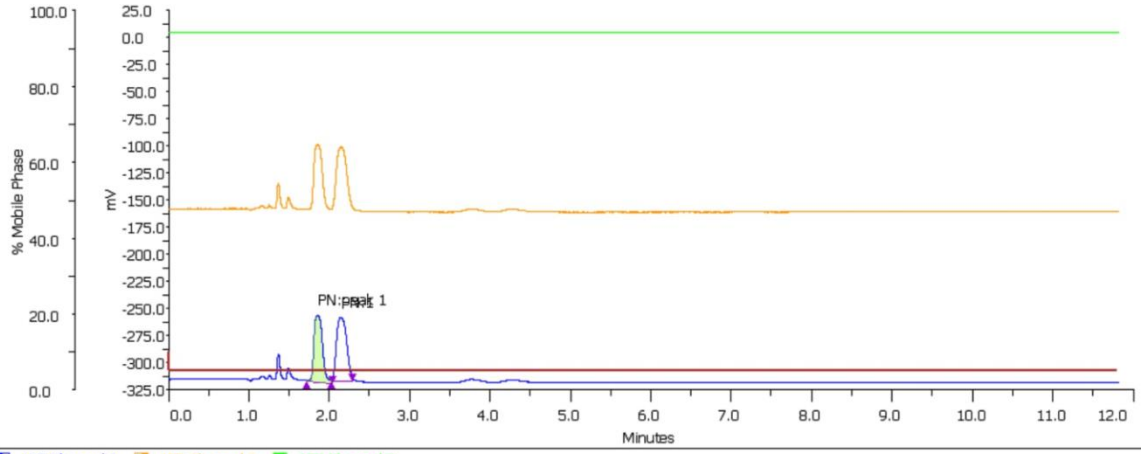
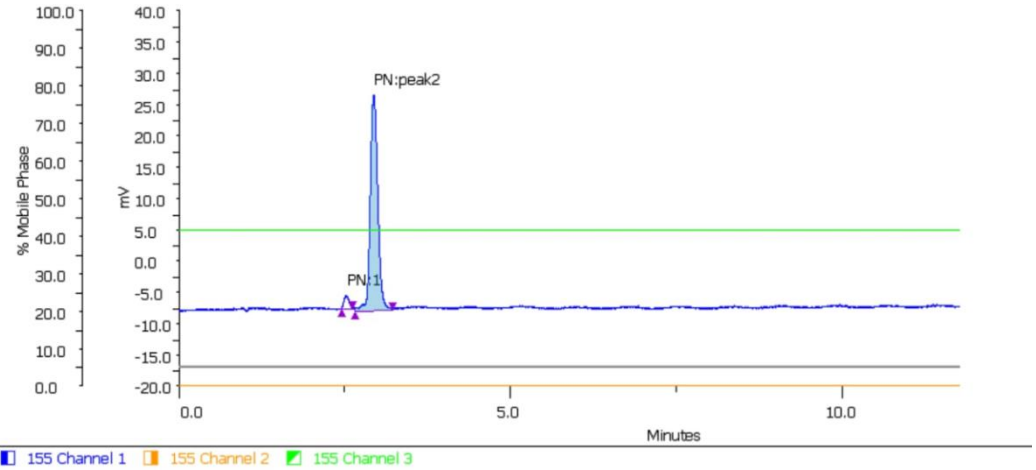


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Area %		
1	peak 1	1.859	764408.1049	61.554	RF072 low 16/6	46.664		
1	1	2.15	873716.7248	59.149	RF072 low 16/6	53.336		

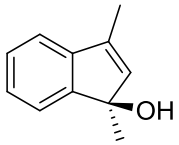
Enantioselective:



Sample Table

Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %			
1	2.529	20290.0727	2.249	4.227			
peak2	2.944	459750.575	34.529	95.773			

(1*R*)-1,3-Dimethylinden-1-ol [(*R*)-82a)]



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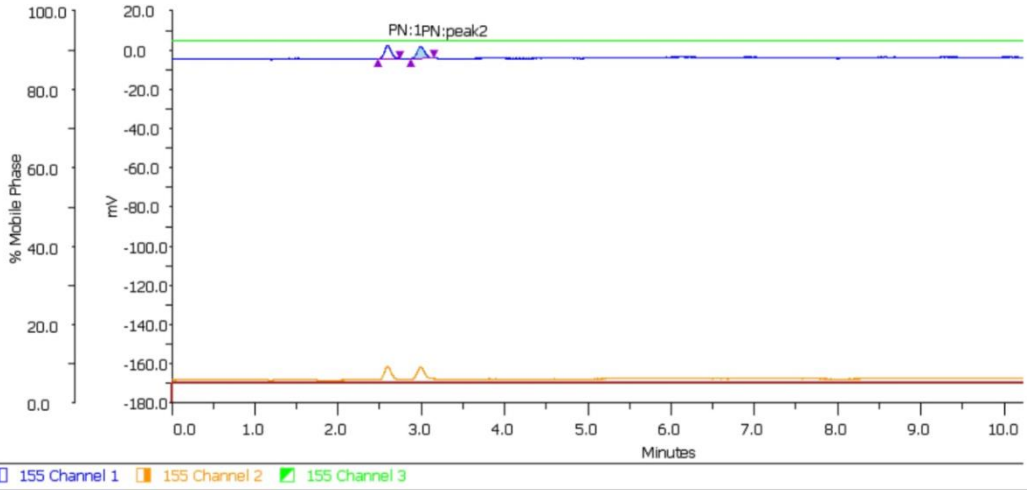
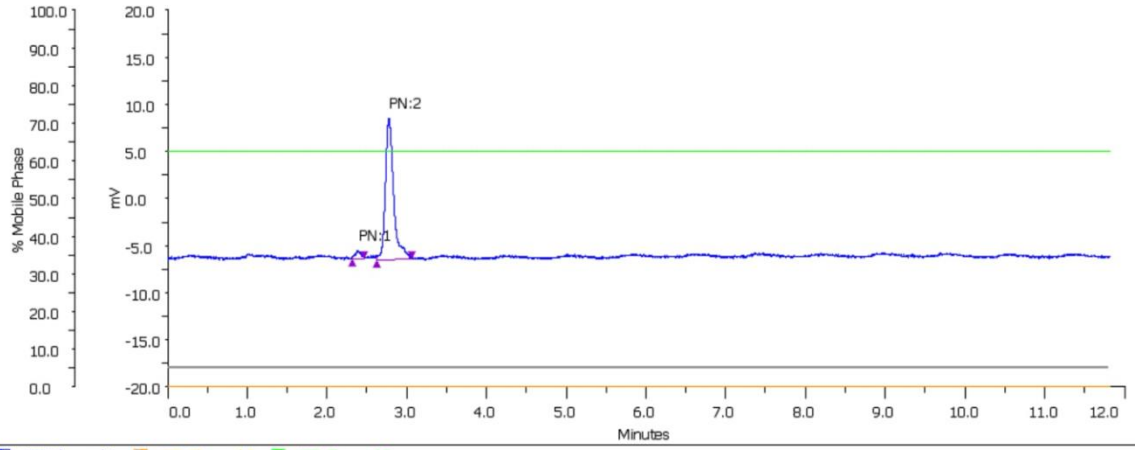


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %	
1	1	2.598	63741.6701	6.829	49.798	
1	peak2	2.996	64259.1672	6.09	50.202	

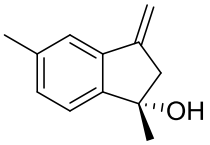
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Area %			
8	1	2.389	7170.9794	3.817			
8	2	2.78	180704.2932	96.183			

(1*S*)-2,3-Dihydro-1,5-dimethyl-3-(methylene)indan-1-ol [(*S*)-70b)]



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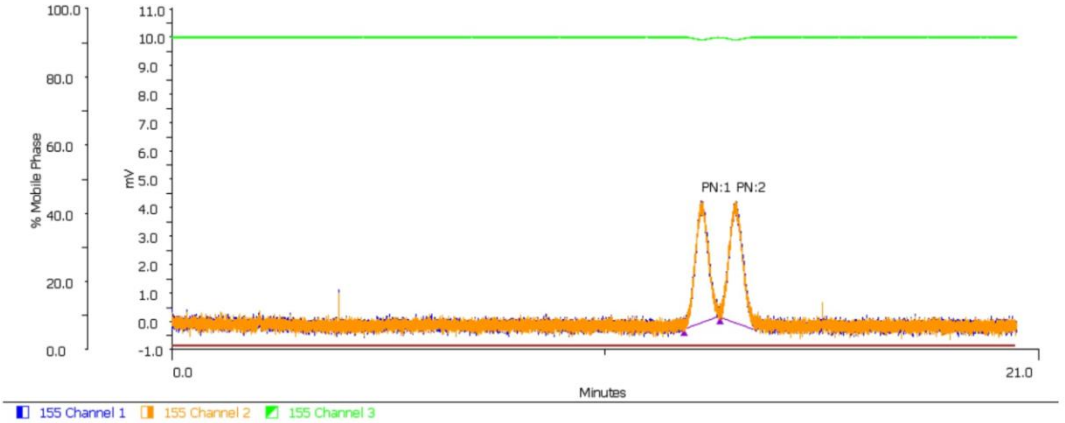
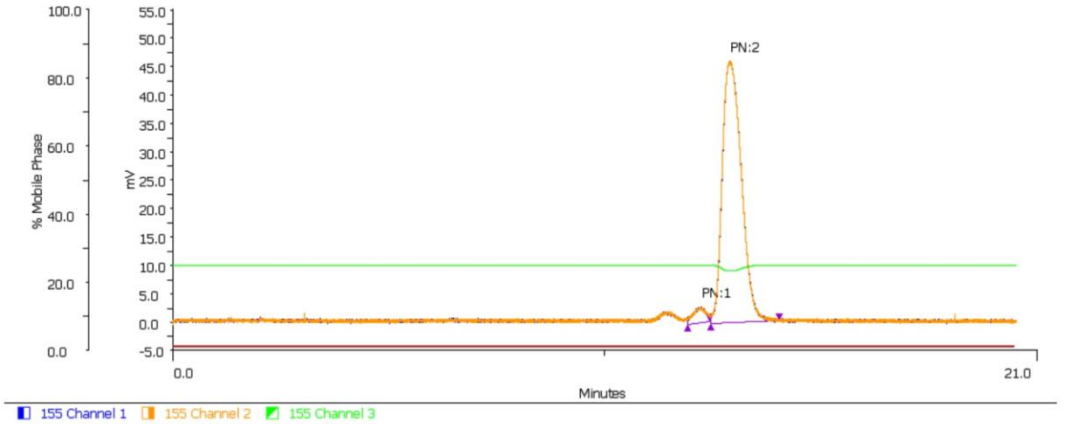


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	1	12.852	154302.9393	4.271	RF140	Sample Zone->5		48.436
1	2	13.687	164265.737	4.307	RF140	Sample Zone->5		51.564

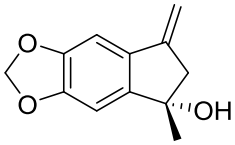
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
2	1	12.876	100353.305	2.822	RF155	Sample Zone->6		3.887
2	2	13.566	2481538.7648	46.063	RF155	Sample Zone->6		96.113

(1*S*)-2,3-Dihydro-5,6-(methylenedioxy)-1-methyl-3-(methylene)indan-1-ol [(*S*)-70c)]



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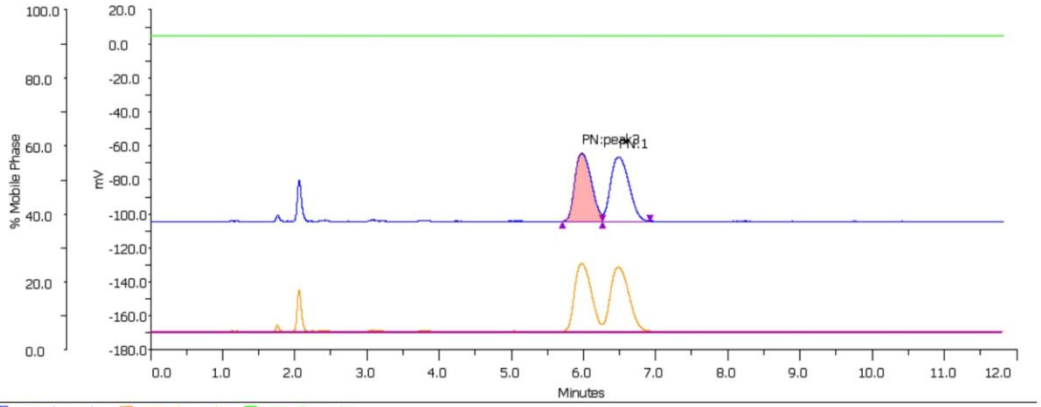
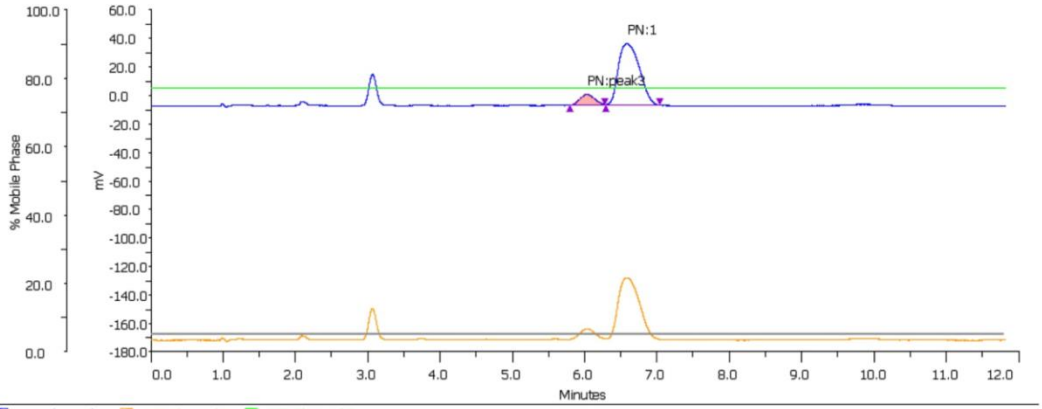


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
3	peak3	5.984	1066989.2009	40.045	RF147 rac	Sample Zone->4		48.855
3	1	6.492	1116992.2087	37.905	RF147 rac	Sample Zone->4		51.145

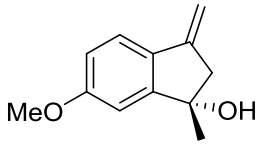
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	peak3	6.037	174202.5005	7.445	RF150 enantiorich	Sample Zone->3		10.743
1	1	6.592	1447280.4145	42.942	RF150 enantiorich	Sample Zone->3		89.257

(1*S*)-2,3-dihydro-6-methoxy-1-methyl-3-(methylene)indan-1-ol [(*S*)-70d)]



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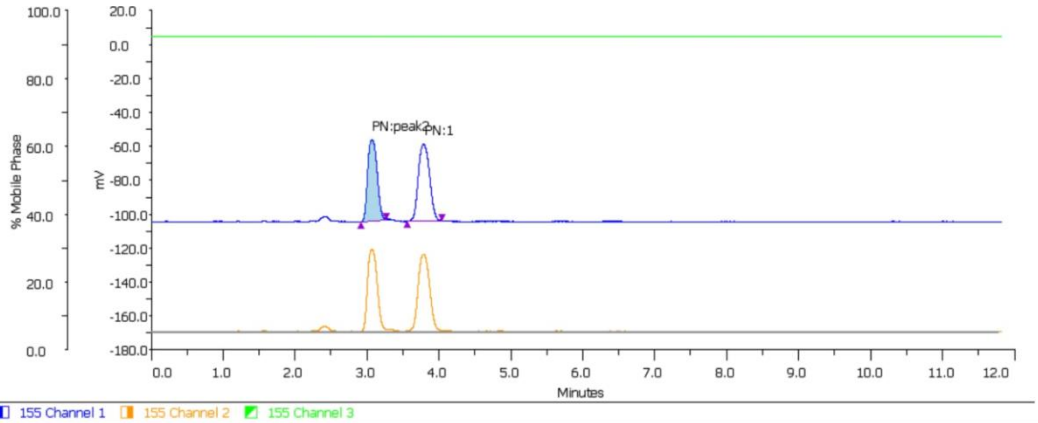
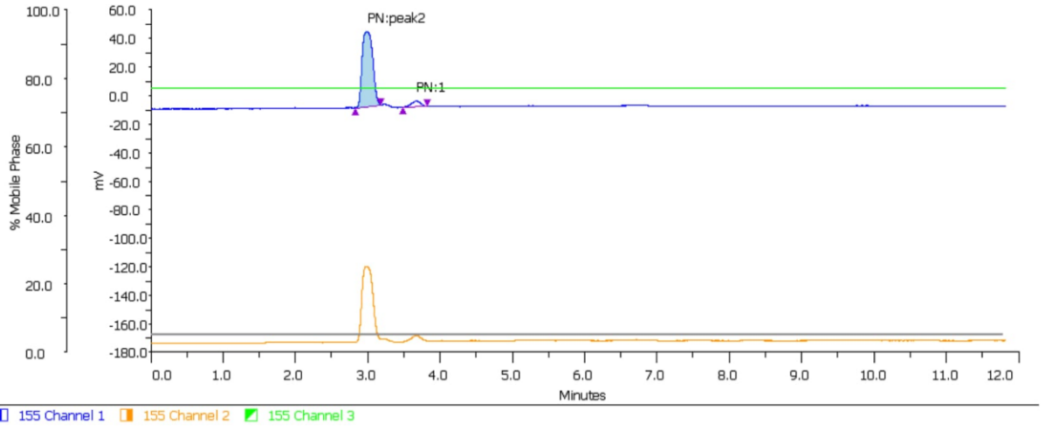


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
2	peak2	3.073	727478.2801	47.993	RF146 rac	Sample Zone->3		46.811
2	1	3.792	826582.5449	45.286	RF146 rac	Sample Zone->3		53.189

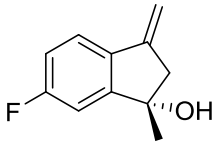
Enantioselective:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	peak2	2.989	888199.1735	52.239	RF149 enantiorich	Sample Zone->2		93.532
1	1	3.674	61422.4945	4.017	RF149 enantiorich	Sample Zone->2		6.468

(1*S*)-2,3-Dihydro-6-fluoro-1-methyl-3-methyleneinden-1-ol [(*S*)-70e)]



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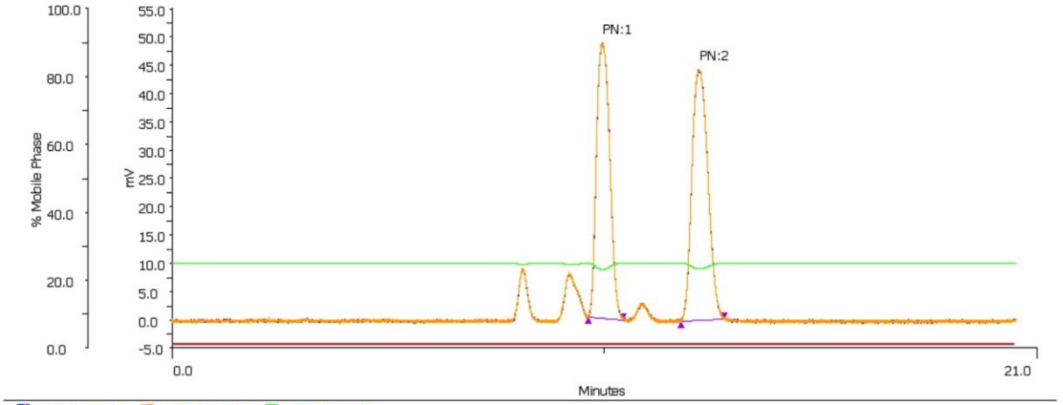
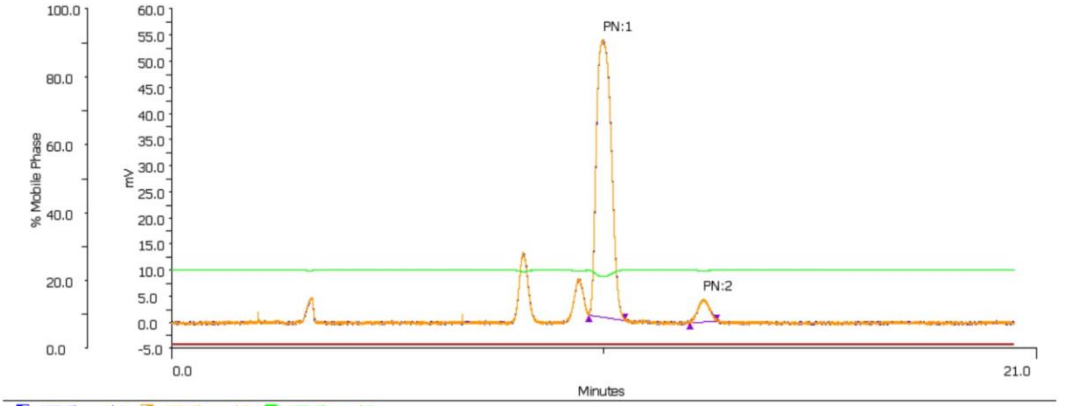


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
3	1	10.472	1823777.9172	48.699	RF136	Sample Zone->2		47.696
3	2	12.822	1999947.5008	44.407	RF136	Sample Zone->2		52.304

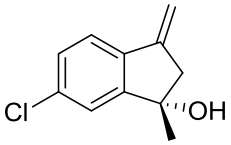
Enantioselective:



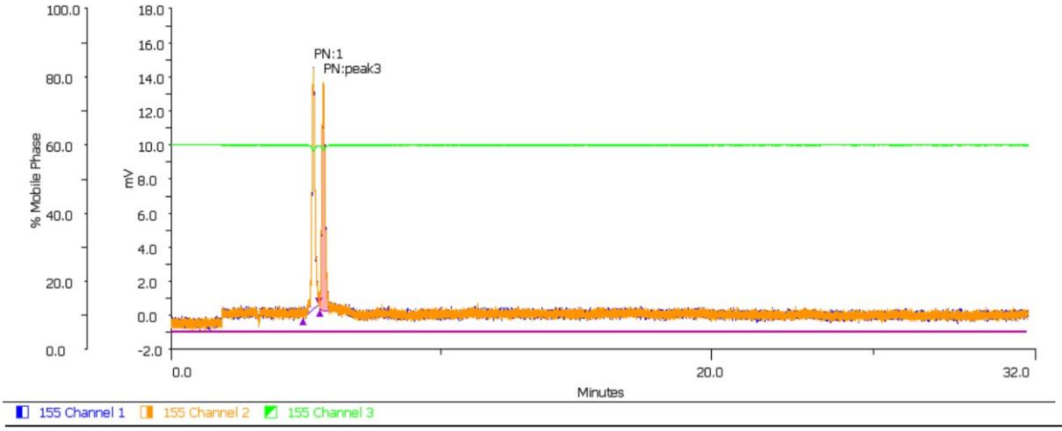
Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
2	1	10.497	2218588.331	52.978	RF130	Sample Zone->5		94.074
2	2	12.92	139749.1665	4.368	RF130	Sample Zone->5		5.926

(1*S*)-2,3-Dihydro-6-chloro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70f)]



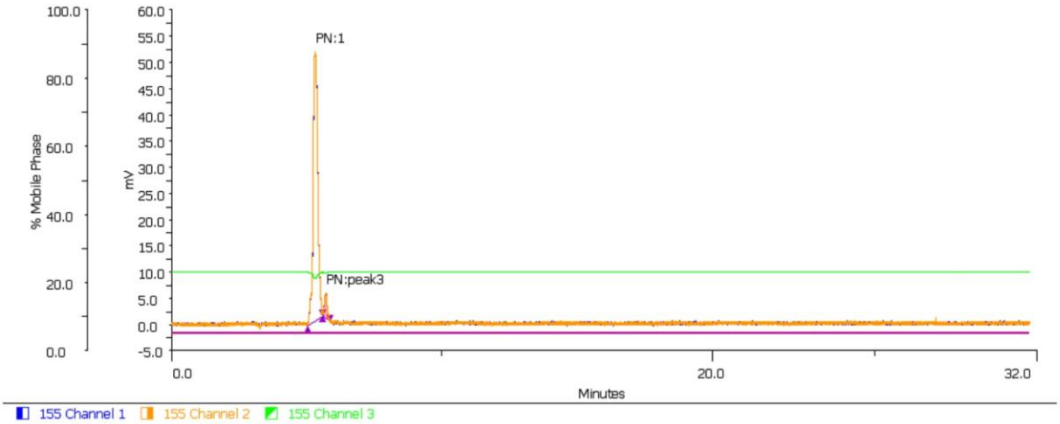
Racemate:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	1	5.285	189892.0594	14.234	RF156	Sample Zone->7		50.652
1	peak3	5.654	185006.512	13.421	RF156	Sample Zone->7		49.348

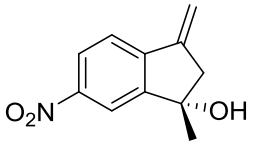
Enantioselective:



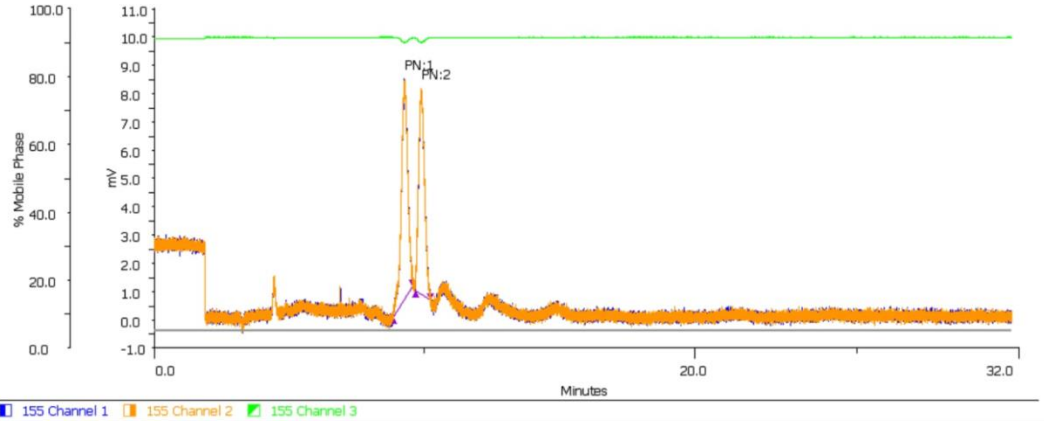
Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
2	1	5.329	1036275.0002	51.372	RF158	Sample Zone->8		94.875
2	peak3	5.721	55976.6664	4.781	RF158	Sample Zone->8		5.125

(1*S*)-2,3-Dihydro-6-nitro-1-methyl-3-(methylene)indan-1-ol [(*S*)-70g)]



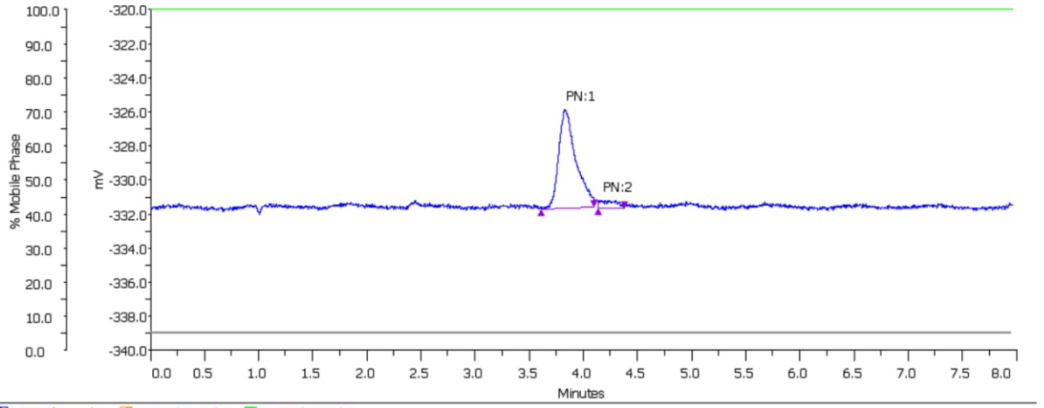
Racemate:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
4	1	9.285	213627.9186	7.795	RF139	Sample Zone->6		53.119
4	2	9.907	188543.3342	7.298	RF139	Sample Zone->6		46.881

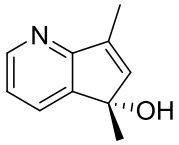
Enantioselective:



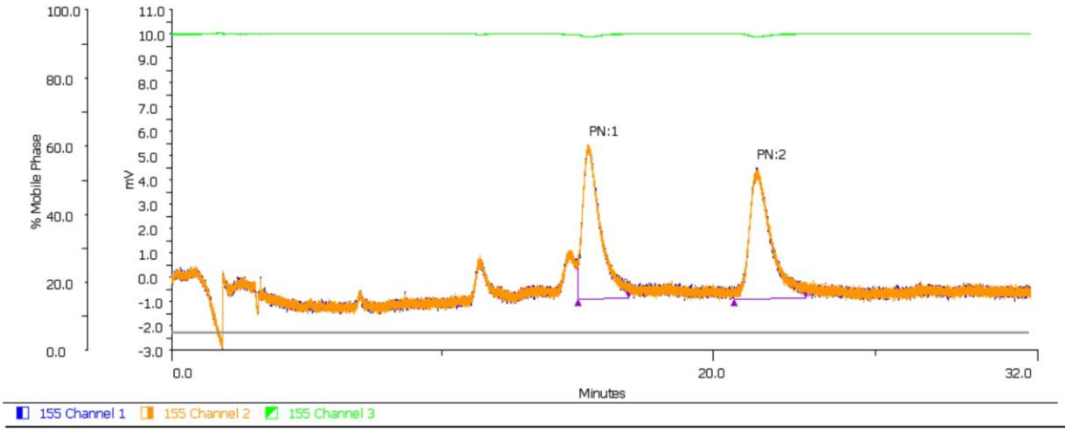
Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	1	3.839	106562.104	5.748	RF131 prepTLC 2ml/min	Sample Zone->3		93.377
1	2	4.179	7558.6157	0.446	RF131 prepTLC 2ml/min	Sample Zone->3		6.623

(5*S*)-5,7-Dimethylcyclopenta[b]pyridin-5-ol [(*S*)-82h)]



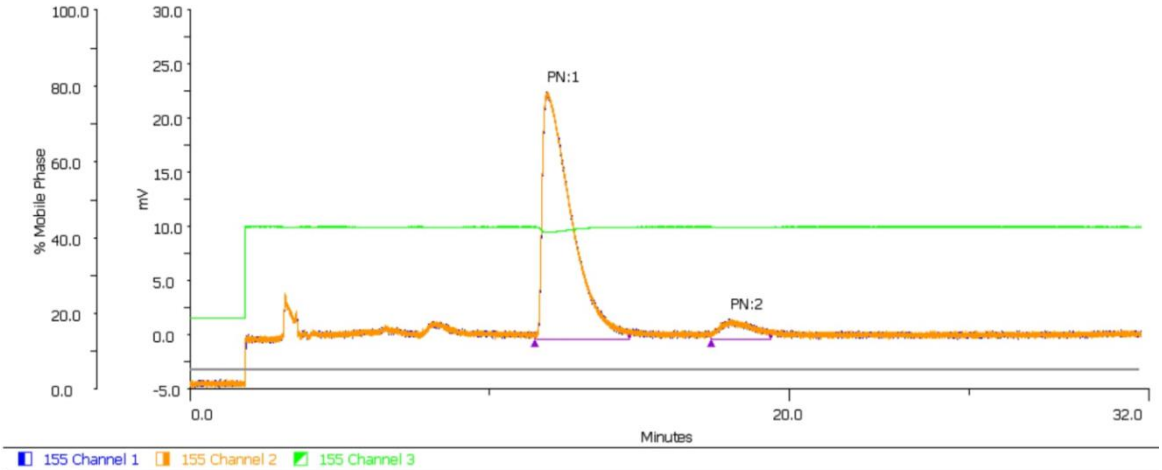
Racemate:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	1	15.423	483273.5655	6.336	RF160	Sample Zone->5		49.31
1	2	21.652	496789.2747	5.38	RF160	Sample Zone->5		50.69

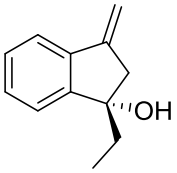
Enantioselective:



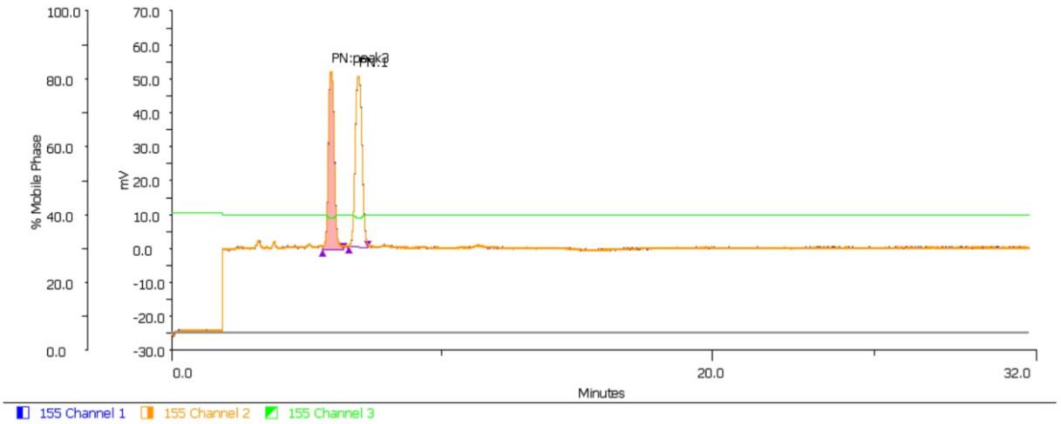
Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %			
1	1	11.947	2529692.9086	22.76	92.265			
1	2	18.051	212090.6468	1.8	7.735			

(1*S*)-2,3-Dihydro-1-ethyl-3-(methylene)indan-1-ol [(*S*)-70i)]



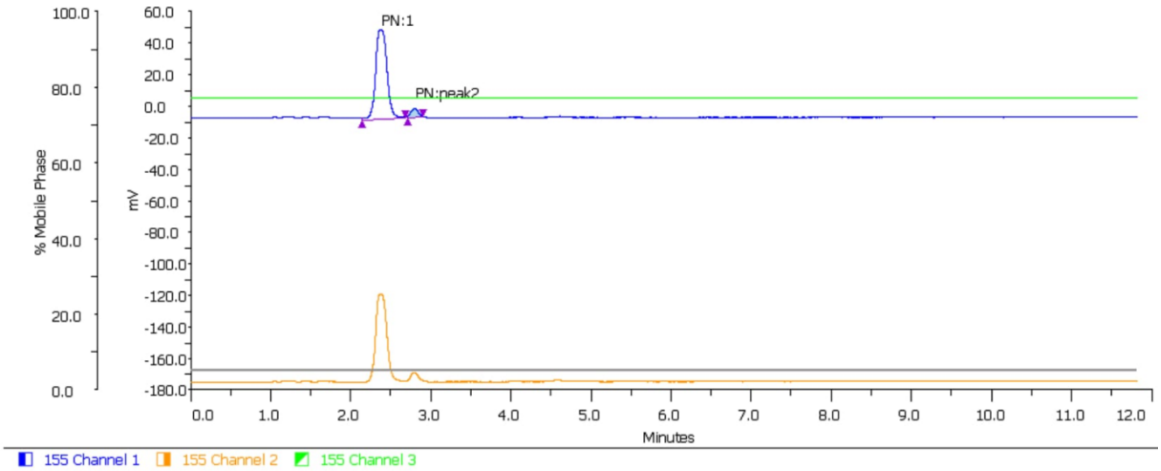
Racemate:



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Fraction Site(s)	Area %
1	peak3	5.918	1371459.7518	52.649	RF184	Sample Zone->5		48.268
1	1	6.931	1469861.5095	50.386	RF184	Sample Zone->5		51.732

Enantioselective:

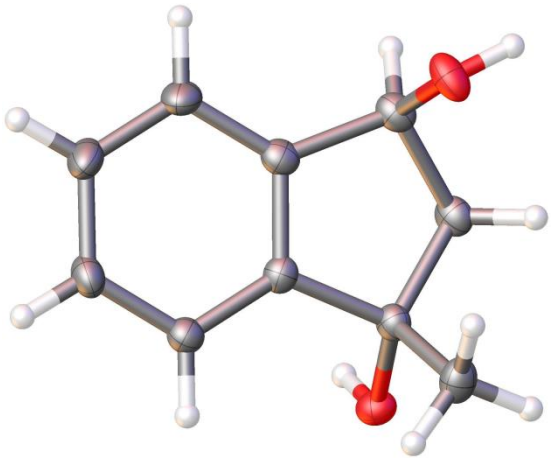


Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Area %			
1	1	2.379	943064.2981	56.947	94.11			
1	peak2	2.799	59022.5386	5.601	5.89			

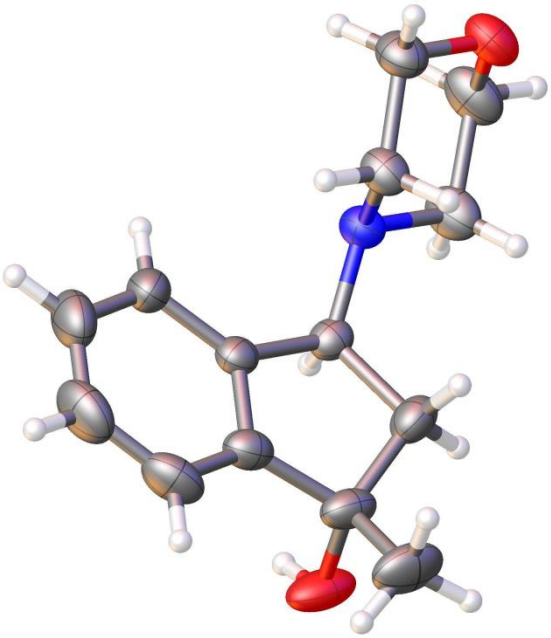
Appendix 2. Crystal structures of diol 84 and amino alcohol 85d

Diol **84** (CCDC 1568110):



View showing the crystal structure of diol **84**; atomic displacement ellipsoids are drawn at the 50% probability level with hydrogen atoms shown as spheres with arbitrary radius.

Amino Alcohol **85d** (CCDC 1568111):



View showing the crystal structure of amino alcohol **85d**; atomic displacement ellipsoids are drawn at the 50% probability level with hydrogen atoms shown as spheres with arbitrary radius.

Crystallographic experimental details: For all structures: trigonal, $P3_2$, Z = 3. Experiments were carried out using Cu $K\alpha$ radiation using a Bruker D8 VENTURE. Refinement was with 1 restraint.

	Diol **84** CCDC 1568110	Amino alcohol **85d** CCDC 1568111
Crystal data		
Chemical formula	$C_{10}H_{12}O_2$	$C_{14}H_{19}NO_2$
M_r	164.20	233.30
Temperature (K)	100	290
a, *c* (Å)	11.1863 (5), 6.1060 (3)	7.7296 (3), 18.3472 (9)
V (Å^3)	661.70 (7)	949.32 (9)
μ (mm^{-1})	0.69	0.65
Crystal size (mm)	0.21 × 0.04 × 0.02	0.41 × 0.27 × 0.12
Data collection		
Absorption correction	Multi-scan *SADABS2016*/2 (Bruker, 2016/2) was used for absorption correction. wR2(int) was 0.1333 before and 0.0653 after correction. Ratio Tmin:Tmax 0.7759.	Multi-scan *SADABS2016*/2 (Bruker, 2016/2) was used for absorption correction. wR2(int) was 0.1616 before and 0.0546 after correction. Ratio Tmin:Tmax 0.9221.
T_{min}, T_{max}	0.585, 0.754	0.638, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	5837, 1761, 1731	10651, 2237, 2214
R_{int}	0.031	0.032
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.625	0.600
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.028, 0.070, 1.03	0.031, 0.080, 0.99
No. of reflections	1761	2237
No. of parameters	118	156
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.17, -0.17	0.11, -0.10
Absolute structure	Flack x determined using 841 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).	Flack x determined using 1061 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.10 (9)	0.08 (8)

Computer programs: *APEX3* Ver. 2016.9-0 (Bruker-AXS, 2016), *SAINT* V8.37A (Bruker-AXS, 2016), *SHELXT* (Sheldrick, 2015), *SHELXL* (Sheldrick, 2015), Olex2 (Dolomanov *et al.*, 2009).