ARYNES IN SYNTHESIS; NEW REACTION AND PRECURSOR DEVELOPMENT

A thesis submitted to the University of Manchester
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By
Donald McAusland
School of Chemistry

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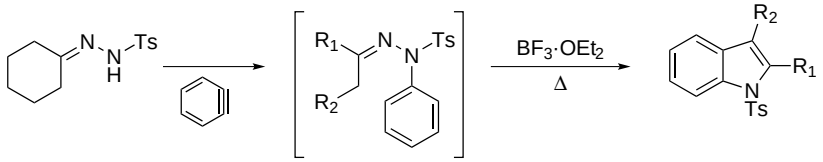
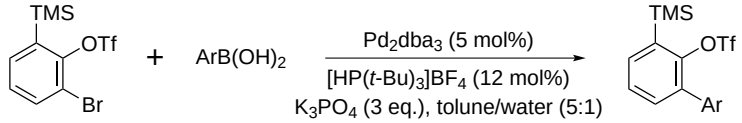
Abstract

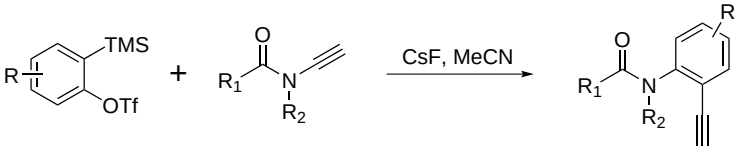
The arylation of readily accessible *N*-tosyl hydrazones has been achieved using arynes generated *in situ* under mild conditions. The resulting *N*-tosyl-*N*-aryl hydrazones undergo a one-pot Fischer indole reaction on the addition of acid, giving a synthesis of protected indoles that avoids handling unstable intermediates and arylhydrazines.



A new route to functionalised 2-(trimethylsilyl)phenyl triflate aryne precursors *via* Suzuki cross-coupling has been developed. The method allows the incorporation of a wide range of aryl and heteroaryl groups and reactions of arynes generated from these novel precursors have been demonstrated, including a cyclotrimerisation and a fluorenone synthesis.



Work was also undertaken on aryne σ-insertion reactions. The addition of benzyne to ynamides was found to result in its net insertion between the nitrogen and acetylene species. The reaction proceeds from attack at the terminal carbon in an analogous manner to C(sp)–O insertions.



Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Acknowledgements

My mother, Tom, Chris and other members of the group for help proofreading this thesis, Tom for assistance with X-ray crystallography, Didier and Kallol for help and advice when I first entered the lab and the rest of the Greaney group throughout my time here. Gill, Ryan and their colleagues at Alderly Park for a pleasant and useful stay. The members of the Procter group and in particular Matt and James for reminding me about the outside. Jurai for constant helpfulness with NMR in Edinburgh, Carol and Gareth for aiding analysis in Manchester and Mike for the opportunity to carry out this work and his assistance during it.

Chapter 1

Introduction

Arynes are didehydro aromatic species, the simplest and most well known of which is *ortho*-benzyne. The transient formation of these highly unstable reactive intermediates, though not always realised, has long been achieved in organic chemistry. Bachmann suggested in 1927 that the biradical "free phenylene" (**1a**) could account for the formation of triphenylene from the action of sodium on chlorobenzene,[1] while Wittig proposed a zwitterionic species (**1b**) during his work with organolithium reagents.[2] Later, Roberts used ^{14}C labelling and degradation experiments to demonstrate that *cine* and *ipso* substitution occurred equally when chlorobenzene was converted to aniline with potassium amide (Scheme 1.1). This result confirmed the existence of a symmetrical intermediate, referred to by Roberts as benzyne (**1c**).[3]

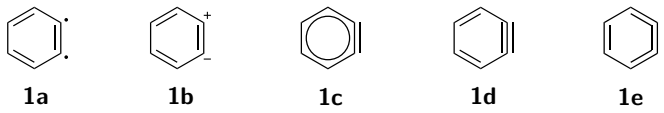
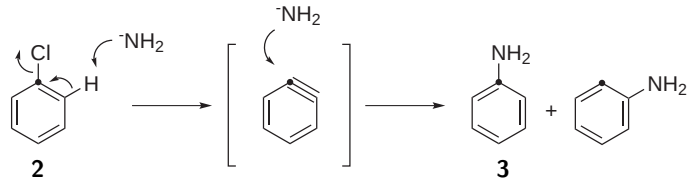


Fig. 1.1 Representations of benzyne. Aromatic alkyne **1d** is most commonly used although it implies full triple bond character; its mesomeric form **1e** suggests interaction with the aromatic π-system, which is minimal.



Scheme 1.1 Early ^{14}C labelling experiment to demonstrate the existence of benzyne.[3]

Since these early studies, *ortho*-benzyne has been subjected to considerable theoretical and experimental investigation and its characterisation has confirmed a degree of bonding interaction between adjacent dehydro sites. The aryne IR stretch was unambiguously assigned as 1846 cm^{-1} with the aid of deuterium and ^{13}C labelling by Radziszewski *et al.*,[4] while Grant and co-workers measured the bond length and chemical shift in the solid state using ^{13}C dipolar NMR, finding a C–C distance of 1.24 Å.[5] These values lie between those of a typical acyclic alkyne C≡C bond and an alkene double bond. Additionally, benzyne has been stabilised and characterised by NMR in a hemicarcerand host-guest complex.[6]

The poor overlap and strained nature of the benzyne triple bond results in a low-lying LUMO, prone to nucleophilic attack and participation in pericyclic reactions, while the relief of ring strain and limited penalty for C≡C cleavage ensures these are enthalpically favoured. Consequently arynes are short-lived intermediates but take part in a wide range of reactions and have been used extensively in organic synthesis.

Benzyne isomers with didehydro sites on non-adjacent carbons also exist as *meta*- or *para*-benzyne.[7] The degree of orbital overlap in these species is significantly lower than in *ortho*-benzyne, giving far smaller singlet–triplet separation, and their energies of formation are somewhat higher.[8] Whilst *para*-benzynes are of some interest in enediyne natural products and antibiotics, their use as intermediates in synthesis is limited. Further discussion of arynes is restricted to unsubstituted and functionalised *ortho*-didehydro benzenes along with polycyclic and heterocycle based arynes (heteroarynes). Strained cycloalkynes bear some similarities to *ortho*-benzyne and are sometimes prepared by the same methods but are not included in this chapter.

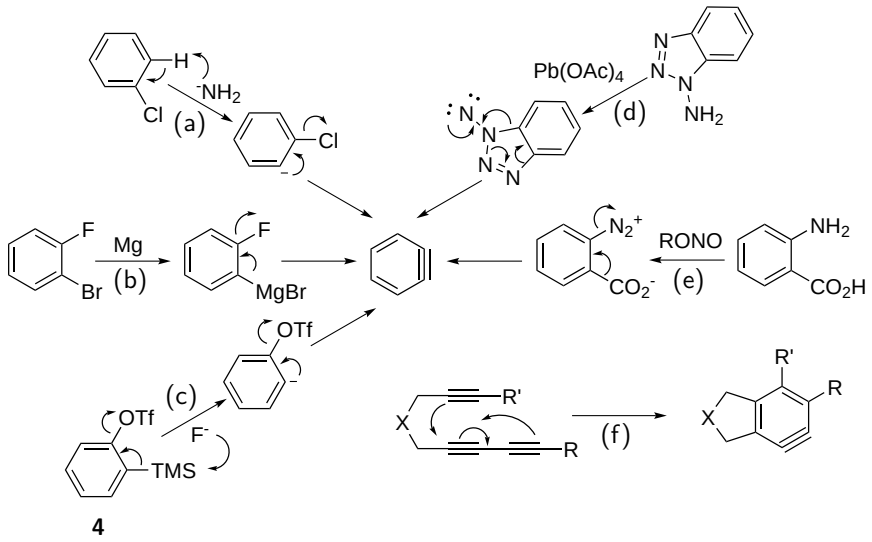
The properties and use of arynes have been the subject of numerous reviews[9–25] and the extensive scope of aryne chemistry can not be covered here. Instead, the generation, modes of reaction and selectivity of substituted arynes is introduced with relevant examples. The syntheses and availability of 2-(trimethylsilyl)phenyl triflate precursors is reviewed more thoroughly and further examples of aryne reactions are also given with a focus on indole syntheses.

1.1 Generation of benzyne

The instability and high reactivity of free arynes necessitates their *in situ* generation during a synthetic procedure. The formation of an *ortho*-didehydro arene requires the loss of two adjacent species from an aromatic species or, less commonly, cyclisation of a suitably unsaturated precursor and examples are given in Scheme 1.2.

ortho-Elimination is most often achieved from an initially formed aryl anion, with rapid (or concerted) loss of a labile group. Commonly employed methods include deprotonation with a strong base (Scheme 1.2, (a)),[26] metal-halogen exchange (b),[27] or fluoride-induced desilylation (c).[28] In each case a choice of functionalities and conditions is available. Of particular historical significance are reactions driven by the expulsion of small molecules from an *in situ* formed zwitterion (e)[29] or nitrene fragmentation (d),[30] which allowed the development of aryne methodology under non-basic conditions. In these processes the high enthalpy of benzyne formation[31] is offset by bond-forming reactions in addition to the entropically favourable processes.

The intramolecular [4+2] cyclisation of a diyne and an alkyne[32] has also received recent interest[33] although is only applicable to the generation of substituted polycyclic arynes rather than benzyne itself (Scheme 1.2, (f)).

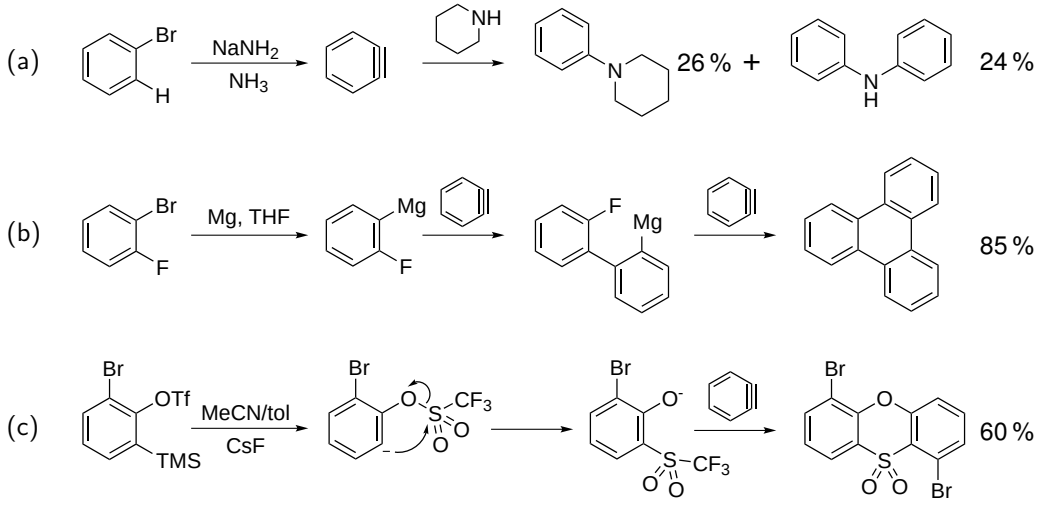


Scheme 1.2 Routes to generate benzyne from stable precursors.

Of particular note is the introduction of 2-(trimethylsilyl)phenyl triflate (**4**) as a benzyne precursor by Kobayashi, which has been largely responsible for the increase in aryne-based methodologies in the last decade, and its appearance in the literature has

grown substantially. The reagent, which is stable under laboratory conditions, permits the generation of benzyne under mild conditions, utilising the high affinity of fluoride for silicon and the excellent triflate leaving group. It allows efficient benzyne generation over a range of conditions, with the rate of aryne release controlled both by temperature and fluoride source solubility, and avoids strong bases, oxidants or unstable precursors required in other methods. The preparation and use of this class of precursor is covered in more detail in Section 1.4.

A further consideration for precursor choice is the stability of the reagents and any precursor-derived intermediates to the aryne-generating conditions. For a base-mediated elimination, other species might compete with the desired addition process (Scheme 1.3, (a)), making their relative nucleophilicities an important factor.[34] Metal-halogen exchange can be achieved with less nucleophilic reagents but this leads to organometallic intermediates. If these are relatively stable towards aryne formation then they may themselves attack any benzyne already present, leading to biphenylene, triphenylene or benzene oligomers (Scheme 1.3, (b)).[35] In some cases Kobayashi-type precursors also form stable anions; thia-Fries rearrangement with the adjacent sulfonyl group can then compete with triflate elimination leading to phenoxathiin-dioxides (Scheme 1.3, (c)).[36] The two latter processes have been optimised as useful protocols by Heaney and Lees and by Greaney and co-workers respectively.



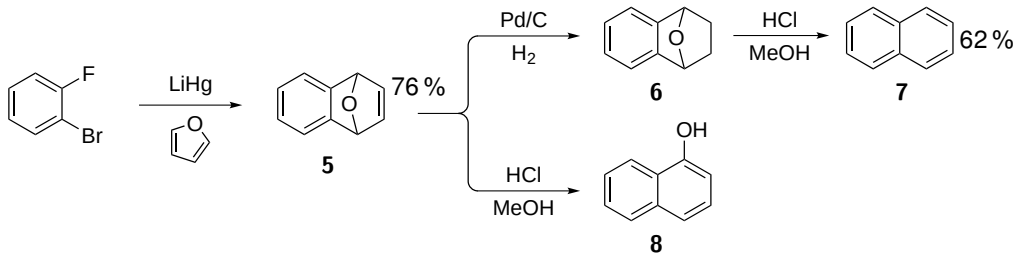
Scheme 1.3 Reactions of aryne precursors.[34–36]

1.2 Reactions of benzyne

Benzyne, with its accessible LUMO, reacts principally through nucleophilic addition or pericyclic reactions in the presence of a suitable second component. When generated in isolation, dimerisation and trimerisation processes may consume the species although reactions with solvent and precursor by-products are common in the solution phase.[37] The ability of arynes to ligate transition metal complexes further expands the broad scope of chemistry available to these reactive intermediates.

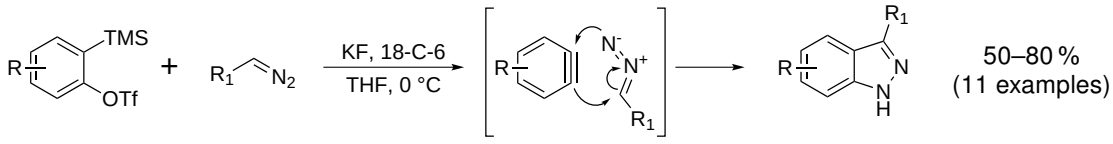
1.2.1 Pericyclic reactions

The observation that arynes underwent analogous Diels–Alder reactions to electron-deficient acetylenes helped to verify their nature as strained aromatic alkynes. Benzyne generated from bromo-fluorobenzene was used by Wittig and Pohmer to prepare the cycloaddition product **5** (Scheme 1.4),[38] and similar reactions have frequently been used to test for the presence of aryne intermediates. Further modification of **5** was achieved by hydrogenation and dehydration yielding **7** and **8**.



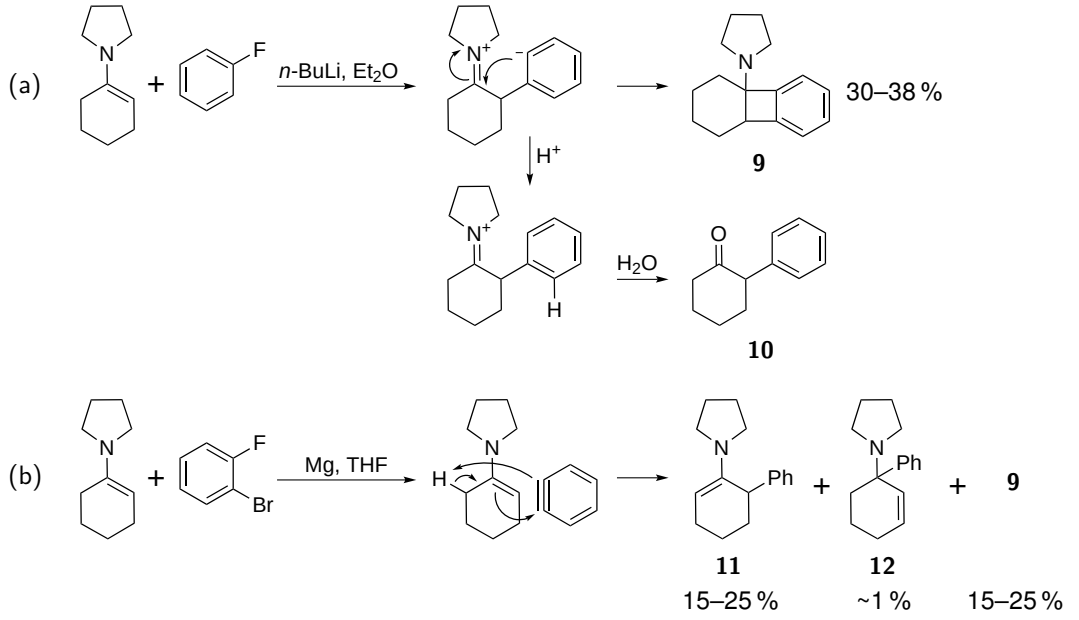
Scheme 1.4 Diels–Alder reaction with furan.[38]

Arynes readily undergo other cycloaddition reactions and these have been used extensively in the preparation of polyaromatic structures. Yamamoto and Jin reported a [3+2] cycloaddition between diazoalkanes and benzyne generated from *ortho*-(trimethylsilyl)phenyl triflates in a synthesis of 1*H*-indazoles (Scheme 1.5).[39] The *N*-aryl indazoles could also be obtained by employing an excess of aryne.



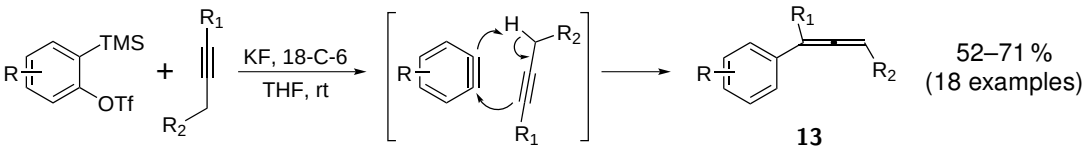
Scheme 1.5 [3+2] cycloaddition with diazoalkanes.[39]

Arynes are also well known for their participation in thermal [2+2] processes including dimerisation to biphenylene, and there are many reactions of benzyne with symmetric and asymmetric olefins. For example, Kuehne and co-workers obtained the benzocyclobutene product **9** on treatment of an enamine with benzyne (Scheme 1.6, (a)).[40] The mechanism was thought to proceed *via* a zwitterionic intermediate, which could also be quenched with a proton to give **10** on hydrolysis.



Scheme 1.6 Enamine–benzyne reactions.[40]

Gingrich, Jones and co-workers later reinvestigated this reaction and argued that the α-arylation product was the result of a [4+2] ene reaction, since they could isolate **11** and **12** if hydrolysis was avoided (Scheme 1.6, (b)).[41] Their conclusion was supported by exclusive ene product formation in a similar reaction with the isolobal *ortho*-carboryne species. Other benzyne ene reactions are known and even aliphatic acetylenes may participate as an ene component under mild conditions, as described by Cheng and co-workers (Scheme 1.7).[42]

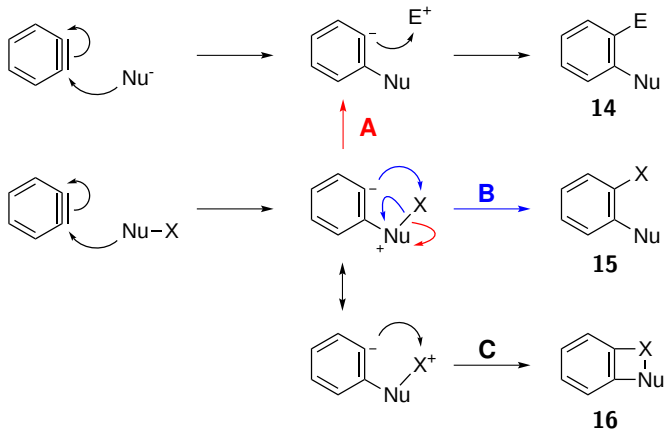


Scheme 1.7 Ene reaction of arynes with alkynes.[42]

1.2.2 Nucleophilic addition to arynes

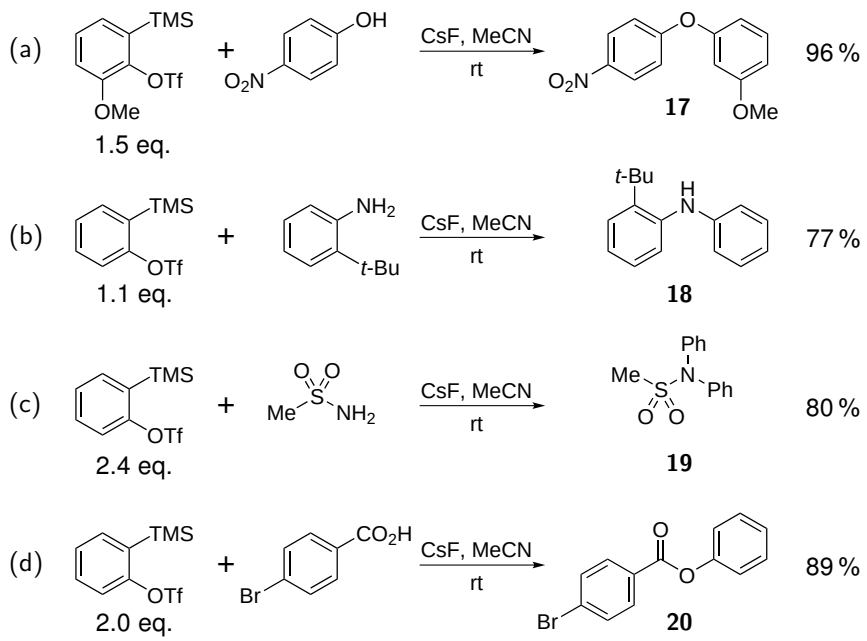
Benzyne is an excellent electrophile that will react with many anionic and neutral species. If attacked by a negatively charged nucleophile the resulting aryl anion can be quenched with a proton, which may originate from the solvent, to give a simple arylation product (Scheme 1.8, **14**, E = H^+) or add to a second electrophile in a three-component coupling (E ≠ H^+).

When a neutral nucleophile attacks an aryne triple bond, a zwitterionic intermediate is formed initially. Deprotonation or some other cation-quenching process gives an aryl anion that may react as before (Scheme 1.8, path **A**). Alternatively, cyclisation to an electrophilic site on the newly incorporated group might occur. Subsequent bond fission leads to insertion products (**15**, path **B**) whereas a stable cyclic structure (**16**) is formally equivalent to a cycloaddition reaction.



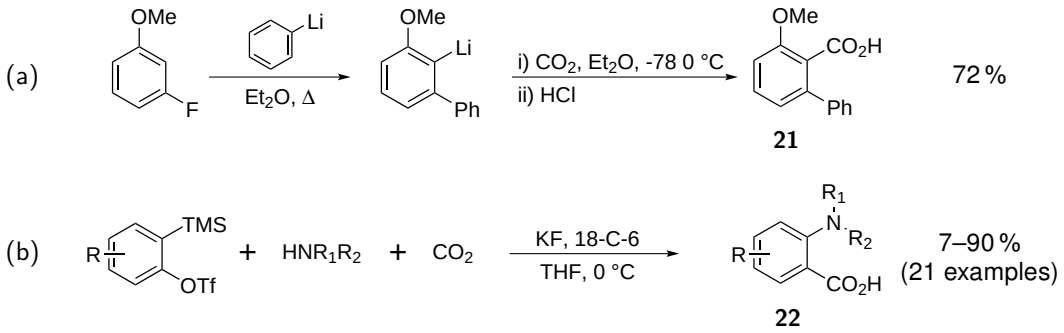
Scheme 1.8 Nucleophilic addition to benzyne.

The simple addition of metal amides and other nucleophilic species to benzyne has been utilised since the onset of aryne chemistry to prepare functionalised arenes, although these older methods often lacked functional group compatibility. Extensive studies on the arylation of neutral species, with 2-(trimethylsilyl)phenyl triflates as benzyne precursors using caesium fluoride in acetonitrile, have been conducted by Liu and Larock. They achieved arylation of many classes of nucleophile including amines and anilines, sulfonamides, carbamates, phenols, benzoic acids, a number of nitrogen heterocycles and thiophenols; generally in good or excellent yields (Scheme 1.9).[43] Double arylation occurred with some species while aliphatic alcohols and benzenesulfonic acid were poor nucleophiles.



Scheme 1.9 Arylation reactions under mild conditions by Liu and Larock.[43]

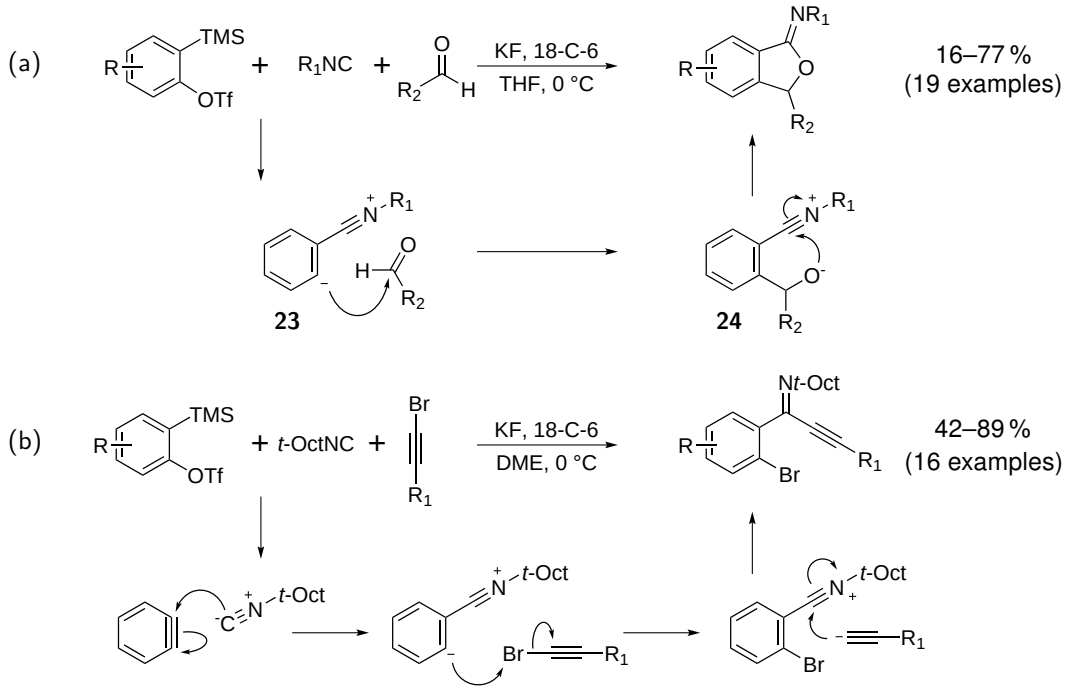
In 1954 Huisgen and Rist showed that the anion formed on addition of phenyl lithium to an aryne could be trapped with carbon dioxide. By using either 2- or 3-fluoroanisole, 3-methoxy-biphenyl-2-carboxylic acid (**21**) could be obtained as the major regioisomer (Scheme 1.10, (a)).[44] Despite this and related early reports, relatively few benzyne three-component couplings with anionic nucleophiles exist. A similar reaction has since been achieved with amine nucleophiles by Yoshida and co-workers (Scheme 1.10, (b)), which allowed the preparation of a range of anthranilic acid derivatives.[45]



Scheme 1.10 Three-component couplings with electrophilic CO_2.[45]

Many recently disclosed benzyne three-component couplings that employ neutral nucleophiles undergo rapid electrophilic attack and the resulting zwitterion may

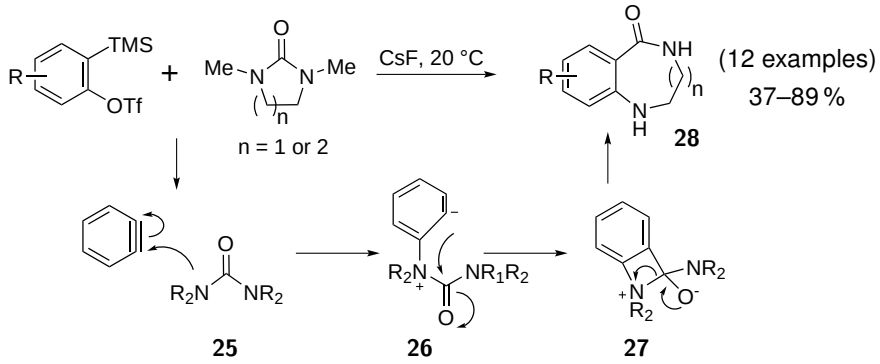
be quenched in other ways. Thus when Yoshida, Kunai and co-workers generated benzyne in the presence of an isocyanide and an aldehyde (Scheme 1.11, (a)), the initial zwitterion **23** reacted with the aldehyde leading to **24**, which underwent self-quenching cyclisation to give benzoannulated iminofurans. An interesting acetylene incorporating reaction was also reported by Yoshida *et al.* (Scheme 1.11, (b)), wherein a bromoacetylene provides the electrophilic Br^+ component whilst the released acetylide attacks the cationic region. Polyfluoro-bromobenzenes could be used in a similar way.[46]



Scheme 1.11 Self-quenching three-component couplings.[47]

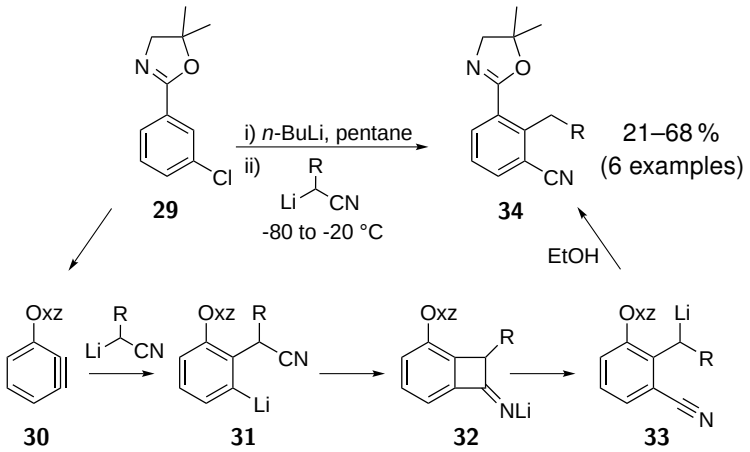
An alternative route to *ortho*-difunctionalised arenes is benzyne σ-insertion and many hetero-groups may be added across the triple bond in this way.[48] The first example of σ-insertion into a heteroatom–C(sp^2) bond under mild conditions was reported by Shirakawa, Hiyama and co-workers.[49] In this work the initially formed zwitterion was assumed to undergo intramolecular attack to form cyclic intermediate **27**, which gave amide products upon ring opening (Scheme 1.12). Similar insertion reactions with anionic carbon nucleophiles have been known for some time but these reactions were typically low yielding and gave multiple products.[50]

Aryne σ-insertion reactions at electrophilic C(sp) sites are also known. Lithioalkyl nitriles were shown by Meyers and co-workers to add to benzyne generated from chlorphenyl oxazoline **29** and *n*-butyl lithium (Scheme 1.13). Intramolecular attack



Scheme 1.12 N–C(sp^2) aryne insertion.[49]

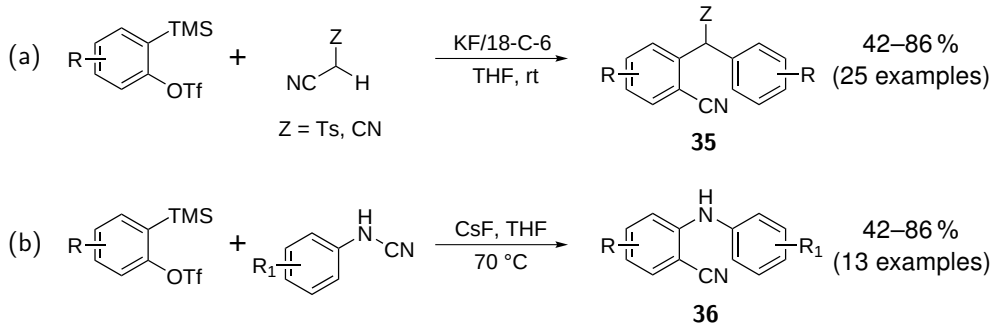
into the nitrile group was thought to give intermediate **32**, which after ring opening and quenching with ethanol led to insertion product **34**. Electrophiles other than H^+ could also be incorporated in the final step.[51]



Scheme 1.13 Organolithium–aryne C–CN insertion.[51]

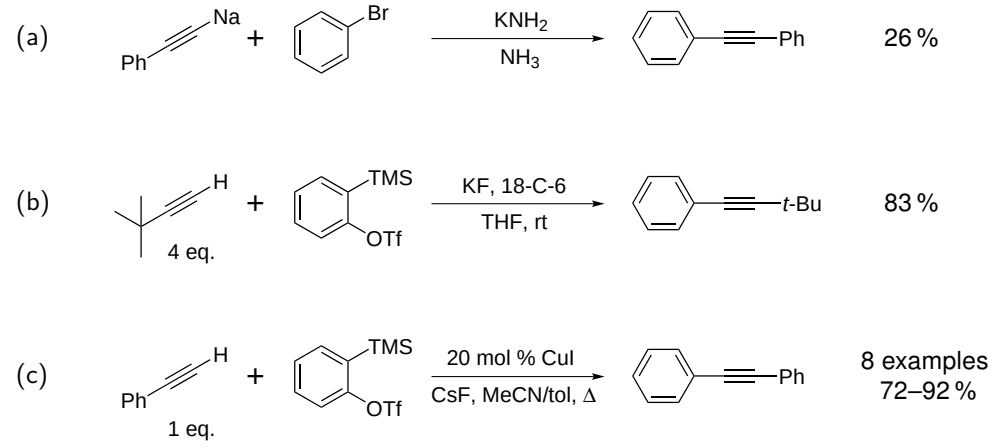
Prior lithiation of the nitrile could be avoided in a similar reaction by Yoshida *et al.* if an additional electron-withdrawing sulfonyl or nitrile group were present (Scheme 1.14, (a)).[52] In this case the benzylic position underwent arylation with a second equivalent of aryne before the anion was quenched, although the monoarylated species was detected as a side product. Recently, a related N–CN σ-insertion was reported by Zeng and Rao.[53] Here, the reaction is initiated by nucleophilic attack of cyanamide nitrogen, resulting in aminocyanation products **36** (Scheme 1.14, (b)).

Nucleophilic reactions involving C≡C bonds are less common. The reaction of phenyl acetylide with benzyne was reported by Roberts and Scardiglia in 1958 (Scheme 1.15,



Scheme 1.14 σ-Insertion reactions at nitrile.[52,53]

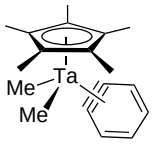
(a)),[54] while a terminal acetylene was later found to be a suitable nucleophile under far milder conditions by Cheng and co-workers (b).[42] Zhang *et al.* noted that phenyl acetylene did not add to benzyne in acetonitrile with caesium fluoride. However, an *in situ* generated acetylide did undergo nucleophilic addition to benzyne (Scheme 1.15, (c)), which constituted the first example of copper catalysis in aryne chemistry.[55] The resulting aryl cuprate could also be trapped with an allyl halide in a metal-catalysed three-component coupling.



Scheme 1.15 Addition of C(sp) nucleophiles to benzyne.[54,55,42]

1.2.3 Transition-metal-catalysed reactions

Like other strained cycloalkynes, benzyne forms transition metal complexes, examples of which have been isolated and characterised.[56] The first η^2-ligated niobium– and tantalum–aryne complexes (**37**) were reported by Schrock and co-workers,[57] although higher coordination modes also exist. When bound in this way, the triple bond behaves primarily as a 2 electron π-donor, the structure of which is equivalent to a three-membered cyclometalated didehydrobenzene (Fig. 1.2).



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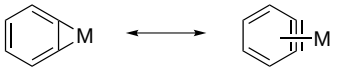


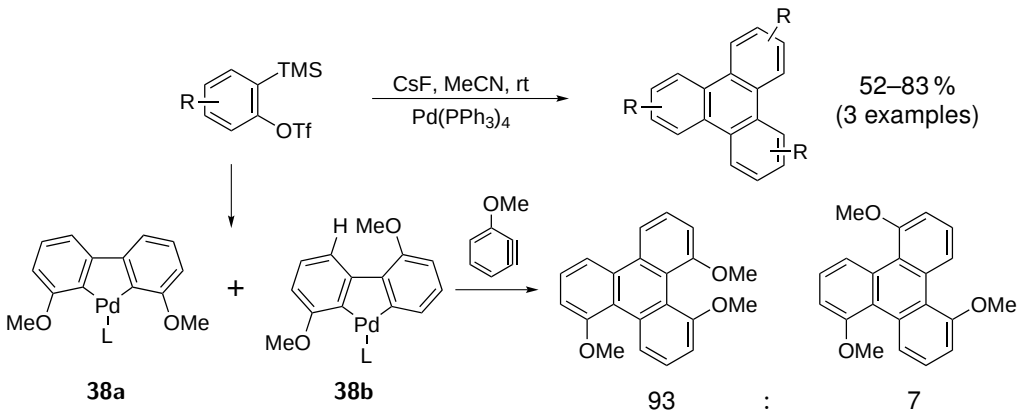
Fig. 1.2 Benzyne–transition metal complexation.[57]

Aryne–transition metal complexes, either preformed or generated *in situ*, may be useful in synthesis since their reactivity and subsequent transformations permit reactions not observed with free benzyne.[58] The accessibility of arynes formed under mild conditions compatible with transition-metal processes, coupled with developments in cross-coupling catalysis has promoted developments in this field.[17,19]

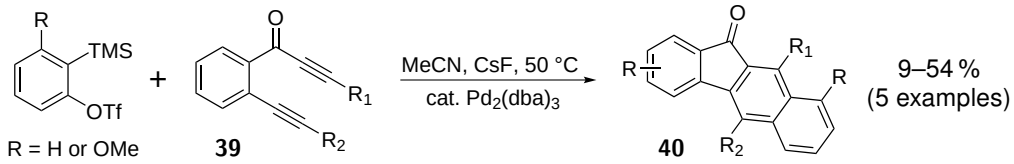
Pérez, Guitián and co-workers reported the first palladium-catalysed reaction of arynes, finding that Pd(0) sources facilitated [2+2+2] cyclotrimerisations of benzyne generated from Kobayashi precursors in high yields (Scheme 1.16).[59] Numerous similar reactions have since been disclosed.[60] The asymmetric triphenylene was the major product from an *ortho* substituted benzyne, a result that may be explained by preferential formation of the less hindered cyclometalated intermediate **38a**. This can only react to give the more hindered product on incorporation of a third equivalent of aryne.

This methodology has since been extended to include co-cyclisation reactions, particularly with other electron-deficient species, as well as intramolecular [2+2+2] reactions for the preparation of fused polycycles. For examples, benzofluorenones **40** may be obtained from the palladium-catalysed co-cyclisation of benzyne with diynes **39** (Scheme 1.17).

Palladium catalysis has also allowed the development of additional benzyne insertion reactions. The first example of this kind was reported by Shirakawa, Hiyama and co-



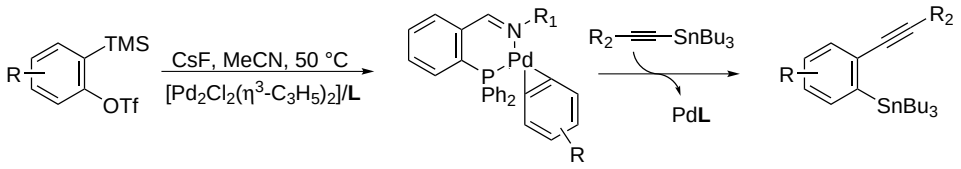
Scheme 1.16 Palladium-catalysed triphenylene synthesis.[59]



Scheme 1.17 Benzyne–alkyne [2+2+2] cycloaddition.[61]

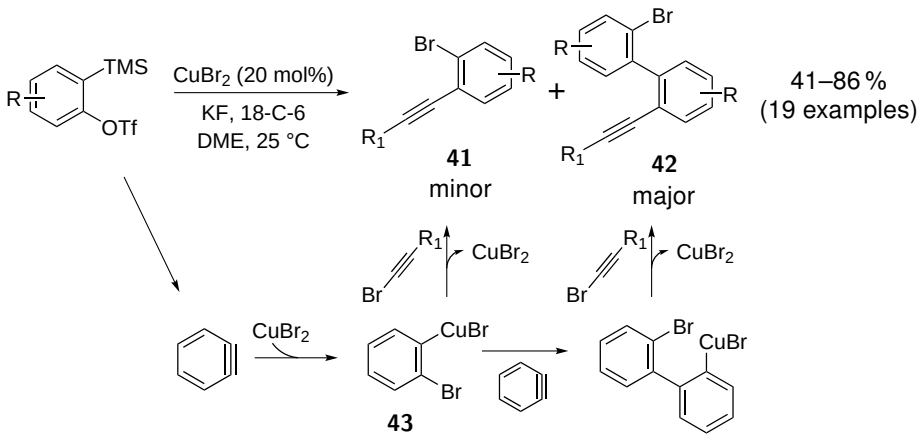
workers,[62] who used a palladium-iminophosphine complex to catalyse the reaction between alkynyl stannanes and benzyne.

Two possible pathways were proposed. In the first (shown in Scheme 1.18) the co-ordinated benzyne complex forms initially prior to reaction with the stannane. Alternatively, oxidative insertion of the stannane might occur first to give a Pd(II) complex that then undergoes carbometalation with benzyne. Notably, the uncatalysed insertion reaction did proceed, albeit in under 10 % yield.



Scheme 1.18 Palladium-catalysed Sn–C(sp) benzyne insertion.[62]

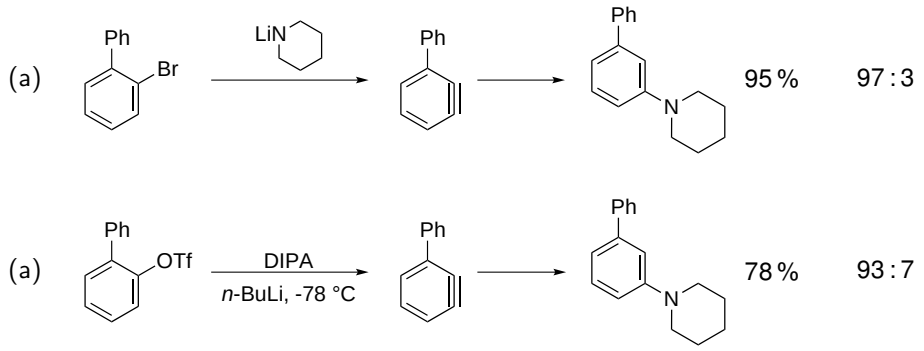
Yoshida and co-workers have also reported the copper-catalysed insertion of benzyne into ethynyl bromides (Scheme 1.19).[63] The reaction is believed to proceed *via* bromophenyl cuprate **43**, which attacks either a second equivalent of benzyne or the acetylene at the 1-position.



Scheme 1.19 C(sp)–Br bond fission in benzyne reactions.[63]

1.3 Selectivity with substituted arynes

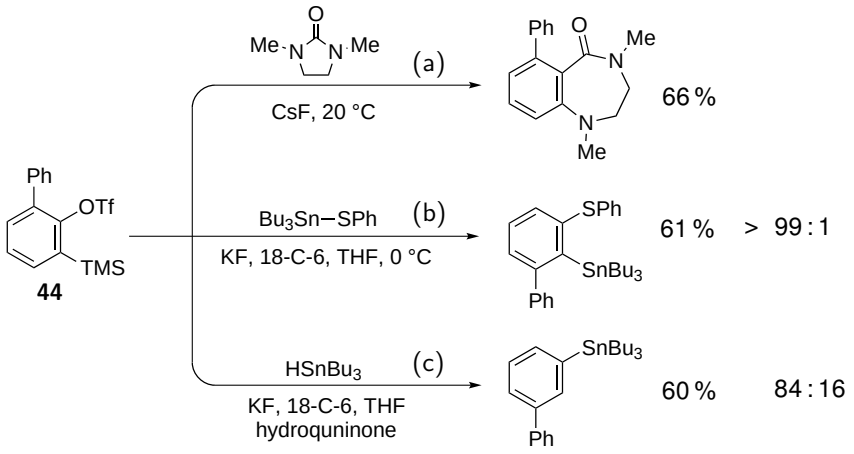
It is well known that arynes bearing sterically demanding 3-substituents undergo preferential *meta*-attack, with the degree of selectivity being dependent on the nature of both the nucleophile and the substituent. Whereas limited discrimination is generally observed with a methyl substituent, good selectivity should be expected for the addition of nucleophiles to 3-phenyl benzyne. Indeed in an early study of substituted arynes, Huisgen *et al.* obtained a ratio of 97 : 3 *meta* : *para* products for the high-yielding arylation of piperidine with 2-bromobiphenyl (Scheme 1.20, (a)).[64]



Scheme 1.20 *ortho*-Biphenyl aryne reactions: a) Huisgen,[64] b) Wickham and Scott.[65]

Despite this result, there have been relatively few additional examples where *ortho*-phenyl benzyne has been used in the synthesis of *meta*-functionalised biphenyls. 2-Biphenyl triflate was used by Wickham, Scott and co-workers for the preparation of diisopropyl amines with a similar regioselectivity (Scheme 1.20, (b)).[65]

ortho-Phenyl substituted 2-(trimethylsilyl)phenyl triflate, **44**, has been prepared and shown by Yoshida *et al.* to undergo σ-insertion with a cyclic urea and with (tributylstannyl)phenyl sulfide (Scheme 1.21, (a) and (b)).[49,66] Both reactions proceeded with excellent regioselectivity, the more nucleophilic substituent being placed *meta* to the phenyl group in each case. **44** has also been utilised in an aryne hydrostanylation by Kazmaier and co-workers, though with reduced selectivity.[67]



Scheme 1.21 Reactions with *ortho*-phenyl Kobayashi aryne precursor: a) and b) Yoshida,[49,66] c) Lakshmi.[67]

Steric arguments have been applied to 1,2-naphthalyne, where the approach of a nucleophile towards C1 is hindered by the *peri* hydrogen (Fig. 1.3, **C**). It seems likely, however, that electronic effects are also relevant for the often good selectivities observed with this aryne.

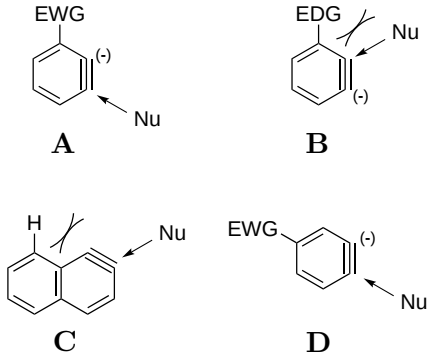


Fig. 1.3 Selectivity in nucleophilic addition to an aryne.

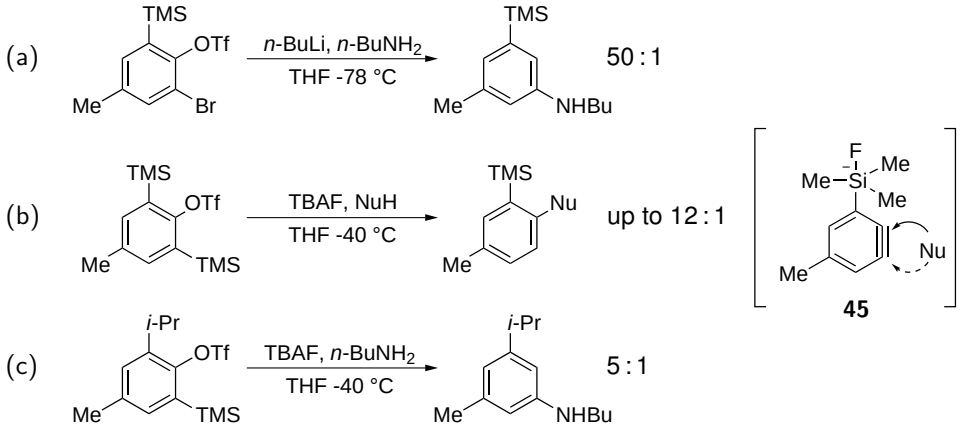
The inductive electronic nature of substituents is also important in determining the regioselective outcome of reactions with arynes. Since the triple bond, and hence any

build up of charge as a nucleophile approaches, is in an sp^2 orbital that is orthogonal to the π-system, mesomeric effects are less relevant.

In addition to any steric preference for *meta*-attack, an electron-withdrawing 3-substituent should best stabilise the transition state when a nucleophile attacks distally (Fig. 1.3, **A**), since the developing charge is placed adjacent to it. By the same argument, an inductively withdrawing 4-substituent will favour *para* attack (Fig. 1.3, **D**), although the remoteness of the stabilising group implies poorer stabilisation and hence poorer discrimination between sites. For example, 3-methoxy benzyne has been used extensively for arylations and often gives predominantly or exclusive *meta*-methoxy products, whereas 4-methoxybenzyne has only a slight preference for *para*-attack.[10]

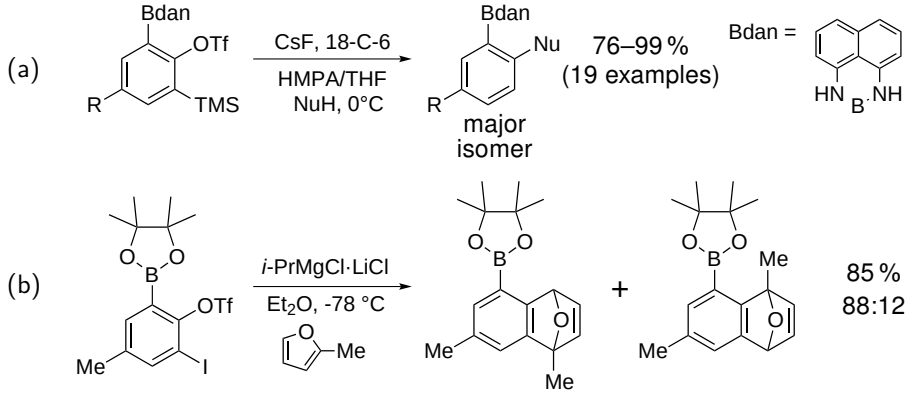
In the opposite sense, electron releasing groups located adjacent to the triple bond destabilise the transition state for *meta* approach of a nucleophile, acting in opposition to steric effects. Lower selectivities might therefore be expected in general (Fig. 1.3, **B**).

Recent studies concerning *ortho* regioselectivities have been conducted by Akai and co-workers, who showed that a trimethylsilyl group is *meta* directing when the aryne is generated by lithium-halogen exchange (Scheme 1.22, (a)),[68] in line with earlier findings.[69] However, when the same aryne was generated from a Kobayashi-type precursor by the addition of fluoride, *ortho* selectivity of up to 12 : 1 was obtained (Scheme 1.22, (b)). Under the fluoride-induced conditions with analogous 3-isopropyl aryne, *meta* selectivity was restored (Scheme 1.22, (c)). A silicate complex **45** was proposed to account for the discrepancy between (a) and (b), its full negative charge allowing sufficient perturbation of the aryne bond to overcome the unfavourable steric repulsion during *ortho* attack.



Scheme 1.22 Fluoride induced selectivity in *ortho*-(trimethylsilyl)arynes.[68]

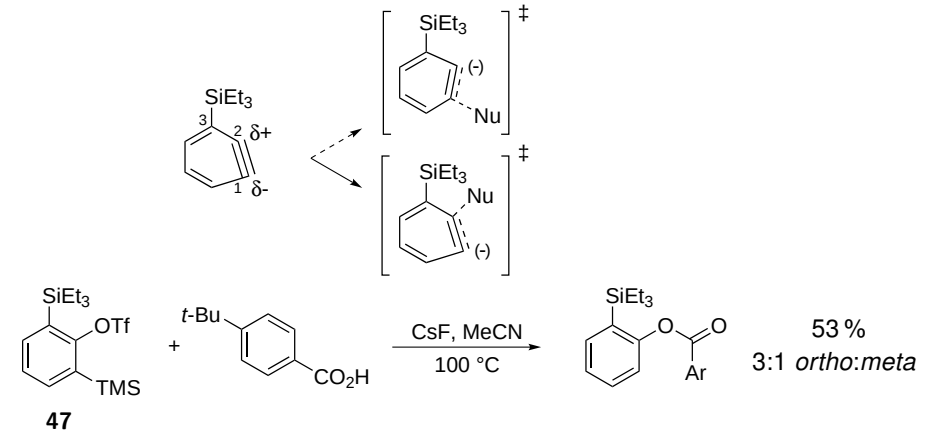
Interestingly, Akai has also achieved preferential *ortho* attack with 3-boryl benzynes by employing a boronamide substituent. Selectivities in excess of 20 : 1 *ortho* : *meta* could be achieved with some primary amine nucleophiles, although secondary amines and *t*-BuNH$_2$ gave lower ratios, and the effect was not thought to arise from a boronate complex. These additions contrast to earlier work in the same group where a boronic pinacol ester was used to exert regiocontrol in aryne cycloaddition reactions (for example, Scheme 1.23, (b)).[70]



Scheme 1.23 Boryl group controlled selectivity.[70,71]

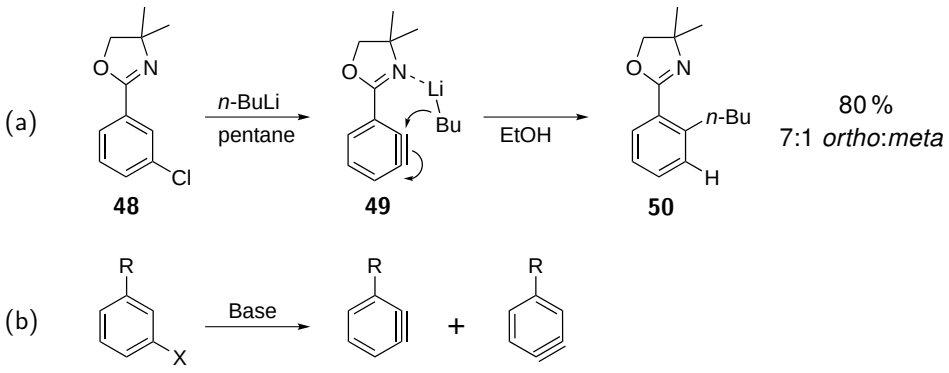
Garg, Houk and co-workers have used an aryne distortion model to explain regioselective outcomes of additions to indolynes and other functionalised arynes.[72] Since the transition state of an aryne is distorted to accommodate the developing negative charge (increasing s-character leads to decreased bond angle), attack is favoured at the site which minimises the change in distortion. The model has been applied to *ortho*-(triethylsilyl)benzyne, which has a greater internal bond angle at C2 and thus would be expected to react at this site.[73] In line with the findings of Akai, experimental *ortho* selectivity could be achieved in some cases when benzyne was generated from **47** and caesium fluoride, although larger nucleophiles gave the opposite isomer. Regioselectivities in cycloaddition reactions were also substrate dependent.

Aside from these steric and electronic effects on the aryne bond, examples in which a coordinating *ortho*-substituent directs nucleophilic attack are also known. Thus Meyers and co-workers reported that the 3-oxazoline benzyne **49** (Scheme 1.25, (a)) underwent preferential *ortho*-attack with organolithium reagents, although selectivity was reduced with more sterically demanding lithium nucleophiles.[74] Furthermore, arynes formed *via* proton abstraction from an asymmetrically substituted arene with two α-protons can give rise to both 3- and 4-substituted benzyne (Scheme 1.25, (b)). Product distributions



Scheme 1.24 *ortho*-Selective addition to (triethylsilyl)benzyne.[73]

will therefore reflect both the selectivity in attack and selectivity during formation of the benzyne; the latter may again result from steric, electronic or directing-group properties of the substituent.



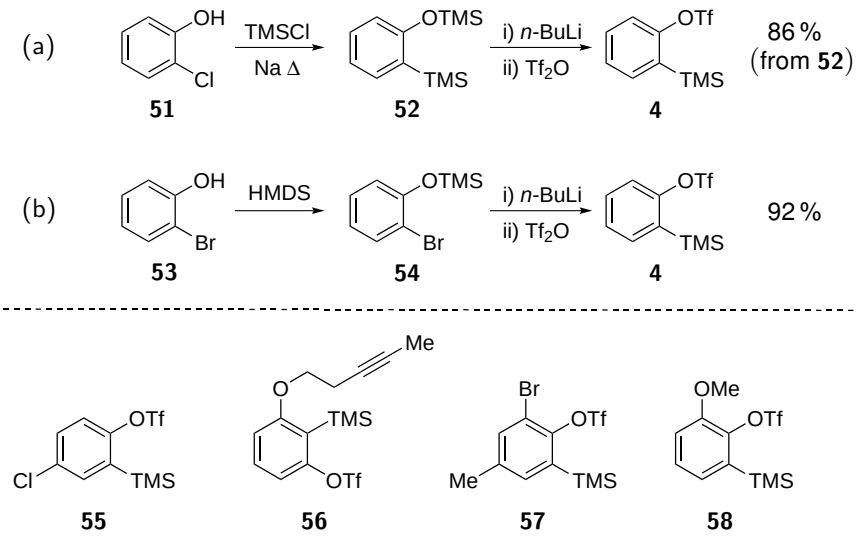
Scheme 1.25 Other effects that may influence regiomeric outcome of aryne reactions.[74]

1.4 (Trimethylsilyl)phenyl triflates and related aryne precursors

As with the majority of protocols for benzyne generation, Kobayashi's precursor requires an *ortho*-difunctionalised arene. These are most commonly derived from 2-halophenols, which may in turn be obtained *via* electrophilic partial halogenation or similar routes. The accessibility of suitable phenols, in addition to conditions subsequently employed to install the triflate and silyl groups, therefore limits the availability of functionalised arynes by this route. Nevertheless a range of Kobayashi-type precursors have been

prepared by several methods and those not discussed elsewhere are reviewed in this section.

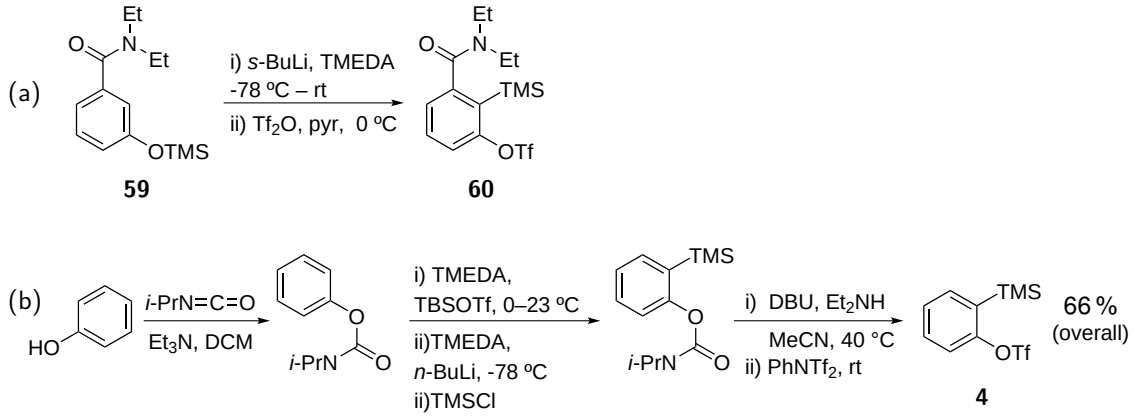
In the original synthesis, *ortho*-(trimethylsilyl)phenoxytrimethylsilane (**52**), obtained from 2-chlorophenol with (trimethylsilyl)chloride using molten sodium, was deprotected with *n*-BuLi and quenched with triflic anhydride to give 2-(trimethylsilyl)phenyl triflate (**4**, Scheme 1.26, (a)).[28] Later, Peña *et al.* used *ortho*-bromophenol in a more general preparation of aryne precursors. A milder *n*-BuLi-mediated retro-Brook reaction from phenoxysilane **54** installed the trimethylsilyl group on the ring, with the phenolate again being quenched *in situ* with triflic anhydride (Scheme 1.26, (b)).[75] The method was also applied to substituted *ortho*-bromophenols, yielding aryne precursors with alkyl, alkoxy and halogen functionality (for example **55**–**58**) and has been employed more widely by other researchers.



Scheme 1.26 (Trimethylsilyl)phenyl triflate synthesis from *ortho*-halophenols.[28,75]

1.4.1 *ortho*-Lithiation

Soon after Kobayashi's report on the synthesis of 2-(trimethylsilyl)phenyl triflate, Snieckus and Shankaran carried out an *ortho*-lithiation/retro-Brook rearrangement on *meta*-siloxy benzamide **60** (Scheme 1.27, (a)). Triflation furnished the *ortho*-benzamide aryne precursor **60**.[76] A range of nucleophilic addition and [4+2] reactions were performed, the former displaying *meta* regioselectivity in line with other electron-withdrawing-substituted 3-benzynes.



Scheme 1.27 Aryne precursors *via ortho*-lithiation.[76,77]

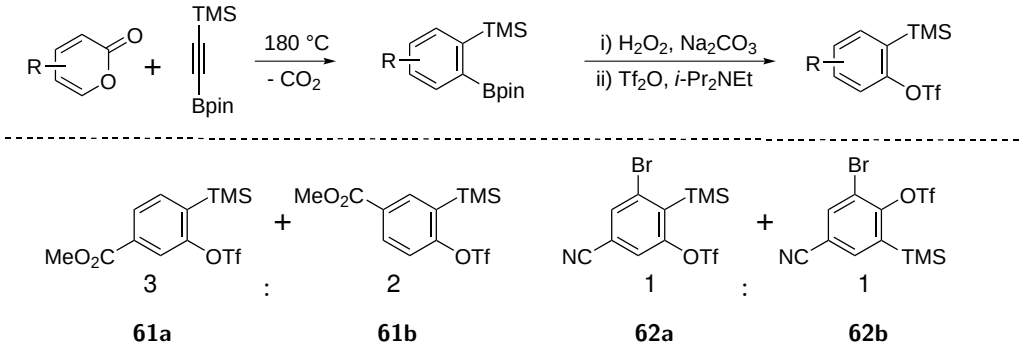
More recently, Bronner and Garg have used a removable directing group *ortho*-lithiation strategy that dispenses with the need for prior halogenation of the phenol (Scheme 1.27, (b)).[77] The carbamate group, introduced with an isocyanate, could be readily cleaved ahead of triflation with $PhNTf_2$ to give **4** and the methodology was also applied to the synthesis of the analogous 4,5-*N*-methylindolyne precursor in similar yield.

1.4.2 [4+2] Cycloaddition

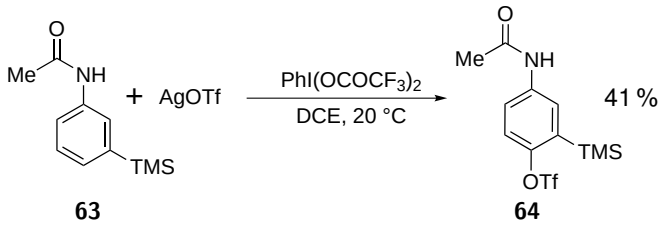
An interesting alternative approach, reported by Harrity and co-workers, completely avoids substituted phenols, instead establishing the required *ortho*-difunctionality by the [4+2] cycloaddition of a trimethylsilyl alkynylboronate with 2-pyrone derivatives (Scheme 1.28).[78] Decarboxylation, oxidation of the boronate and triflation gave the usual 2-(trimethylsilyl)phenyl triflate. Functionality could be introduced *via* the pyrone and although mixtures of regioisomers were obtained, both would result in the same aryne intermediates on treatment with fluoride, making their separation unnecessary. The methodology appears applicable to the synthesis of electron deficient aryne precursors and only halogen groups were installed adjacent to the triple bond.

1.4.3 Oxidative *para*-triflation of acetanilides

A recent report by Taillefer and co-workers described an iodine(III)-mediated *umpolung* reaction of acetanilides with nucleophilic triflate.[79] Although only a single example of triflation *ortho* to a TMS group was given (Scheme 1.29), the authors did note the potential application of **64** in aryne generation.



Scheme 1.28 Preparation on substituted aryne precursors by a [4+2] cycloaddition–decarboxylation approach.[78]



Scheme 1.29 Oxidative *para*-triflation of Acetanilides.[79]

1.4.4 Commercially available precursors

A number of *ortho*-(trimethylsilyl)phenyl triflates have been commercially available for several years including simple methyl- or methoxy-substituted derivatives, 1- and 2-naphthalyne precursors and polycyclic structures facilitating di- and triyne intermediates (Fig. 1.4).[80] Other substituted benzyne and indeed heterocyclic pyridyne and indolyne precursors may also be purchased but their cost is likely to be prohibitive for many purposes.

1.4.5 Precursors for the synthesis of polyaromatic structures

A range of more complex *ortho*-(trimethylsilyl)polyaromatic triflates have been prepared as aryne precursors. Typically, this is achieved by the functionalisation of the existing aromatic scaffold to afford an *ortho*-bromophenol motif – which often requires a multi-step synthesis – followed by silylation and triflation using the procedure of Peña *et al.*

The most common use of these substrates is in metal-catalysed [2+2+2] reactions for the synthesis of even larger polyaromatic materials, either by cyclotimerisation

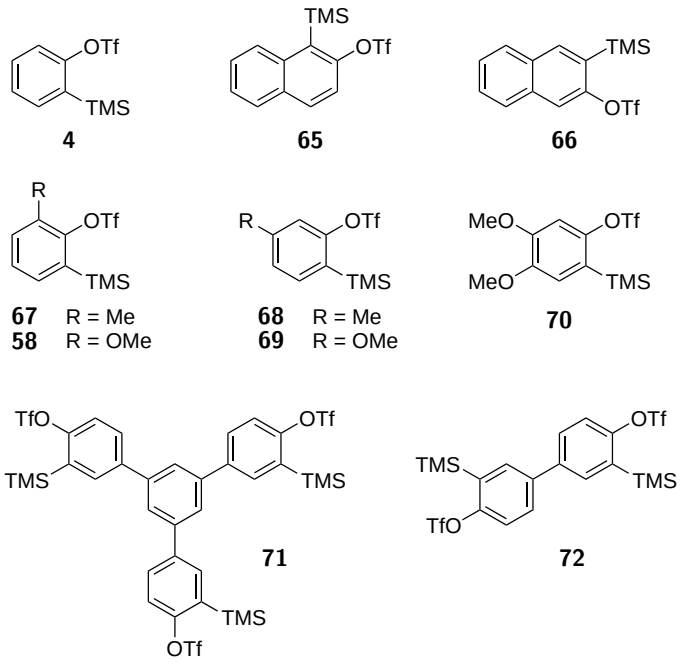


Fig. 1.4 Commercially availble *ortho*-(trimethylsilyl)aryl triflates

or co-cyclisation with one or two equivalents of another 2π-component such as DMAD. Much of this work has been carried out by Pérez, Guitián and co-workers, who first reported the synthesis of substituted triphenylenes from Kobayashi aryne precursors with catalytic palladium (see Section 1.2.3).[59]

They have since prepared anthracene-, biphenylene- and even triphenylene-based aryne precursors **73**, **78** and **74**, all of which have been successfully employed in the preparation of triphenylenes and other materials.[81–84] Notably, **78** was obtained from cobalt-catalysed cycloaddition of diyne **76** with bis(trimethylsilyl)acetylene to install the TMS group, rather than the *ortho*-halogenation routes used more generally (Scheme 1.30). Maly and Lynett have also prepared dialkoxynaphthalyne precursors **75** (Fig. 1.5) *via* the bromonaphthol, which was obtained in over 6 steps from 2,3-naphthalenediol, and used them in similar triphenylene syntheses.[85]

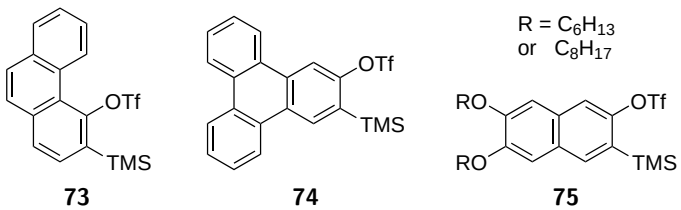
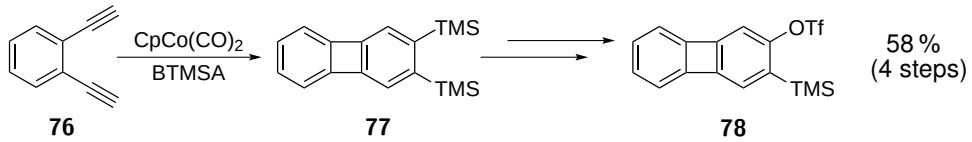
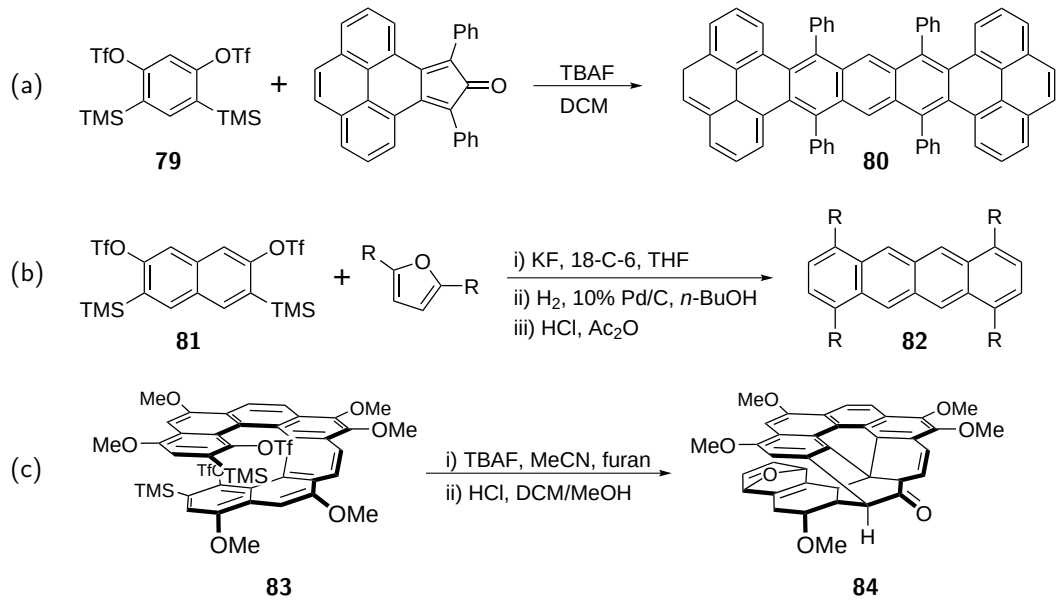


Fig. 1.5 Larger polycyclic *ortho*-(trimethylsilyl)aryl triflates.[81,83,85]



Scheme 1.30 Introduction of *ortho*-difunctionality *via* Cobalt-catalysed cycloaddition.[82]

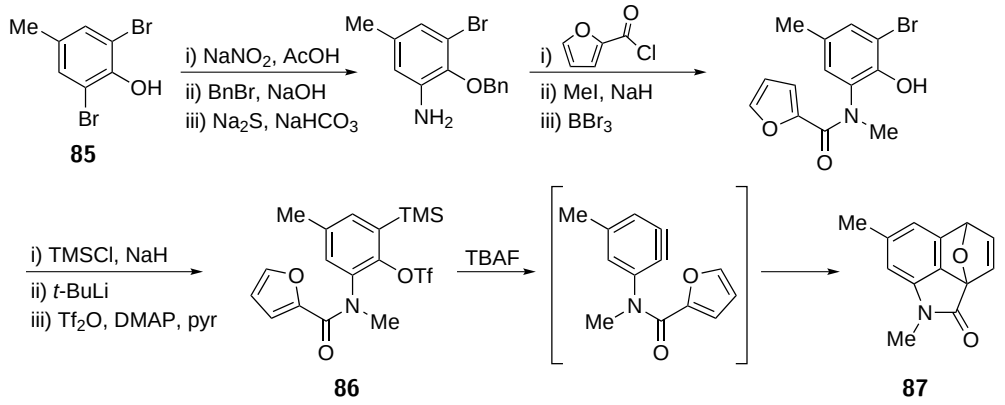
Dibenzyne and dinaphthalyne precursors **79** and **81** are also accessible and have both been employed in polyacene synthesis. Wudl and co-workers used a cyclopentadienone [4+2] addition/decarbonylation protocol (Scheme 1.31, (a)),[86] while Kitamura *et al.* have prepared a range of tetracenes *via* furan cycloaddition (Scheme 1.31, (b)).[87] A similar strategy was attempted by Katz and co-workers for the extension of an interesting [7]helicene based aryne precursor **83**.[88] However, the intermolecular reaction occurred at only one site, with an intramolecular [4+2] cyclisation being favoured at the second aryne bond, leading to the fused helical structure **84** (Scheme 1.31, (c)).



Scheme 1.31 Diaryne precursors for acene and helicene extension.[86–88]

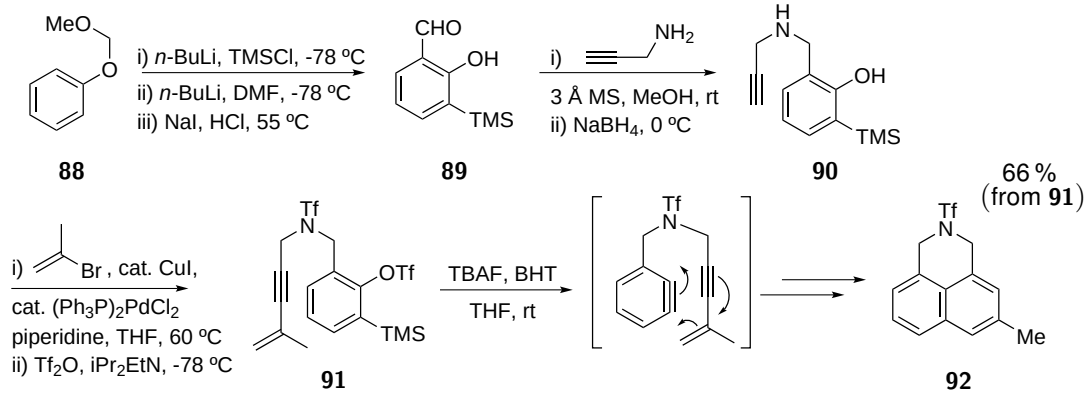
1.4.6 Other functionalised Kobayashi precursors

Aside from Snieckus's *ortho*-benzamide substrate, one of the earliest examples of a substituted 2-(trimethylsilyl)phenyl triflate was given by Quayle and co-workers (Scheme 1.32).[89] Their 9 step synthesis from the readily accessible dibromophenol **85** gave aryne precursor **86**, possessing a tethered furan group. The expected [4+2] intramolecular cycloaddition provided a route to the interesting epoxy-benzoindalone **87**.



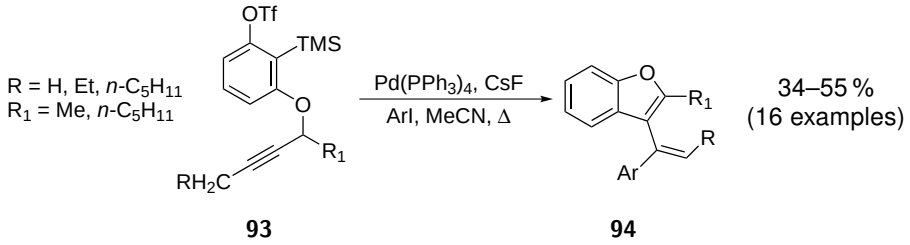
Scheme 1.32 Aryne precursor with pendant furan.[89]

Danheiser and co-workers have synthesised various *ortho*-substituted (trimethylsilyl)-phenyl triflates suitable for intramolecular cycloaddition. In their strategy, 2-hydroxy-3-(trimethylsilyl)benzaldehyde (**89**) was first prepared in three steps from a protected phenol and subsequent reductive amination with propargylamine led to their common intermediate **90**. This was diversified by Sonogashira coupling prior to triflation to give various areneyne- or eneyne-containing aryne precursors (Scheme 1.33). Dienes could also be introduced *via* cross-metathesis. Fluoride-induced aryne generation led to the desired [4+2] reaction and a range of dihydro-benzoisoquinoline-based structures of type **92** could be prepared in this way.



Scheme 1.33 Aryne precursors for intramolecular [4+2] reactions.[90]

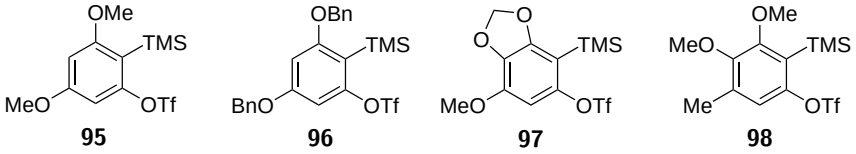
Several other aryne precursors bearing pendant acetylenes were also reported by Yuan and Ma.[91] These could undergo a palladium-catalysed ene-cyclisation-arylation cascade to afford a range of benzofurans (Scheme 1.34).



93 **94**

Scheme 1.34 Tethered acetylene precursors for benzofuran syntheses.[91]

Stoltz and co-workers have prepared a number of alkoxy-substituted precursors using a combination of phenol bromination/retro-Brook reactions and Garg's *ortho*-lithiation approach, including the first examples of trisubstituted 2-(trimethylsilyl)phenyl triflates.[92] The *meta*-directing influence of these substituents could be used in various aryne reactions, which proceeded in good regioselectivities, and these substrates have been exploited for the synthesis of several natural products (for example see Section 1.5). Silyl[73,93] and boryl[71] functionalised aryne precursors have also been prepared for the control and study of regioselectivity in aryne reactions, examples of which are given in Section 1.3.



95 **96** **97** **98**

Fig. 1.6 Alkoxy-substituted Kobayashi aryne precursors.[92]

1.4.7 Related aryne precursors

Although 2-(trimethylsilyl)phenyl triflate-based precursors are perhaps the most widely used reagents for aryne generation under mild conditions, a number of similar methods have also been reported. These tend to retain the fluoride-induced elimination of a silyl group from Kobayashi's method while altering the *ortho*-leaving group, although modifications to initial anion formation also exist.

Kitamura *et al.* dispensed with the triflate group in favour of the hypervalent iodine species **99** (Fig. 1.7), prepared from bis(trimethylsilyl)benzene and (diacetoxyiodo)-benzene with triflic acid. Their precursor is an easily handled crystalline solid and may confer improved yields and reduced reaction times compared to **4** in some cases.[94] More recently Novák and co-workers prepared a range of *ortho*-(trimethylsilyl)phenyl imidazolylsulfonates (**100**) from the respective phenols with sulfonyldiimidazole. These

demonstrated similar reactivity to the analogous triflates in fluoride-induced benzyne reactions.[95]

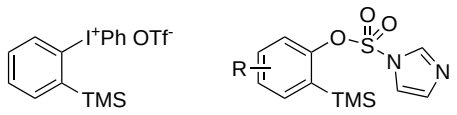
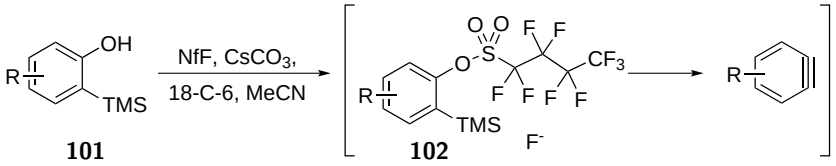


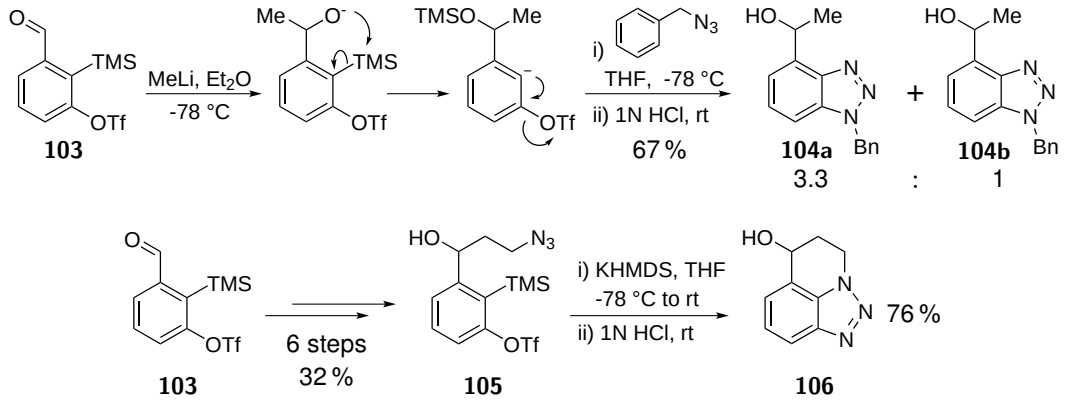
Fig. 1.7 Alternative fluoride activated aryne precursors.[94,95]

A related approach to aryne generation with a phenol-derived leaving group was introduced by Akai and co-workers (Scheme 1.35). They used nonafluorobutanesulfonyl fluoride (NfF) both to prepare the sulfonate group, *in situ* from an *ortho*-(trimethylsilyl)phenol, and as the source of fluoride. Thus 1,2-elimination from **102**, which is not isolated, forms the reactive intermediate in a domino process. Arynes generated in this way could undergo [4+2] or [3+2] cycloadditions, amination and a three-component coupling reaction.[96] *ortho*-(Trimethylsilyl)phenyl nonaflates may also be isolated prior to benzyne generation and Greaney and Michel have reported an efficient flow synthesis of such precursors. The more usual triflate-based substrates could be obtained in large scale in a similar way.[97]



Scheme 1.35 Nonafluorobutanesulfonyl fluoride-induced aryne formation.[96]

A less conventional anion relay mode of aryne generation from substituted 2-(trimethylsilyl)phenyl trilfate precursors has been used by Smith and Kim.[98] By locating an aldehyde or ketone adjacent to the TMS group and adding an anionic nucleophile, Brook rearrangement was induced (Scheme 1.36, top). After loss of the triflate group the resulting arynes could undergo various cycloaddition reactions. The *ortho*-formyl precursor **103**, which was prepared from 2-bromo-3-hydroxybenzaldehyde in three steps, could itself serve as a substrate for further elaboration. For example, a pendant azide group was incorporated into **105**, which underwent an intramolecular [3+2] reaction after deprotonation with KHMDS to form the tricyclic structure **106** (Scheme 1.36, bottom). Although these preparations are generally long and employ forcing conditions, they do afford various exotic aryne precursors.



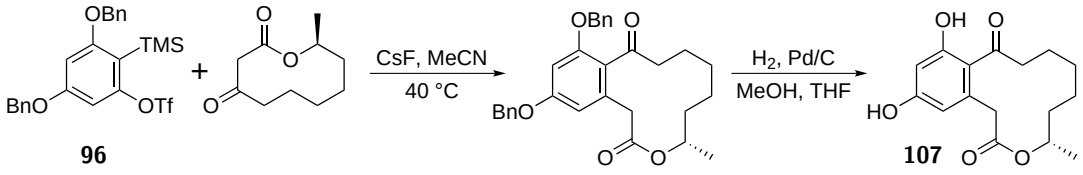
Scheme 1.36 Arynes by anion relay route.[98]

1.5 Arynes in synthesis

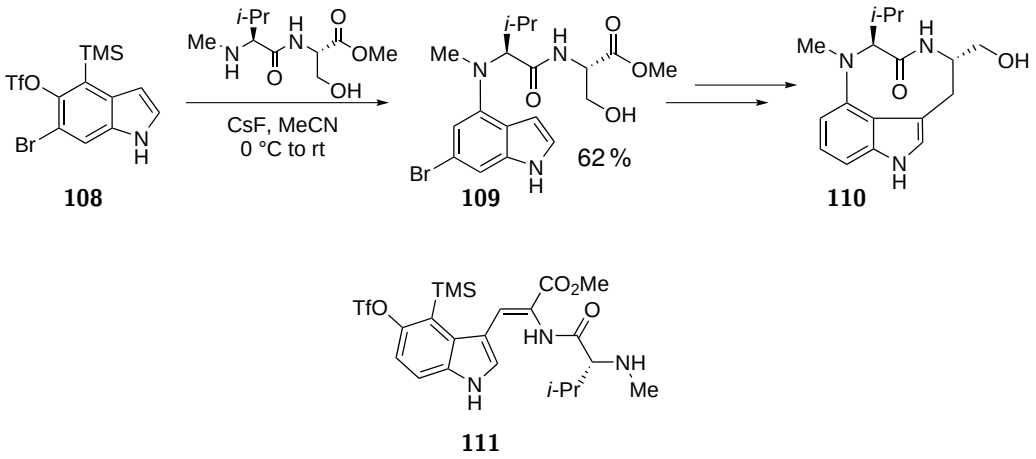
Benzyne methodology has been developed to target important heterocycle classes and reactions have emerged that make otherwise unusual or challenging motifs accessible. It has also found use in natural product syntheses,[22,23] though these steps are often restricted to intramolecular reactions with arylhalides, which require highly basic conditions.

Kobayashi aryne precursors have also been employed but the difficulties involved in synthesising large fragments of this type have limited their use. Stoltz and co-workers prepared a number of natural products *via* C–C σ-insertion reactions with appropriately functionalised alkoxy 2-(trimethylsilyl)phenyl triflates, including (-)-curvularin (**107**, Scheme 1.37).[99]

6-Bromo indolyne precursor **108** has been used by Garg and co-workers to obtain 4-substituted indoles, reversing the usual preference for C5 attack on indolyne. The technique could be applied to the total synthesis of indolactam V (**110**, Scheme 1.38). This proved more effective than intramolecular cyclisation, although indole **111**, which was prepared during the course of their investigations, is an interesting Kobayashi-type precursor.[100]



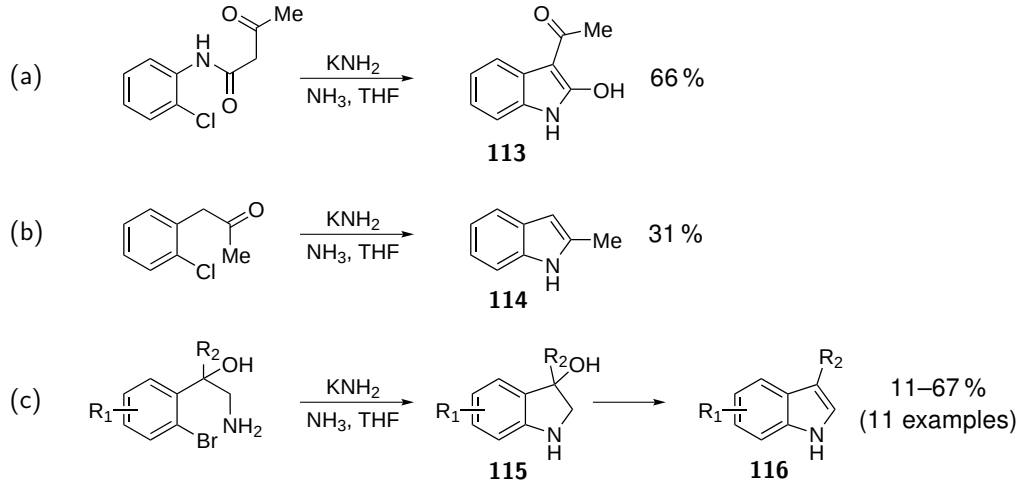
Scheme 1.37 (-)-Curvularin synthesis from polysubstituted benzyne.[99]



Scheme 1.38 Indolyne indolactam V synthesis.[100]

1.5.1 Indole syntheses

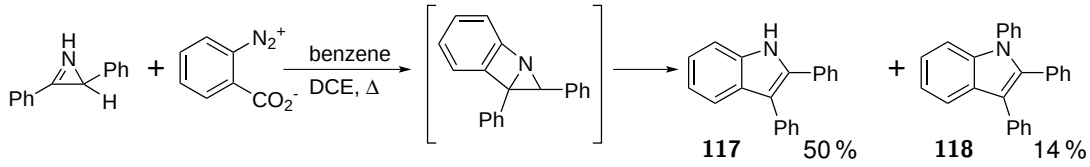
A number of intramolecular cyclisation routes to indoles have been known for some time. Bunnett and Hrutfiord reported several aryne-mediated heterocycle syntheses using potassium amide in liquid ammonia, including indoles **113** and **114**.[101] Fleming and Woolias also reported a direct route to indoles from tethered amino-alcohols (Scheme 1.39),[102] which avoided the separate oxidation step required when indolines were prepared from tethered amines in a similar way.



Scheme 1.39 Intramolecular cyclisation indole aryne syntheses.[101,102]

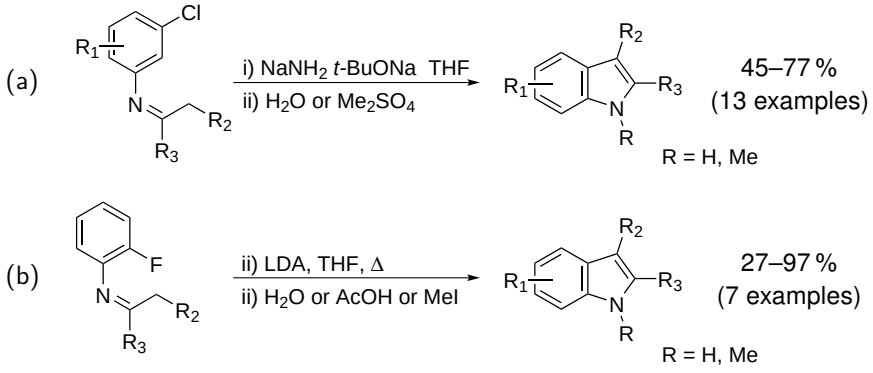
An early indole synthesis using intermolecular benzyne, generated from benzenediazonium-2-carboxylate, was reported by Nair and Kim.[103] The reaction with di-

phenylazirine was thought to proceed *via* a [2+2] intermediate and up to 50 % 2,3-diphenylindole (**117**) could be isolated from this reaction.



Scheme 1.40 Aziridine–aryne indole synthesis.[103]

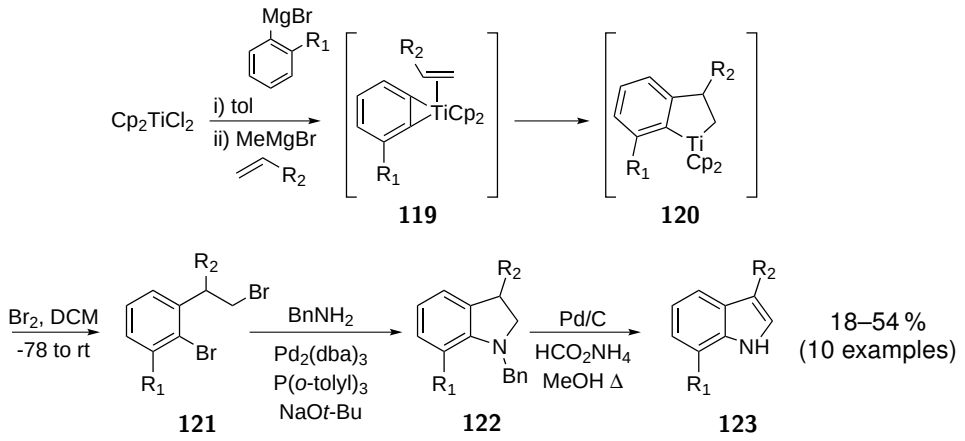
Jamart-Grégoire and co-workers synthesised indoles *via* imines (or enamines) formed from *meta*-chloroanilines and a suitable enolisable ketone (Scheme 1.41).[104] The strong base $NaNH_2 \cdot t$-BuONa was used to generate the aryne, which underwent intramolecular attack from the tethered nucleophile. Quenching with water or methylsulfate led to N–H or N–Me indoles. A similar route was employed by Kudzma using fluoroanilines and LDA and an aryne pathway confirmed by deuterium labelling studies.[105]



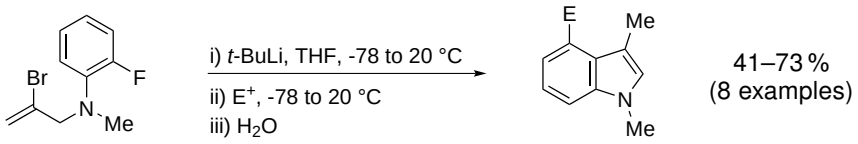
Scheme 1.41 Jamart-Grégoire[104] and Kudzma indole syntheses.[105]

Buchwald and co-workers reported benzyne–zirconocene and benzyne–titanocene indole syntheses.[106,107] After formation of the aryne–metal complex **119**, bromination of the resulting insertion product **120** led to the isolated intermediate **121**. This could undergo Buchwald–Hartwig coupling/cyclisation and finally oxidation to give the desired indoles.

Barluenga *et al.* also used an intramolecular carbon nucleophile to close the 5-membered ring during a 3-methylindole synthesis.[108] Aryne formation and lithium-halogen exchange were both accomplished with *t*-BuLi and the resulting indole anion could be quenched with a range of electrophiles (Scheme 1.43).

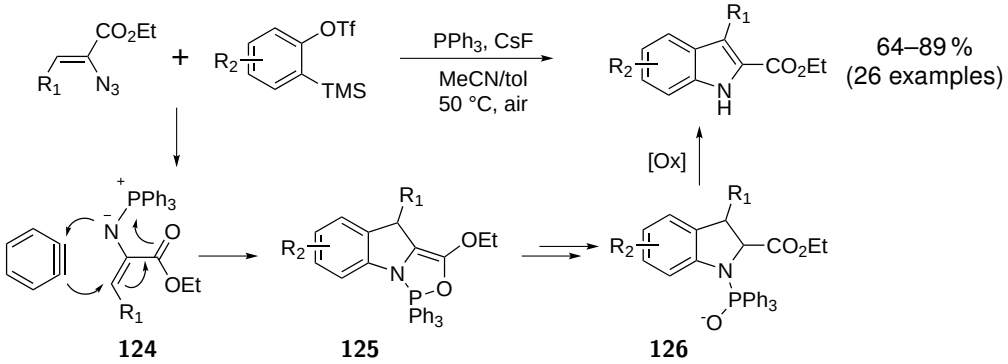


Scheme 1.42 Benzyne–titanocene indole synthesis.[107]

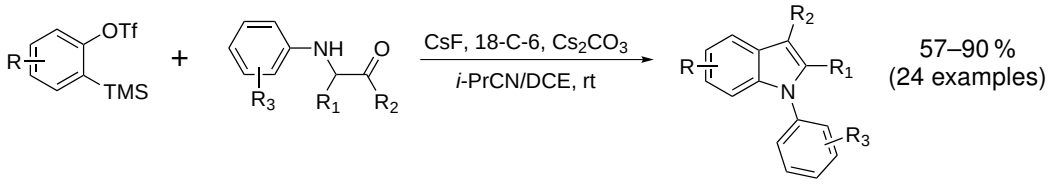


Scheme 1.43 Indoles by intramolecular cyclisation/trapping.[108]

More recently, indoles have been synthesised from arynes and vinyl iminophosphoranes **124**, which were formed *in situ* from 2-azidoacrylates with triphenylphosphine. The presumed cyclic intermediate **125** was then thought to proceed by hydrolysis and aerobic oxidation to the isolated products. However, the methodology is limited to 2-carboxyester indoles.[109] New aryne-mediated indole syntheses continue to be reported; Zhu and co-workers recently described a benzyne Bischler–Möhlau-like indole synthesis using *N*-aryl-α-aminoketones in place of α-bromo ketones (Scheme 1.45).[110]



Scheme 1.44 2-azidoacrylate benzyne indole synthesis..[109]

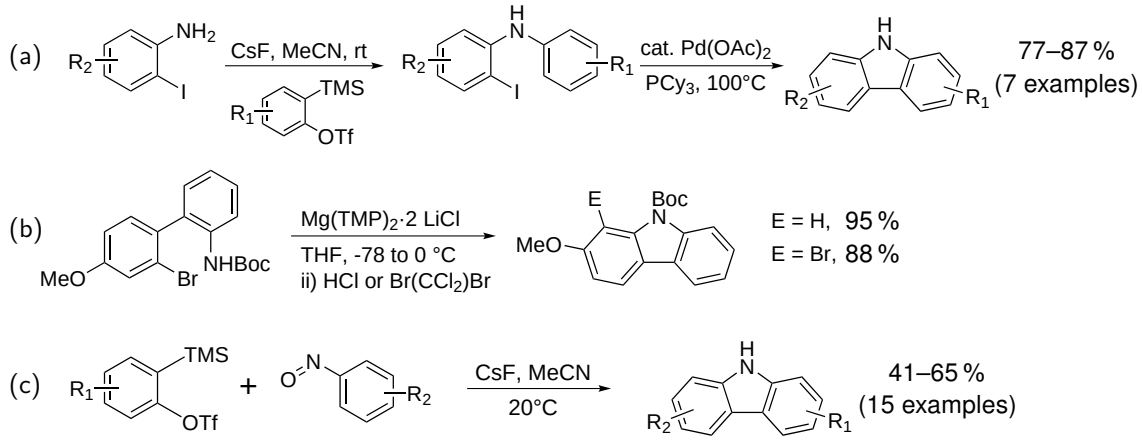


Scheme 1.45 Benzyne Bischler–Möhlau indole synthesis.[110]

Various related heterocyclic scaffolds have also been synthesised using aryne chemistry. In an extension to their aniline *N*-arylation methodology, Larock and co-workers used a palladium-catalysed intramolecular C–H activation to obtain carbazoles in a one-pot synthesis (Scheme 1.46, (a)).[111] Benzoxazoles and a dihydrophenanthridine could be prepared in the same way.

More recently, Tokuyama and co-workers prepared carbazoles using a biphenyl aryne generated from the arylbromide with $Mg(TMP)_2 \cdot 2\,LiCl$ (Scheme 1.46, (b)).[112] As well as quenching the intermediate aryl anion with a proton, a 7-bromo substituent could be incorporated. This technique could also be used to obtain indolines, which have previously been formed from tethered amines in a similar manner.[113]

Another recent carbazole synthesis was reported by Studer and co-workers, who used arynes to prepare the heterocycles directly from nitrosoarenes (Scheme 1.46, (c)).[114] The mechanism of nitrosoarene addition is thought to proceed *via* a [2+2]–ring-opening–ring-closing cascade to give (N–H) free products in moderate to good yields. *N*-Aryl carbazoles could be obtained under modified conditions if an excess of aryne were employed in a reaction similar to one reported earlier by Henry and Steinhof.[115]



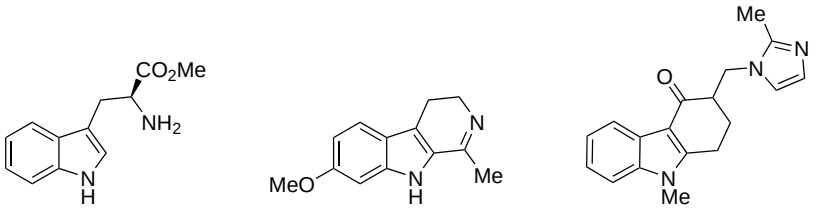
Scheme 1.46 Benzyne carbazole syntheses.[111,112,114]

Chapter 2

The Benzyne Fischer Indole Reaction

2.1 Introduction

The indole heterocycle is abundant in biology, occurs in many natural products[116] and is a frequently used scaffold in pharmaceutical research.[117] One of the oldest routes to functionalised indoles is the acid-catalysed cyclisation of an arylhydrazone, first performed by Fischer.[118] This method has undergone considerable study and has been employed extensively for the preparation of indoles and related products.[119–122]

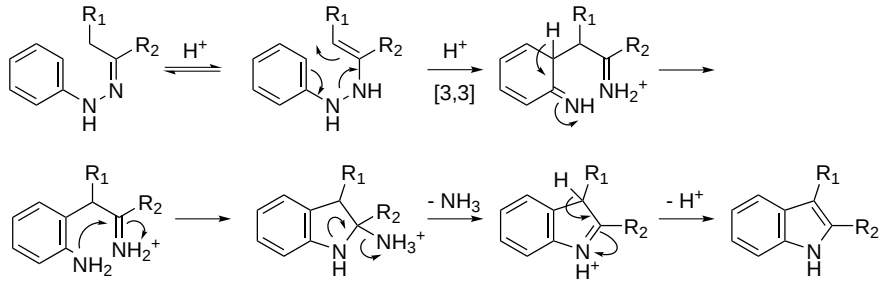


127 **128** **129**

Fig. 2.1 Indole-containing compounds: tryptophan (**127**) a proteinogenic amino acid, harmaline (**128**) a β-carboline alkaloid, ondansetron (**129**) an important antiemetic drug that may be prepared *via* Fischer indole synthesis.

Given the importance of the structure, many alternative indole syntheses have since emerged.[123] However, the Fischer indole reaction remains an important technique in heterocycle synthesis, allowing a simple metal-free preparation of indoles, particularly with 2- or 3-substituents, from accessible ketones or aldehydes and continues to be an active area of research.[124]

The mechanism of the Fischer indole reaction proceeds from an arylhydrazone which is in equilibrium with its ene-hydrazine form under acidic conditions. A [3,3] sigmatropic shift from this tautomer results in C–C bond formation, leading to the indole after rearomatisation and elimination of ammonia. The reaction as drawn in Scheme 2.1 may be conducted under Brønsted acid catalysis, although Lewis acids are also applicable and the role of the catalyst in the [3,3] rearrangement step may vary. In substrates with two distinct α-proton sites, selectivity during cyclisation is dictated by their relative tendency to tautomerise or by steric factors, depending on the particular system in hand.



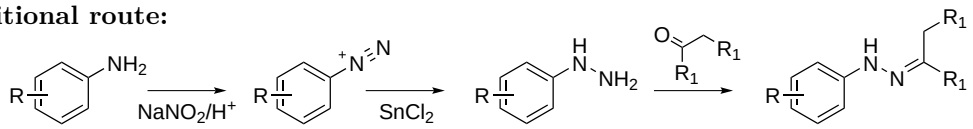
Scheme 2.1 The Fischer indole reaction from an *N*-phenylhydrazone.

2.1.1 Buchwald modification

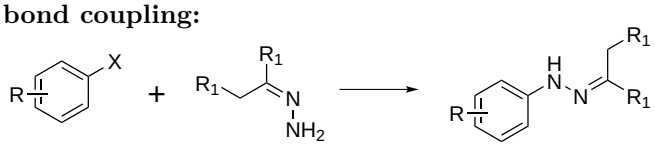
While the formation of arylhydrazones is readily achieved *in situ* from an aldehyde or ketone and an arylhydrazine, the requirement for the latter has been a key limitation of the Fischer indole reaction (Scheme 2.2, top). Hydrazines are generally unstable with respect to both oxidation and reduction, are toxic and their synthesis often hazardous, thus restricting their availability. This in turn limits the functionality that may be incorporated onto the indole scaffold. An alternative approach is to couple pre-existing hydrazones with functionalised arenes in a C–N bond forming step (Scheme 2.2, bottom).

The Buchwald–Hartwig coupling has become an important method to form C–heteroatom bonds and has been employed widely as an arylation process.[125,126] In line with other cross-coupling reactions it proceeds from the oxidative insertion of, most frequently, a Pd(0) species to an aryl halide. After association of a heterogroup to the metal centre and deprotonation, elimination of the coupled product may occur (Fig. 2.2). This C–N bond forming strategy was first developed as a preparation of *N*-arylhydrazones for indole synthesis by Buchwald and co-workers.[127]

Traditional route:



C–N bond coupling:



Scheme 2.2 Traditional and C–N routes to arylhydrazones.

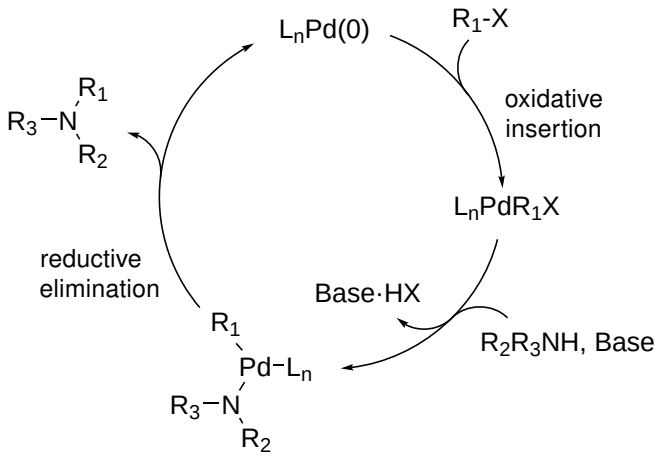
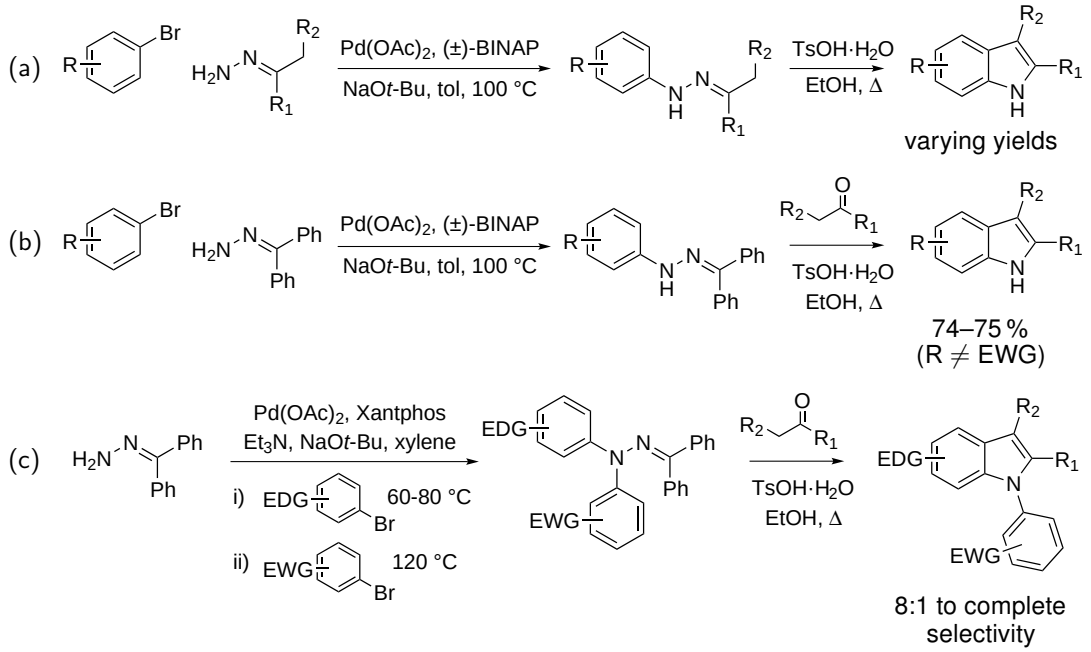


Fig. 2.2 Buchwald–Hartwig catalytic cycle for a 2° amine.

Initially cross-coupling was performed on hydrazones with an enolisable α-proton since the arylated products could directly undergo Fischer indole cyclisation (Scheme 2.3, (a)). However, both the starting materials and the resulting *N*-arylhydrazones were unstable and varying yields of indole were obtained in this way. Instead, benzophenone hydrazone was the preferred coupling reagent and subsequent ketone exchange *in situ* under acidic conditions allowed the Fischer indole reaction to proceed (Scheme 2.3, (b)). Refinement of the catalyst system gave enhanced yields at lower loadings and further developments included the twofold arylation of benzophenone hydrazone under slightly modified conditions.[128] These *N*,*N*-diarylhydrazones also underwent cyclisation, showing the usual selective incorporation of the more electron-rich arene into the indole core (Scheme 2.3, (c)).[129]

Since this work, a number of other techniques have been developed that utilise an *N*-arylation strategy to obtain precursors for the Fischer indole reaction. Palladium[130] or copper[131,132] mediated arylations of Boc-hydrazine or other hydrazides have



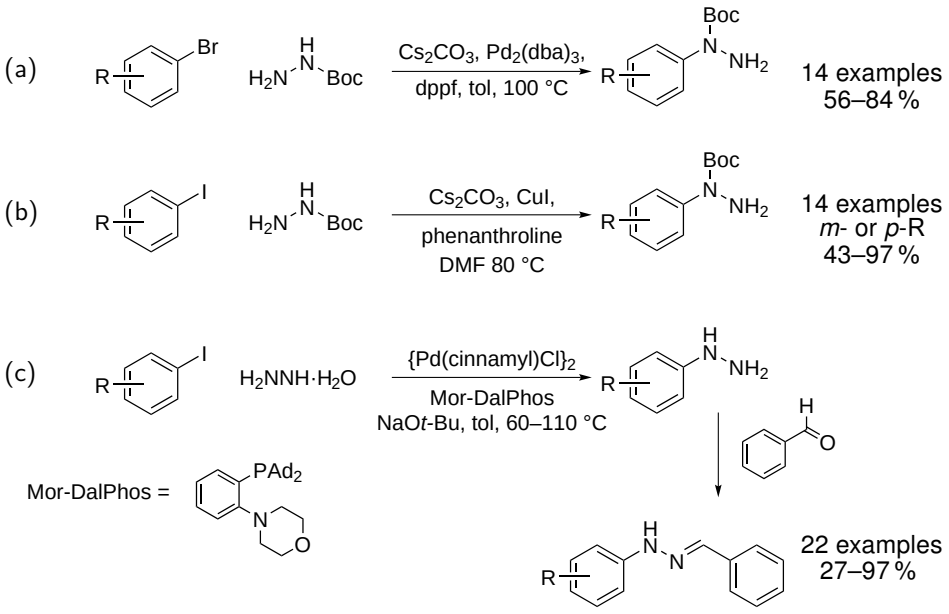
Scheme 2.3 Buchwald's palladium catalysed synthesis of arylhydrazones and subsequent transformation into indoles.[127,128]

been reported, giving substrate dependent regioselectivity (Scheme 2.4). The copper-based methodology has subsequently been employed by Cheon-Gyu Cho and co-workers for the synthesis of indoles (Scheme 2.5).[133,134] Cbz protection of the aryl substituted nitrogen could survive the acidic cyclisation conditions whereas Boc-protected hydrazines gave free (N–H) products.

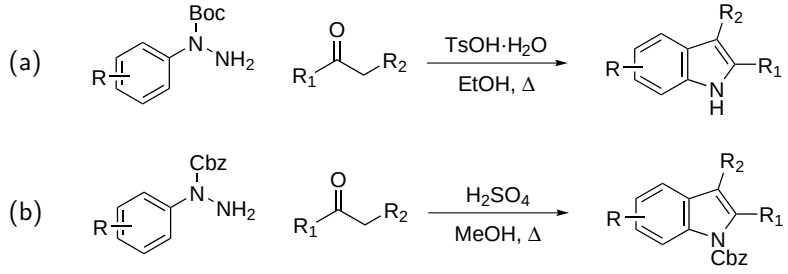
Later, Lundgren and Stradiotto devised a method to couple unprotected hydrazine hydrate directly (Scheme 2.4, (c)).[135] The products were trapped as benzaldehyde hydrazones and 1-*H*-indazoles could be obtained with an *ortho*-aldehyde in this way. Trapping with an enolisable ketone or aldehyde was not reported by this group.

Copper catalysed arylation of protected hydrazines with triarylbismuthanes has been reported[136] and was later extended to hydrazones.[137] Although the authors noted the relevance of these substrates to indole and other heterocycle preparations, no attempt at a Fischer synthesis was made.

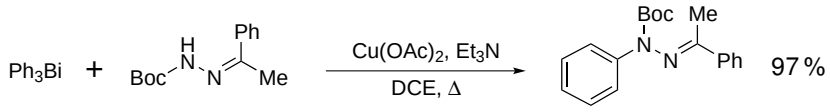
Buchwald has utilised palladium cross-coupling to arylate ethyl *N*-hydroxyacetimidate (**130**). Exchange with an enolisable ketone allowed benzofurans to be prepared in an analogous manner to his original Fischer indole methodology (Scheme 2.7).[138] Deprotection in the absence of a ketone allowed *O*-arylhydroxylamines to be isolated.



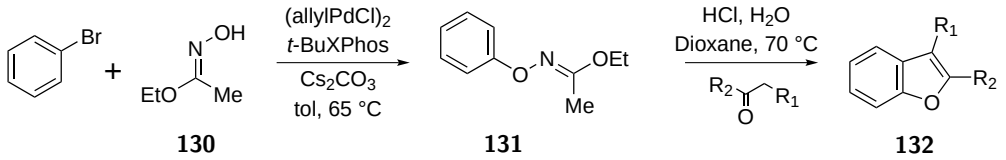
Scheme 2.4 C–N bond forming cross-couplings with hydrazines: (a) Skerlj,[130] (b) Buchwald,[132] (c) Stradiotto.[135]



Scheme 2.5 Fischer indole syntheses with cross-coupling derived hydrazines.[133,134]



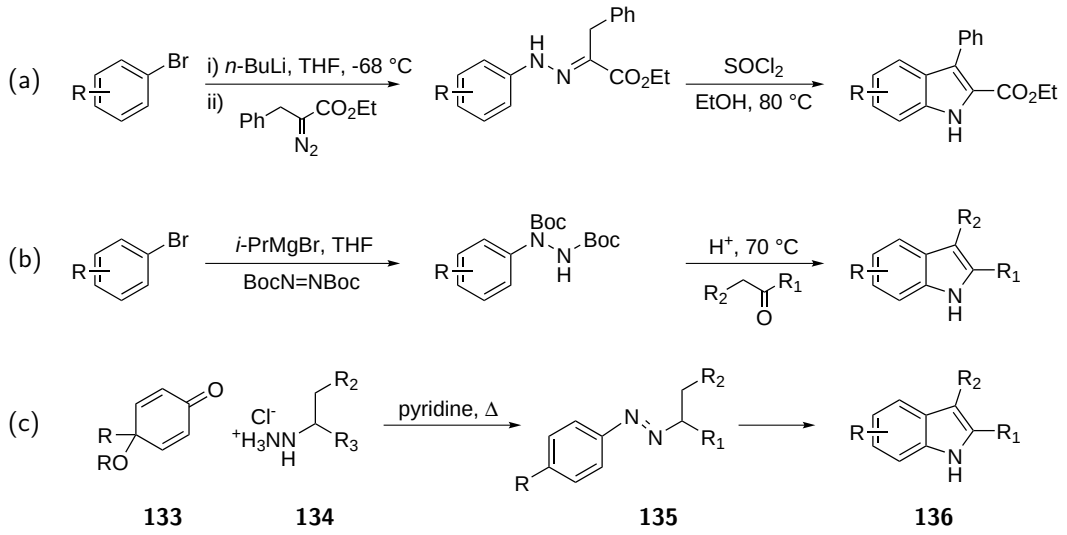
Scheme 2.6 Triarylbismuthane synthesis of *N*-aryl hydrazones.[137]



Scheme 2.7 Analogous C–O bond approach to benzofurans.[138]

The same C–N disconnection may be achieved in the absence of a transition metal if electrophilic nitrogen sources are used. The addition of aryllithium or Grignard reagents to diazo esters and subsequent Fischer cyclisation with thionyl chloride was reported by Takamura and co-wokers (Scheme 2.8, (a)).[139] This method compares to the Japp–Klingemann Fischer indole synthesis, which uses aryldiazonium salts and a β-ketoester to prepare the arylhydrazone. In Takamura's protocol the site of nucleophilic carbon and electrophilic nitrogen species are reversed, but it shares with the Japp–Klingemann reaction complications of handling diazo compounds and has limited scope.

Recently, di-*tert*-butyl azodicarboxylate has been used with aryl Grignard reagents by Moody and co-workers as an alternative electrophilic species. The resulting hydrazines undergo acid catalysed deprotection in the presence of a ketone, leading to *in situ* hydrazone formation and Fischer indole reaction (Scheme 2.8, (b)).[140] The Grignard nucleophile may be replaced with an *ortho*-lithiated species, if a suitable directing group is present.[141]



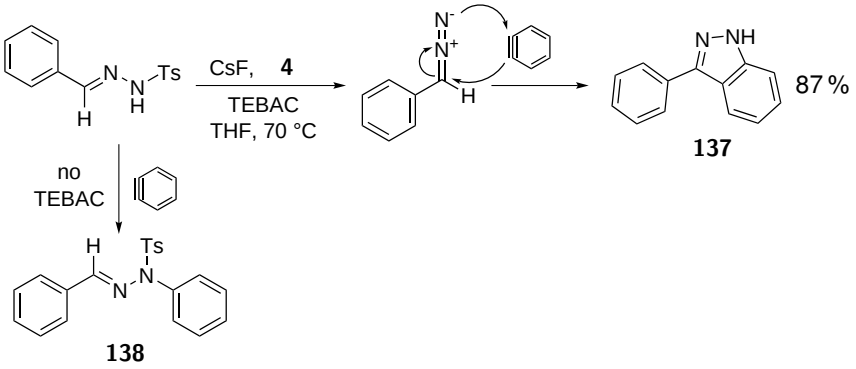
Scheme 2.8 Transition-metal-free C–N hydrazone syntheses: (a) Takamura,[139] (b) Moody,[140] (c) Zheng.[142]

Aryl halides were dispensed with altogether in a procedure reported by Zheng and co-workers.[142] Here aliphatic hydrazines give 1,2-addition products with quinone monoketals (**133**) in the C–N bond-forming step. Rearomatisation and isomerisation led to *N*-aryl hydrazones, which could undergo Fischer indole cyclisation in one pot if the hydrochloride salt (**134**) was used initially (Scheme 2.8, (c)).

Whilst transition-metal-catalysed C–N bond formation is an elegant route to *N*-arylhydrazones, it relies on relatively basic conditions, often expensive catalyst systems that may themselves confer functional group limitations, and the benzophenone protection of hydrazine reduces the atom efficiency of the process. Other arylhydrazone preparations employ harsh conditions or have limited scope. An alternative method for heteroatom arylation is the treatment of a suitable nucleophile with an aryne reactive intermediate. Using modern techniques for aryne generation such species could provide a mild, transition-metal-free route to the intermediate *N*-arylhydrazones. This project aimed to develop such a methodology and apply it to the synthesis of indoles.

2.1.2 The arylation of hydrazones with benzyne

Prior to the investigations in this chapter and the studies in our group that initiated them, no examples of aryne-mediated arylation of a hydrazone were known. At the same time as this research, Shi was also working with aldehyde-derived tosylhydrazones for use with arynes in the synthesis of 1*H*-indazoles such as **137** (Scheme 2.9).[143] Although this reaction was thought to proceed primarily by the [3+2] cycloaddition of an *in situ* generated diazo compound rather than nucleophilic addition of the hydrazone itself, arylation of the tosylhydrazone was observed as a side product.

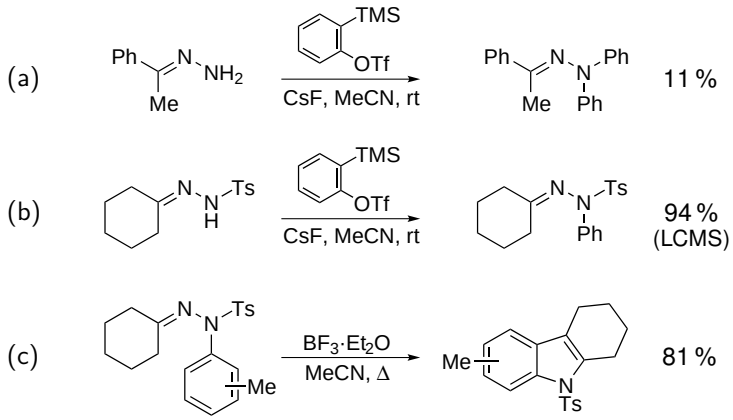


Scheme 2.9 Arylation of aldehyde tosylhydrazone also observed by Shi.[143]

2.2 Application of aryne electrophiles to the Fischer indole synthesis

Initial work in our laboratory by Sangwon Seo and Didier Pintori demonstrated the feasibility of hydrazone arylation with benzyne generated from 2-(trimethylsilyl)phenyl triflate (**4**) and various fluoride sources (Scheme 2.10, (a)). However, the reaction was

not general, required several equivalents of benzyne and was prone to side-reactions and hydrolysis.

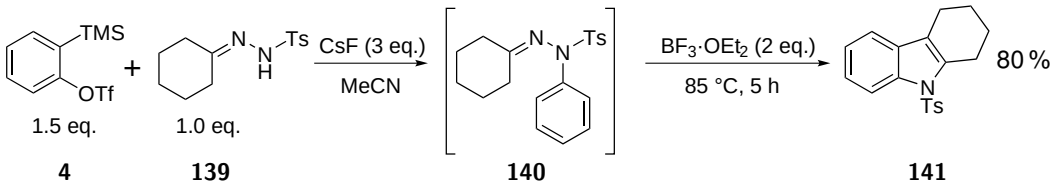


Scheme 2.10 Initial results within our laboratory.[144]

The protection of hydrazones as their *para*-tolyl sulfonamides was discovered by Seo to facilitate more effective arylation and it was further shown that such an *N*-phenyl-*N*-tosylhydrazone could, upon treatment with *para*-toluene sulfonic acid, undergo Fischer cyclisation to give an *N*-tosyl indole.[144] Pintori demonstrated that the cyclisation of *N*-aryl-*N*-tosylhydrazones was possible with substituted aryl groups using boron trifluoride diethyl etherate in acetonitrile (Scheme 2.10, (c)) and Seo found that the addition of either acid to the crude arylation product in one pot could effect the Fischer indole reaction, although in varying yields and purities.

My contributions to this project include refinement of the conditions required to synthesise indoles from *N*-tosylhydrazones, examination of the reactions of *N*-functionalised hydrazones with benzyne more generally, and a full exploration of the substrate scope. The work described in the rest of this chapter is my own.

Work began with the *N*-tosyl cyclohexanone hydrazone (**139**), which was known to be a competent nucleophile. Reliable arylation could be achieved with 1.5 eq. of **4** and 3 eq. of caesium fluoride in acetonitrile after 12 h (Scheme 2.11). These conditions gave **140** in high purity by LCMS (see Fig. 2.3, (c)) and lower loadings of the aryne precursor led to inconsistent results, with a small proportion of the hydrazone remaining unreacted in some cases. After evaporation of the solvent, **140** could be isolated in 61 % yield by recrystallisation from hot methanol. LCMS analysis confirmed the stability of this substrate to the elution conditions and matched the retention time and mass observed in the crude reaction mixture.



Scheme 2.11 Optimised conditions for the one-pot benzyne Fischer indole reaction.

Initial studies typically used a slight excess of acid to enact Fischer indole cyclisation, but questions remained over the stoichiometry required when the reaction was conducted in one pot from the *N*-tosylhydrazone. Since both the arylation and cyclisation steps were viable in the same solvent and since isolation of the aryl hydrazones intermediates was neither required nor beneficial in light of their potential instability, this method was considered particularly desirable.

In the optimised arylation reaction 1.5 eq. excess of caesium fluoride should remain. If this is not sequestered in some other process ahead of the second step, then it will compete as a Lewis base for BF_3. Assuming $CsBF_4$ formation is fast then the Fischer indole reaction, for which acidic conditions are required, will not proceed unless the stoichiometry of acid exceeds that of the residual fluoride. Indeed, on addition of only 1.5 eq. of acid with respect to hydrazone, incomplete cyclisation was observed.

Control reactions showed that the cyclisation could occur with a substoichiometric quantity (0.5 eq. as a stock solution) of $BF_3{\cdot}Et_2O$ if removal of CsF by aqueous workup was first performed. Further studies found that 2 eq. of $BF_3{\cdot}Et_2O$ was in general sufficient to bring about complete reaction after 5 h of heating when added to the crude arylation product in one pot.

Monitoring of the reaction by LCMS indicated that cyclisation was essentially complete within 20 min at 85 °C with arylated cyclohexanone *N*-tosylhydrazone (*N*-phenyl-**139**), but further heating was not detrimental to the product and 5 h was retained for the general protocol. The small excess of aryne was responsible for a detectable level of by-product formation but this did not consume the limiting reagent and could be removed during purification by column chromatography, which is required in any case after the Fischer indole step.

It is worth commenting that the accurate measurement of hygroscopic caesium fluoride, although possible with care, is typically unnecessary when used with **4**, due to its limited solubility in acetonitrile, straightforward removal on workup and since it is employed as an excess. In this case, however, accurate control of fluoride stoichiometry is necessary.

Alternatively, increasing the stoichiometry of $BF_3{\cdot}Et_2O$ to 3 eq. does not appear to be detrimental to yields and ensures acidic conditions are achieved. In general, however, the optimised conditions of 1.5 eq. aryne precursor with 3 eq. of caesium fluoride followed by 2 eq. of boron trifluoride diethyl etherate were preferred.

2.2.1 Aryne reactions of other hydrazones

The role of the protecting group was also investigated. The *N*-carboxybenzoyl- and *N*-*tert*-butoxycarbonyl-protected cyclohexanone hydrazones, **142** and **143**, could be synthesised in an analogous manner to the tosyl-protected substrate and gave surprising results.

The reaction of Cbz-hydrazone **142** (Fig. 2.3 (a)) gave a number of products visible in the HPLC trace including the expected monoarylation as a minor component ($m/z = 323.2$). The most prominent peak however ($m/z = 399.3$) showed a mass corresponding to a two-fold arylation of the starting material. A similar, though cleaner, result was obtained when using the Boc-hydrazone **143** (Fig. 2.3 (b), $m/z = 365.3$) to give the apparent double arylation product, **144**.

Initially these results were attributed to a benzyne insertion at the carbonyl protecting groups. Such reactions are well known for amides[145,146] and other groups, though have not been previously reported with carbamates.* An *N*-arylation with a second equivalent of benzyne would lead to products of the observed molecular weights (Scheme 2.12, (a)). The anionic Fries-type rearrangement depicted in the first step is known to occur with Boc-protected anilines.[147]

Such an *N*,*N*-diaryl substrate might be of synthetic use, particularly given its straightforward preparation from the hydrazone and if the Fischer reaction could still occur. Since this is disfavoured on electron-poor arenes, selective cyclisation onto the less hindered ring might be envisaged. Attempts to enact cyclisation of the postulated crude **144′** with $BF_3{\cdot}Et_2O$ were, however, unsuccessful with no indolic products being detected.

Isolation of **144** permitted full characterisation of the double arylation product. Notably, a strong IR absorption at 1698 cm^{-1} was observed and this is not consistent with the presumed ester of **144′**. Furthermore a ^{13}C NMR peak at 70.0 ppm, which also gave an HMBC correlation to the aromatic region, suggests the hydrazone group has been transformed to leave a C–N single bond during benzyne-mediated attack.

* A few examples of arylation of *N*-aryl carbamates without further rearrangement were known.[43] Insertion of arynes into *N*-methyl-2-oxazolidinone has been reported more recently[148,149]

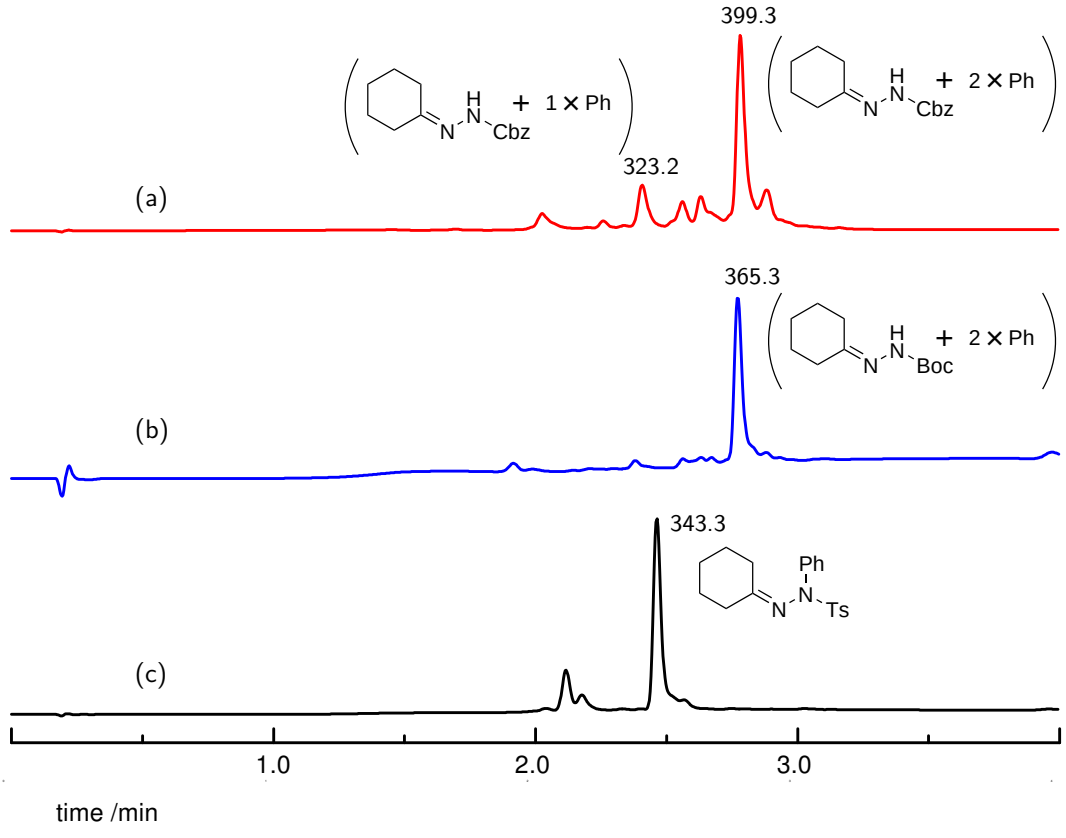
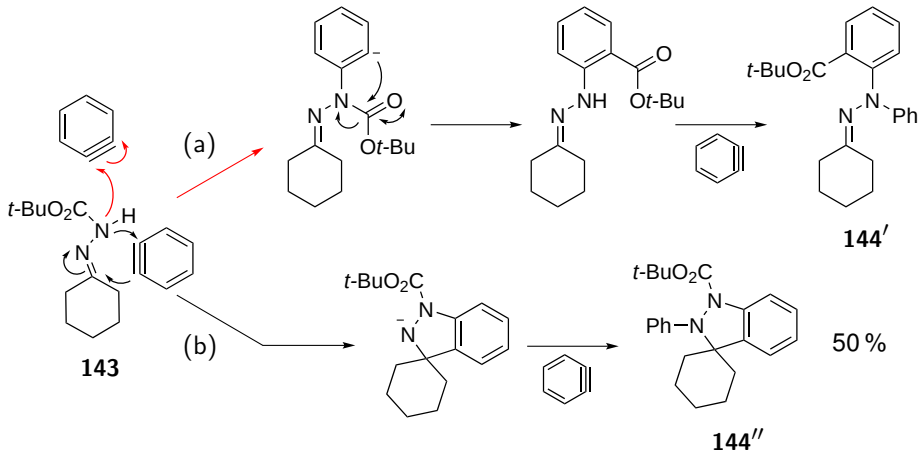


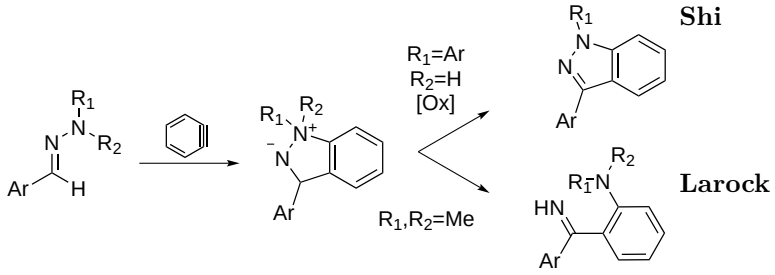
Fig. 2.3 LCMS traces from the arylation of *N*-protected cyclohexanone hydrazones. a) Cbz-hydrazone, b) Boc-hydrazone, c) Ts-hydrazone. Reaction conditions: protected hydrazone (1 eq.), **4** (1.5 eq.), CsF (3 eq.), 0.1 M in MeCN, rt 16 h. Separation was performed on a C-18 reverse phase column 20×3.0 mm, particle size 3 µm. Eluents were water containing 0.2 % formic acid (A), and methanol : IPA 9 : 1 containing 0.2 % formic acid (B). The flow rate was set to 0.9 ml min^{-1}. The gradient was increased linearly from 98 : 2 A : B to 2 : 98 A : B over 0–3.5 min and then held at the final ratio for the remainder of the run. Detection by UV was performed at 254 nm.



Scheme 2.12 Double arylation of Boc-protected cyclohexanone hydrazone; a) by aryne insertion and b) by [3+2] cycloaddition.

Whilst the identity of **144** could not be unambiguously determined, the alternative spirocyclic isomer **144″** seems more likely. A plausible mechanism would proceed through a [3+2] cycloaddition shown in Scheme 2.12, (b), with arylation by a second equivalent of benzyne then forming the observed product.[150]

A similar reaction, occurring *via* nucleophilic attack of a tertiary hydrazone nitrogen and subsequent cyclisation (Scheme 2.13 bottom), has given Larock and Dubrovskiy, after rearrangement, *ortho*-(dimethylamino)phenyl imines.[151] Shi and co-workers also considered the zwitterionic 1*H*-indazole species as a potential intermediate in their *N*-substituted pyrazole synthesis (Scheme 2.13 top).[152] By contrast, oxidation or rearrangement (as in Scheme 2.13) would be inhibited by the additional substituent of a ketone derived hydrazone such as **143**, allowing isolation of the stable dihydro-1*H*-indazole structure (**144″**).†

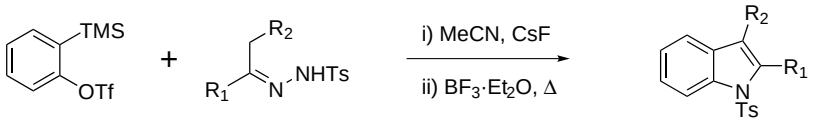


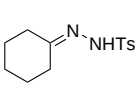
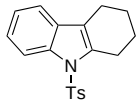
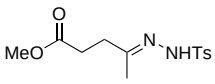
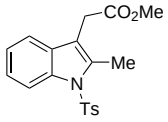
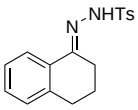
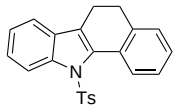
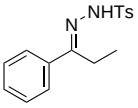
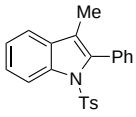
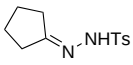
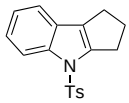
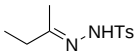
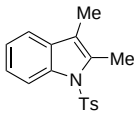
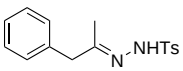
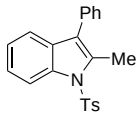
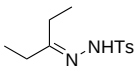
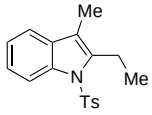
Scheme 2.13 Formal [3+2] reactions of hydrazones and arynes.[151,152]

† Shi was unable to trap the proposed intermediate with an external electrophile, even when ketone-derived hydrazones were used. Trapping with benzyne appears favourable with ketone hydrazones under our conditions.

2.2.2 Scope of the benzyne Fischer indole reaction

Table 2.1 Benzyne-mediated *N*-arylation and Fischer cyclisation of *N*-tosylhydrazones.[a]



entry	hydrazone	product	yield(%)
1	**139** 	**141** 	80
2	**145** 	**146** 	66
3	**147** 	**148** 	76
4	**149** 	**150** 	67
5	**151** 	**152** 	54
6	**153** 	**154** 	69
7	**155** 	**156** 	63
8	**157** 	**158** 	68

[a] Conditions: hydrazone (1 eq.), aryne precursor (1.5 eq.), CsF (3 eq.), MeCN (0.1 M), rt, 12 h; then $BF_3{\cdot}Et_2O$ (2 eq.), 80 °C, 5 h.

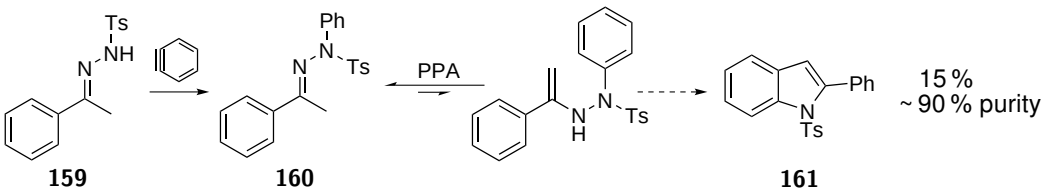
Having ascertained that carbonyl protecting groups led to double arylation products, our attention could be returned to the use of *N*-tosylhydrazones. As the initial tetrahydrocarbazole **141** could be obtained *via* a one-pot benzyne Fischer indole reaction in good 80 % yield, the scope of this methodology with respect to the hydrazone was next investigated (Table 2.1).

Additional aromatic groups could be introduced to the hydrazone such as the α-tetralone based substrate **147**, which furnished the dihdrobenzocarbazole **148** in comparable yield. Ester functionality was well tolerated, allowing the preparation of 1,2-unsymmetrically functionalised indole **146**. Synthesis of the 5-membered fused cycle **152** proceeded from **151** as for other examples, although in lower yield than the less strained or open-chain substrates.

Where a choice of two sites for enamine formation was present, as with tosylhydrazones **145**, **149**, **153** and **155**, cyclisation occurred at the most substituted position. Indeed the Fischer indole reaction became problematic when attempted with the acetophenone derived substrate **159** (Scheme 2.14), for which enolisation at an unsubstituted methyl group was required. Arylation with benzyne proceeded normally to give **160** but on introduction of the Lewis acid and heating, the expected product could not be detected.

Employing instead a large excess of polyphosphoric acid or increasing the stoichiometry of $BF_3{\cdot}Et_2O$ to 30 eq. did permit formation of the desired *N*-tosyl indole **161**, although this was only obtained in poor yield with an inseparable minor impurity. Cyclisation at the most substituted position *via* the more stabilised ene-hydazine is consistent with fast, reversible enamine formation with a later step being rate-determining, and is commonly observed in the Fischer indole reaction.

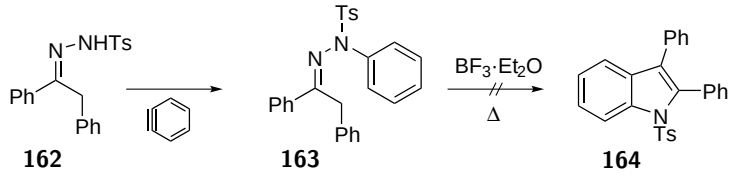
Steric factors were also relevant for a successful Fischer indole reaction; whilst the phenylpropanone hydrazones **149** and **155** underwent arylation and subsequent cyclisation (Table 2.1, entries 4 and 7), the more hindered 2,3-diphenylindole **164** could not be synthesised in a similar manner (Scheme 2.15, (a)). Although arylation of **159** did take place (by LCMS), the addition of $BF_3{\cdot}Et_2O$ to the presumed crude



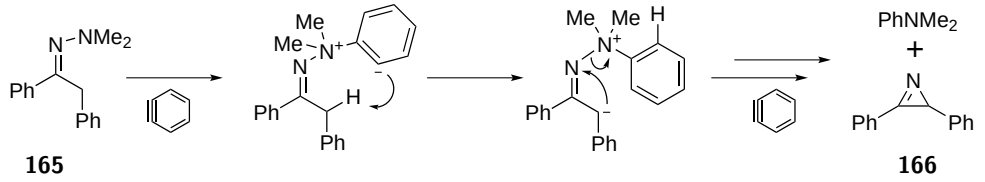
Scheme 2.14 Challenging synthesis of 3-unsubstituted indole.

arylhydrazone **163** led only to a complex mixture. Similar free (N–H) indoles have been synthesised, typically in refluxing acetic acid,[153] and either phenyl substituent is tolerated individually with our protocol. It therefore seems likely that the presence of the *N*-tosyl group at an already crowded substrate may disfavour cyclisation to **164**, especially under the milder conditions attempted here.

a) Attempted benzyne Fischer indole synthesis



b) Larock benzyne Neber azirine synthesis



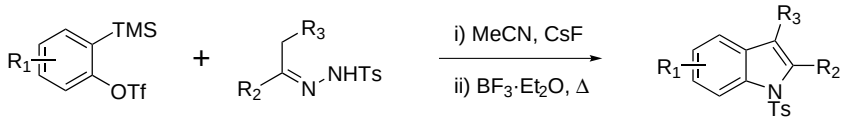
Scheme 2.15 Arylation of (1,2-diphenylethylidene)hydrazones with benzyne in acetonitrile with CsF (3 eq.): a) this work (1.5 eq. **4**, rt); b) Dubrovskiy and Larock (1.1 eq. **4**, 65 °C).[151]

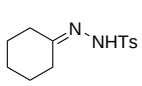
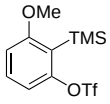
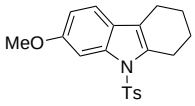
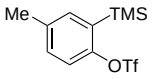
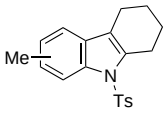
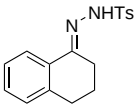
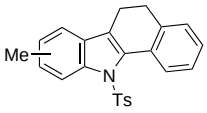
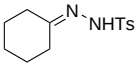
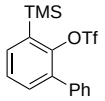
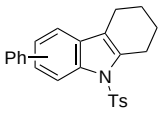
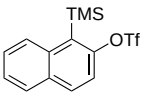
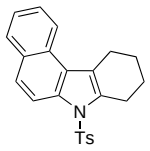
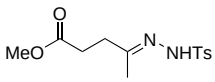
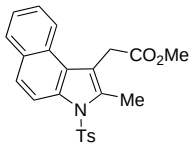
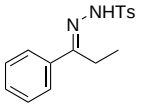
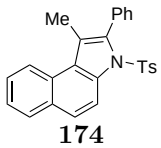
Shortly after this work was completed, it was reported that benzyne-mediated abstraction of the α-proton from a quaternary (1,2-diphenylethylidene)hydrazone led to breakdown products including an unexpected azirine (Scheme 2.15, (b)).[151] It is also of note that Neber-type rearrangement with a deoxyanisoin-derived hydrazone has been suggested as an alternative pathway under Fischer indole conditions,[154] while azirines have themselves been used as substrates in a benzyne indole synthesis (see Section 1.5).[103]

2.2.3 Substituted arynes

ortho-Methoxy benzyne typically undergoes preferential *meta*-attack through inductive electron withdrawal and on steric grounds (Section 1.3). Similarly, *N*-(*m*-methoxyphenyl)hydrazones have been known for some time to exhibit a good degree of regiocontrol, cyclising *para* to the directing group to give 6-substituted indoles.[155,156] Although more recent findings by Grandberg indicated reduced selectivity with $BF_3 \cdot Et_2O$ (in acetic acid) than with ethanolic HCl,[157] we persisted with the standard conditions of $BF_3 \cdot Et_2O$ in acetonitrile. Good selectivity was apparent in both steps when arylation was conducted with methoxy benzyne, as demonstrated by the isolation in 61 % yield of **167** (Table 2.2, entry 1) in favour of several alternative indole products.

Table 2.2 *N*-Arylation and Fischer cyclisation of *N*-tosylhydrazones with substituted arynes.[a]

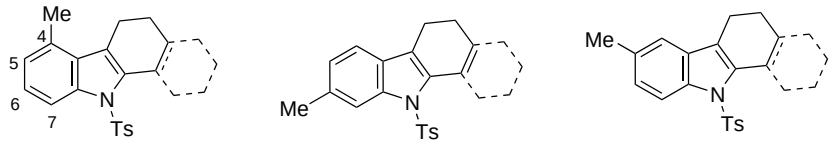


entry	hydrazone	aryne precursor	product	yield(%)
1	 **139**	 **58**	 **167**	61 [b]
2	**139**	 **68**	 **168**	72 [c]
3	 **147**	**68**	 **169**	73 [c]
4	 **139**	 **44**	 **170**	57 [d]
5	**139**	 **171**	 **172**	51 [b]
6 [e]	 **145**	**171**	 **173**	68 [b]
7	 **149**	**171**	 **174**	27 [b]

[a] Conditions: hydrazone (1 eq.), aryne precursor (1.5 eq.), CsF (3 eq.), MeCN (0.1 M), rt, 12 h; then $BF_3{\cdot}Et_2O$ (2 eq.), 80 °C, 5 h. [b] Isolated yield of the major regioisomer. [c] As a mixture of three regioisomers. [d] As a mixture of two regioisomers. [e] 3 eq. $BF_3{\cdot}Et_2O$.

With 4-methyl aryne precursor **68**, an inseparable mixture of all three possible indoles was given (Fig. 2.4). Analysis of the ^{1}H NMR spectra shows the ratio of regioisomers **168a** : **168b** : **168c** to be approximately 1 : 1.4 : 2.2. A statistical mixture over both steps would give a 1 : 1 : 2 ratio, since initial arylation *para* to the methyl group can result in only **168c** whereas **168a** and **168b** are both formed from initial *meta* attack. The observed ratio therefore implies very little selectivity in the *N*-arylation step and increased, though still limited, selectivity in the Fischer step; cyclisation between the methyl group and the hydrazone nitrogen being disfavoured.

Unsurprisingly the tetralone derived hydrazone, **147**, gave similar results when it was arylated with 4-methylbenzyne in the same way. A ratio of approximately 1 : 1.8 : 2.6 for **169a** : **169b** : **169c** indicates that cyclisation at the more hindered position was slightly more unfavourable than with the smaller cyclohexanone hydrazone. In both examples the ratio of isomers was calculated from the relative ^{1}H NMR integrations and the assignments were corroborated by two-dimensional NMR experiments.

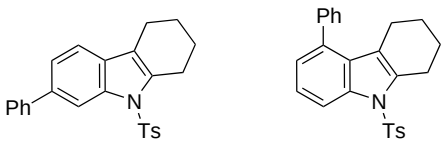


	a		b		c
168	1	:	1.4	:	2.2
169	1		1.8		2.6

Fig. 2.4 All three possible isomers of **168** and **169** were formed during the Fischer indole synthesis in 72 % and 73 % overall yield respectively.[‡]

The presence of a bulky *ortho* substituent on an aryne should permit high selectivity for the arylation step and indeed almost complete regiocontrol was apparent with *ortho*-phenyl benzyne generated from precursor **44**. Disappointingly, the selectivity for the boron trifluoride catalysed cyclisation was still limited. The 6- and 4-substituted indoles **170b** and **170a**, which both exhibit the expected *meta* relationship between the hydrazone-derived nitrogen and the phenyl substituent, were isolated in a ratio of 1.5 : 1. It should be noted that the true preference for distal cyclisation is slightly in excess of 1.5 : 1 as the 6-phenyl indole was more abundant in additional mixed fractions, with complete separation of **170** from all additional impurities proving difficult. Signals resembling the 7-isomer, resulting from *ortho* attack on the aryne, could be observed only as a trace component and were not unambiguously assigned.

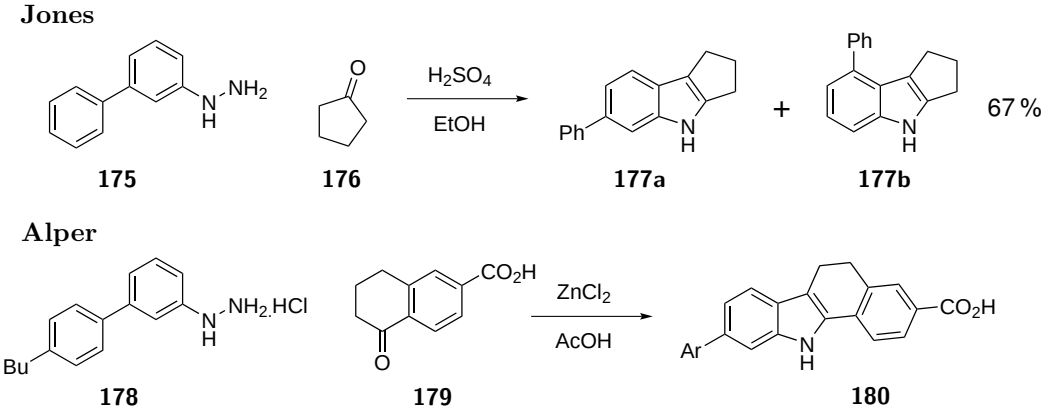
[‡] Numbered according to indole scaffold for consistency



170b **170a**

1.5 : 1

Fig. 2.5 Two of the three possible isomers of phenylindole **170** were isolated as a mixture in 57 % yield.



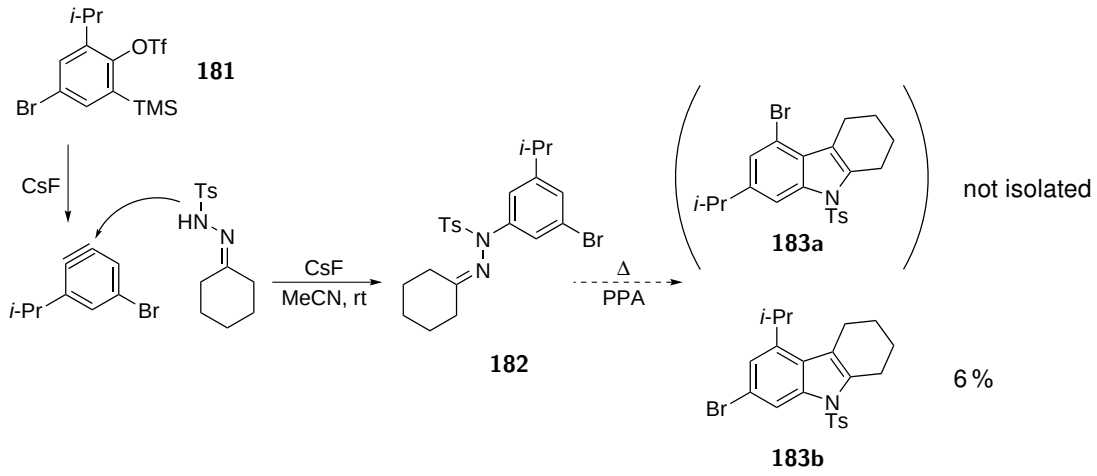
Scheme 2.16 Fischer indole syntheses with *meta*-biphenylhydrazines by Jones and Tringham,[158] and by Alper *et al.*[159]

Reports of the Fischer indole reaction from *meta*-aryl substituted phenylhydrazines are somewhat rare in the literature, presumably due in part to the limited availability of such hydrazines. Jones and Tringham reported that biphenyl-3-ylhydrazine and cyclopentanone gave a mixture of indole regioisomers which could not be separated by chromatography although **177b** preferentially crystallised.[158] A number of *meta*-biphenyl hydrazine reagents were used by Alper *et al.* while investigating indole-based thrombopoietin agonists. For example the dihydro-5*H*-benzocarbozole **180** illustrated in Scheme 2.16 was obtained as a single regioisomer *via* a zinc chloride mediated cyclisation.[159]

In their protocol, the phenylhydrazone was prepared by Suzuki coupling, diazotization, and reduction with $SnCl_2$. An aryne-mediated route would be particularly attractive given the greater ease of *meta*-biphenylhydrazone synthesis if a similar level of discrimination were achieved in the cyclisation step. The use of tetralone derivatives as the ketone may be of some relevance to the observed regioselectivity and interestingly, Alper *et al.* found no selectivity with 3-(bromophenyl)hydrazines.

Having observed exclusive *meta*-arylation with aryne precursor **44**, application of the benzyne-Fischer indole reaction to a further sterically encumbered aryne precursor, **181**, was also attempted (Scheme 2.17). Since initial nucleophilic attack should preferentially occur at the site *meta* to both substituents, only two major cyclisation pathways are likely as with the *ortho*-phenyl aryne discussed above. Furthermore, in the second step the isopropyl group should favour distal cyclisation on steric grounds while a *meta*-halogen substituent has been shown to favour proximal cyclisation in some cases.[157,160] A more favourable distribution of products biased towards one major product (**183a**) might therefore be attainable. In addition the substrate would allow access to a bromine substituted indole, which would be difficult to incorporate by palladium-catalysed methods and might permit scope for further elaboration.

Arylation of hydrazone **139** proceeded as expected with one intermediate hydrazone predominating. However, treatment with $BF_3 \cdot Et_2O$ gave poor conversion and numerous unidentified by-products were also formed. By contrast excess polyphosphoric acid, again added in one pot, did result in indole formation. Unfortunately separation of the indole products proved challenging and the low isolated yield of **183b** (6 %) does not reflect the observed conversion of the *N*-aryl-*N*-tosylhydrazone, which was complete. The substitution pattern in the isolated *N*-tosyl indole was determined by NOESY and corresponds to the anticipated minor cyclisation product. This substrate may benefit from a two step procedure with purification of the presumed intermediate **182** or additional screening of cyclisation conditions if further investigations are pursued.



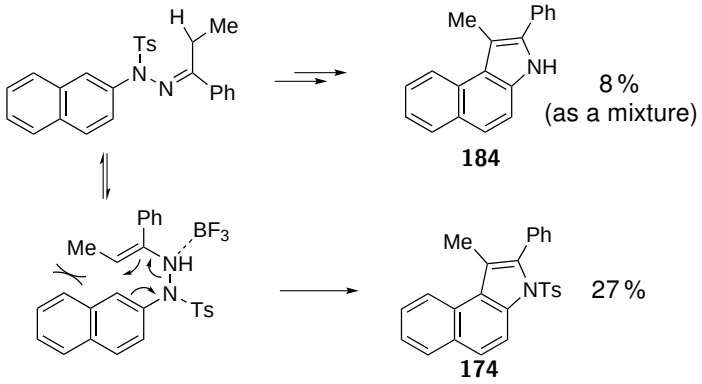
Scheme 2.17 Arylation of tosylhydrazone **139** with disubstituted aryne precursor **181**.

Finally the naphthyne precursor **171** was examined. 2-Napthylhydrazines are known to exhibit excellent regioselectivity in the Fischer indole reaction, generally cyclising to

the 1-position exclusively. Since nucleophilic additions to 1-naphthalynes are known to be favoured at the 2-position, a single indole isomer was to be expected. This proved to be the case with benzoindoles **172** and **173** isolated in 51 % and 68 % yields respectively. The cyclisation reaction did, however, appear slow and an additional equivalent of $BF_3 \cdot Et_2O$ was necessary to drive the reaction to completion in the latter example.

Interestingly, the polyaromatic *N*-tosyl indole **174** from hydrazone **149** and naphthalyne was formed in combination with a significant closely eluting impurity by tlc. The ^{1}H NMR spectrum (taken as a mixture with **174**) resembled the expected indole core but lacked any peaks from the *N*-tosyl group and the identity of this impurity was confirmed as the free (N–H) indole by comparison to the known spectra of **184**[161] (Scheme 2.18). The low yield of **174** itself (27 % isolated, up to 60 % including mixed fractions) thus results both from this undesired reaction and from difficulty in separating the two indole components.

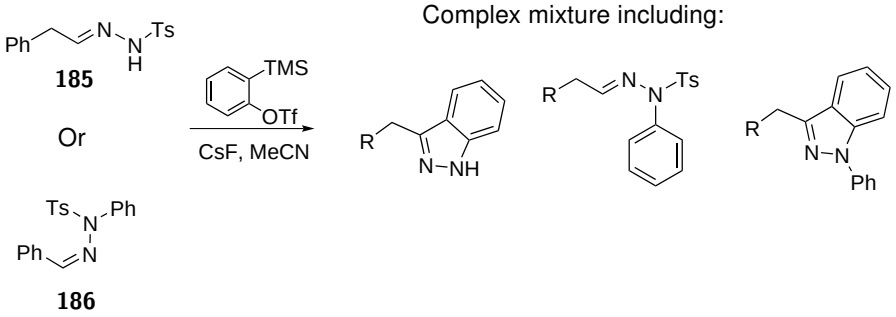
Examination of the by-product fractions collected from the earlier naphthalyne reactions also showed small amounts of detosylated-**172**[162] and trace quantities of peaks attributable to detosylated-**173**. No evidence was found for deprotection when the *N*-tosylhydrazone **149** was used in conjunction with benzyne. It is not clear at what stage this *in situ* deprotection occurs but it seems reasonable to assume that the transition state for the [3,3] sigmatropic reaction is particularly hindered with the larger naphthyl group, allowing alternative pathways to become competitive. However, the benzo[*e*]indole may be sufficiently stabilising to permit hydrolysis and detosylation on workup was not ruled out.



Scheme 2.18 Free (N–H)-indole **184** isolated in 8 % as a mixture with the more abundant *N*-tosyl indole **174**.

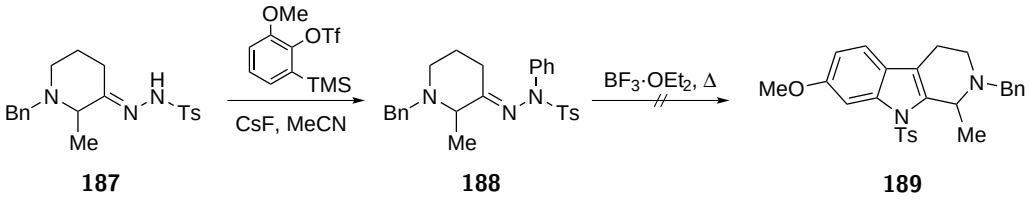
2.2.4 Miscellaneous tosylhydrazones

The tosylhydrazones of aldehydes were examined as substrates for the reaction. However, in line with the findings of Shi,[143] which were reported after this work, complex mixtures were obtained when hydrazones **185** and **186** were used under the optimised conditions (Scheme 2.19). Re-examination of the mass spectrometry data for these mixtures in light of Shi's findings did indicate the presence of indazoles and *N*-arylated indazoles among other unidentified products. Aromatic aldehydes, which were found to be more suitable substrates for indazole formation, were not explored in the course of this work since the Fischer cyclisation would not be possible in the absence of an α-enolisable site. Aldehyde-derived tosylhydrazones were thus not further pursued for benzyne-mediated arylation.



Scheme 2.19 Arylation of aldehyde derived tosylhydrazones.

The 3-piperidinone based hydrazone **187** (Scheme 2.20) was also employed as a substrate for benzyne arylation since cyclisation at the less hindered site would lead to **189**, the core for several β-carboline natural products (see for example Fig. 2.1). Reaction with **58** under the typical conditions gave a mixture of products of which a monoarylation product was the apparent major component (by LCMS). Treatment of this crude reaction mixture with $BF_3{\cdot}Et_2O$, however, did not lead to **189**. The failure of Fischer cyclisation was presumably due to competing ene-hydrazine formation although the identity of the intermediate was not confirmed as **188** by other means.



Scheme 2.20 Arylation of a more highly substituted hydrazone.

2.3 Conclusions

N-tosyl hydrazones, which are stable, easily accessible substrates, may be arylated under mild conditions with arynes generated from *ortho*-(trimethylsilyl)phenyl triflates. The resulting *N*-aryl-*N*-tosylhydrazones will, in general, undergo Fischer indole cyclisation in a one-pot manner on addition of $BF_3{\cdot}Et_2O$ and a range of protected indoles have been synthesised in this way.

Particular advantages include the direct Fischer synthesis of the useful *N*-tosylindole scaffold, which avoids the handling and isolation of unstable *N*-aryl-*N*-tosylhydrazines,[163] the stepwise preparation of *N*-aryl-*N*-tosylhydrazones of which only a few examples exist,[164,165] or tosylation of the free indole in a separate operation. This method allows the synthesis of protected indoles from simple, readily available starting materials whilst requiring only a single chromatographic purification. It avoids the use and exposure of the chemist to toxic aryl hydrazines and accomplishes an otherwise challenging transition-metal-free coupling.

Given the increasing availability of Kobayashi precursors and the difficulties associated with substituted phenyl hydrazines for traditional Fischer indole reactions, it may be of interest to expand the scope of the aryne protocol in this regard. Symmetric 3,6-disubstituted aryne precursors, which were not examined during the course of this work, would be expected to give single 4,7-disubstituted indole products if the [3,3] reaction continues to be favourable. In addition, bulky *ortho*-monofunctionalised arynes could prove useful for the synthesis of 7-substituted indoles. Whilst only moderate selectivity for the 6-phenyl indole **170** was achieved in the cyclisation step under the typical one-pot protocol, no attempt has been made to optimise selectivity in this step. Increasing bulk or altered electronics of the substituent may be of assistance if such investigations were pursued. Finally, the proposed 2,3-dihydro-indazole **144**, resulting from the action of benzyne on *N*-carbonyl hydrazones, may warrant further examination. Additional functionality could be introduced using substituted arynes or alternative *N*-Boc hydrazones.

Chapter 3

Synthesis and Applications of New Aryne Precursors

3.1 Introduction

3.1.1 Palladium cross-coupling chemistry

The palladium catalysed cross-coupling of an organometallic species with an electrophilic organohalide has become one of the most widespread and synthetically useful methods for C–C bond formation. It is related to the more recent Buchwald–Hartwig coupling, which introduces a C–N or C–O bond and was mentioned briefly in the previous chapter.

A range of organometallic species have been employed as stoichiometric carbon nucleophiles, each affording a distinct name to the reaction in which they participate, but perhaps the most useful are organoboron reagents. These were first developed into a catalytic process by Miyaura and Suzuki[166] and have low toxicity, are relatively air stable, undergo limited uncatalysed reaction with other functionality and may be prepared by a number of routes.

3.1.2 The Suzuki reaction

The importance and widespread use of the Suzuki reaction, especially industrially,[167] has resulted in much study and its scope has been the subject of numerous reviews.[168–171] Only a brief overview of the reaction is given here, including recent developments in the methodology and mechanistic understanding.

The Suzuki reaction is initiated by the oxidative addition of a low valent transition metal complex to an organohalide or pseudohalide, resulting in an organo–transition-metal species. It then follows a transmetallation–reductive elimination sequence to complete the catalytic cycle (Fig. 3.1). The metal catalyst, typically Pd(0), is thus regenerated and one equivalent each of organohalide and organoboron reagent consumed as the new C–C bond is formed. There are many other processes and equilibria occurring alongside these required steps but most important is the generation of an active catalytic species *via* dissociation/association of one or more ligands and, where a Pd(II) precursor is used, *in situ* reduction.

Early mechanistic studies concluded that oxidative insertion with tetrakis(triphenylphosphine)palladium proceeded from the PdL_2 species[172] and that this step is rate-limiting with an arylbromide, but faster than transmetallation with aryliodides.[173] The relative rate of oxidative insertion was found to follow the trend I > OTf > Br > Cl with the same palladium source in DMF.[174]

Since then, 3 coordinate 14 electron LPdArX complexes, where L = 2-Ad$P(t\text{-Bu})_2$ or $P(t\text{-Bu})_3$, have been isolated after oxidative insertion[175] and recent work has shown that the monoligated palladium species is the active catalyst, if very bulky ligands are used.[176] Highly sterically encumbered phosphines such as $P(t\text{-Bu})_3$ favour ligand dissociation[177] and these electron-rich coordinatively unsaturated PdL complexes may give accelerated oxidative insertion.

When a boronic acid is used in a Suzuki coupling, prior activation as a 4-coordinate boronate species has often been considered important or necessary for the transmetallation step (Fig. 3.1, pathway **A**).[173] Hydroxide is often implicated if water has been added with the inorganic base or used as a cosolvent, although boron might be attacked by various other Lewis bases if present in the reaction. Once formed, the boronate species would associate to a palladium(II) complex, during or after the loss of the halide, to facilitate transmetallation.

Recent studies, however, have favoured an alternative oxo-palladium pathway, in which the halide ligand is exchanged for a hydroxide after oxidative addition (Fig. 3.1,

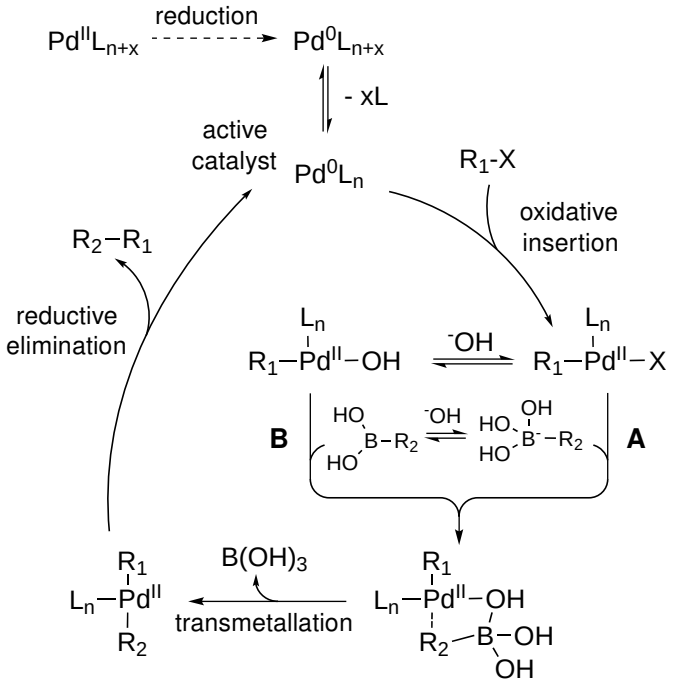
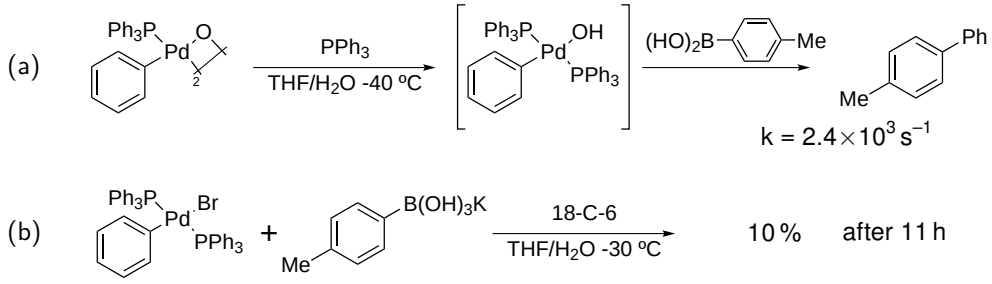


Fig. 3.1 The catalytic cycle of the Suzuki reaction.

pathway **B**). Hartwig and Carrow found the rate of transmetallation, as measured by ^{31}P NMR, to be significantly greater for a preformed oxo-palladium complex and a phenylboronic acid than the pre-formed boronate species with a palladium halide complex (Scheme 3.1).[178] Measurement of the two equilibrium constants showed that comparable concentrations of the phenylboronic acid/phenylboronate and palladium halide/oxo-palladium are present under typical Suzuki coupling conditions and so the reaction should only proceed by pathway **B**.



Scheme 3.1 Rates of transmetallation: a) rapid with oxo-palladium complex and b) slow with boronate species.[178]

Amatore, Jutand and Le Duc used electrochemical techniques to monitor the rates of transmetallation to palladium(II) in DMF.[179] On biasing the equilibrium of the

palladium species towards $[(PPh_3)_2PhPdBr]$ they found a slow rate despite high $ArB(OH)_3^-$ levels, suggesting low reactivity *via* pathway **A**. The rate of transmetallation also displayed a bell-shaped curve on varying hydroxide concentration. The limited rate at low $[HO^-]$ was attributed to insufficient oxo-palladium complex formation (excess $ArB(OH)_2$ sequesters HO^-), whereas at high concentrations the boronic acid is not available for reaction.

These findings are of particular relevance for the optimisation of base and water content for Suzuki methodology when oxidative insertion is rapid. A similar effect was subsequently found for the fluoride anion despite the poorer Pd–F–B bonding interaction and interestingly, coordination of either base at palladium also appeared to accelerate reductive elimination.[180] These and other developments in the study of boron transmetallation have been reviewed recently.[181,182]

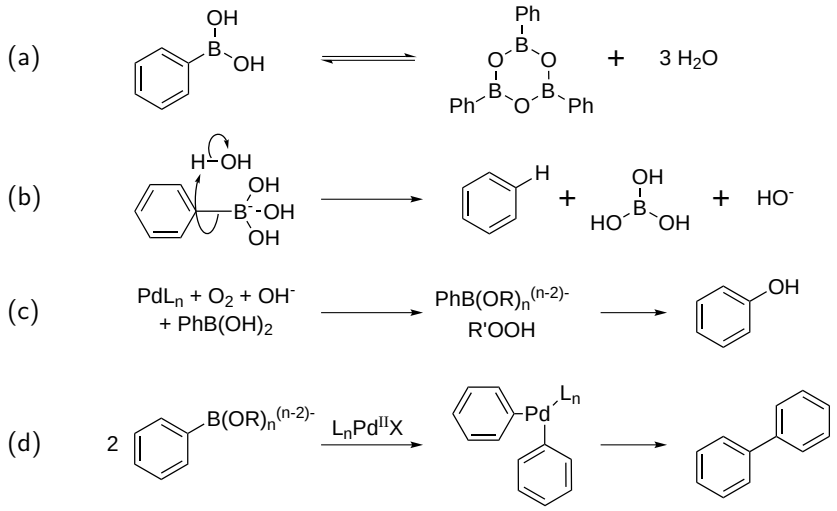
Reductive elimination, at least during C–C bond forming reactions, is generally fast and is of less importance in reaction design. It is favoured by electron poor ligands that destabilise the Pd(II) centre but a sufficiently hindered catalyst may facilitate the process regardless of substantial electron donation.

3.1.3 Organoboron reagents

Despite the relative stability of organoboron reagents they are nevertheless susceptible to breakdown *via* several pathways and the success of a particular Suzuki coupling will often be dependent upon the rate of these processes relative to the catalytic turnover. The most prevalent side reactions of boronic acids are oxidation, homocoupling and protodeboronation. Oligomerisation or cyclotrimerisation by dehydration are also common for boronic acids and, although reversible, may reduce the availability of the free acid for transmetallation.

Homocoupling requires two transmetallation events at the same high valent catalytic site, which must be formed by some other mechanism than the desired oxidative insertion. It can therefore be limited by the exclusion of additional oxidants and minimising or avoiding the use of Pd(II) precatalysts. A boronic acid may also be converted to the corresponding phenol with a strong oxidant or, in the presence of a transition metal catalyst, with atmospheric oxygen derived peroxide.[183] Thus inert conditions are important to maximise the efficiency of cross-coupling if these processes are likely to occur at an appreciable rate in a particular procedure.

Protodeboronation is less readily controlled. Base catalysed deboronation is particularly rapid with electron-deficient boronic acids since boronate formation is favoured



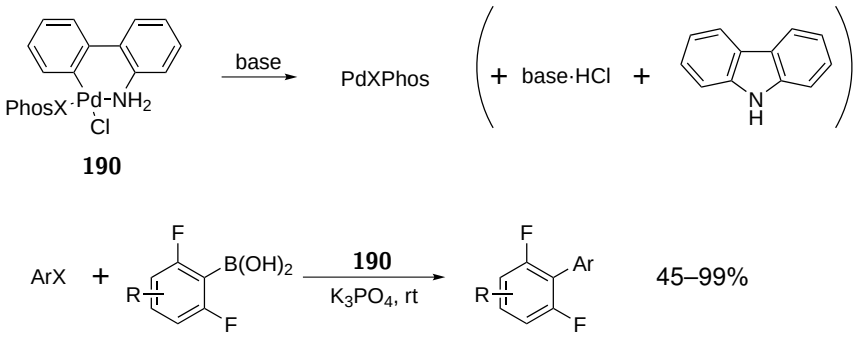
Scheme 3.2 Reactions of Boronic acids: a) reversible trimerisation and irreversible processes: b) protodeboronation, c) oxidation, d) homocoupling.

at elevated pH.[184] Furthermore, electron-poor organoboron reagents – which are of reduced nucleophilicity – often undergo slow transmetallation, increasing the time period over which a protodeboronation pathway can operate. Species for which the rate of transmetallation is slowed on steric grounds may also be susceptible.

Clearly it is advantageous to minimise the exposure of any sensitive boron reagent to conditions liable to induce decomposition. Lowered temperature or pH might slow these pathways but would also reduce the rate of catalytic turnover. In some cases, elevated temperatures are required only for the formation of the active catalyst, with the catalytic cycle itself operating effectively under milder conditions. A preformed palladium–ligand complex that readily liberates the necessary Pd(0) species *in situ* can therefore be advantageous with unstable boronic acids. This approach was found to be useful for rapidly protodeboronating polyfluoro-phenylboronic acids by Buchwald and co-workers (Scheme 3.3).[185]

The most common coupling reagents in Suzuki reactions are boronic acids, especially for biaryl synthesis, but other boron species have also been used widely or developed as alternatives. Notable examples include boronic esters (Fig. 3.2, **191**), MIDA boronates (**192**),[186] and trifluoroborate salts (**193**).[187] Alkyl boranes have also been employed, in particular 9-BBN derivatives (**194**) for alkyl group transfer.[188]

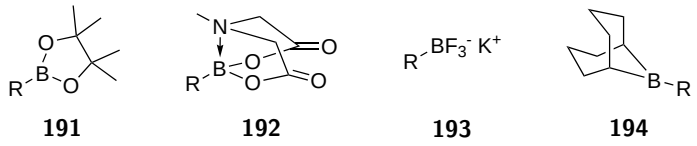
These reagents may be more readily isolated, purified, characterised and stored than the boronic acid itself for certain substrates but they are particularly useful when the parent acid is prone to decomposition under Suzuki reaction conditions. If the organoboron



Scheme 3.3 Room temperature coupling of electron-poor boronic acids.[185]

reagent is slowly hydrolysed to the boronic acid *in situ* then the concentration of free acid, which need not greatly exceed that of the active Pd(II) catalyst, will be reduced and thus limit the rate of side reaction. Since the rate of catalytic turnover varies from reaction to reaction and the rate of hydrolysis, for a given set of conditions, depends both on the nature of the boron reagent and on the organic R-group, a boron species may be chosen to suit the particular reaction or substrate in hand.

This slow hydrolysis strategy was a key factor in the development of MIDA boronates by Burke *et al.*, whilst trifluoroborate salts, popularised by Molander and others, fulfil a similar role. Although aryltrifluoroborates and their partial hydrolysis products may undergo transmetallation directly, this occurs less rapidly than for the parent acid and does not appear to contribute significantly to the overall reaction.[189] The nature of the transmetallation species when boronic esters are employed is not always clear but it seems likely that an *in situ* hydrolysis pathway will be accessible in most cases.



191 **192** **193** **194**

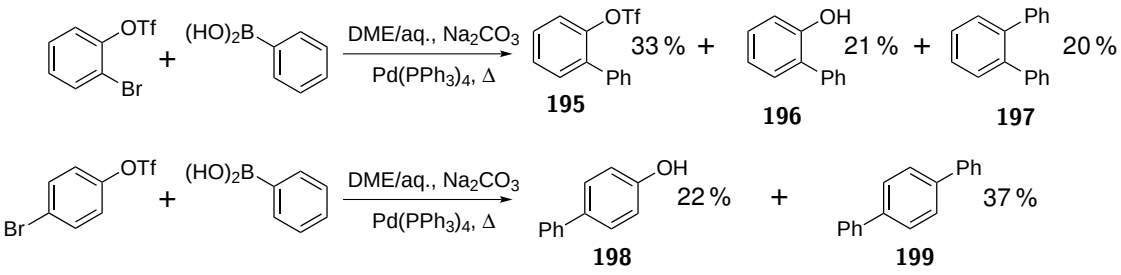
Fig. 3.2 Prominent organoboron cross-coupling reagents: **191** boronic pinacol ester, **192** MIDA boronate, **193** potassium trifluoroborate, **194** 9-BBN species .

3.1.4 Chemoselectivity in Suzuki couplings

Aryl iodides typically undergo rapid oxidative insertion but are often expensive and their availability limited. Chlorides react slowly and although useful couplings have been developed, arylbromides are generally preferred when accessible. Electron deficient alcohol derivatives may act as pseudohalides for oxidative insertion and the most reactive and widely employed of these is the trifluoromethanesulfonate group. Since the insertion of phenyltriflate at palladium triphenylphosphine occurs at a slightly higher rate than phenylbromide (in DMF)[174] some degree of selectivity for the former might be anticipated.*

Cross-coupling reactions in the presence of both bromides and triflates are relatively rare as alcohol derivatisation may be planned to avoid this. However, the chemoselectivity and reactivity of aryltriflates in general is of particular relevance to aryne chemistry where they are often employed as the leaving group. With these considerations in mind, a review of Suzuki cross-couplings on compounds that contain both functional groups is given below.

The first investigations of halide/triflate chemoselectivity with an organoboron species under palladium catalysis were performed by Snieckus and Fu (Scheme 3.4).[190] They found that 2-bromophenyl triflate reacted preferentially at the bromide, giving the biphenyl triflate **195** and its hydrolysed phenol **196**. No 2-bromobiphenyl was formed although the presence of triphenyl **197** demonstrated that significant insertion at triflate also occurred. With the *para*-isomer (Scheme 3.4, bottom) no triflate survived the reaction as cross-coupling and hydrolysis took place more rapidly at this less hindered site. Similar results were obtained with the analogous iodophenyl triflates.

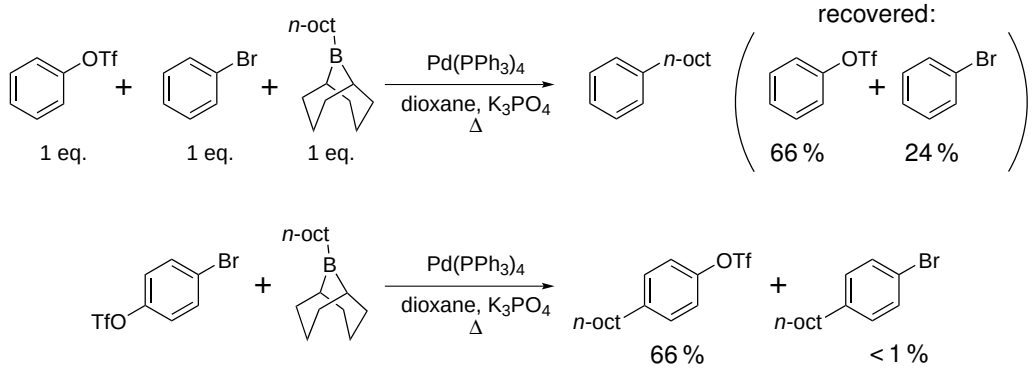


Scheme 3.4 Chemoselectivity between *ortho*- and *para*-halophenyl triflates.[190]

By examination of the recovered starting materials, Suzuki and Miyaura found only a moderate, 2.2-fold, preference for reaction at bromide in an intermolecular

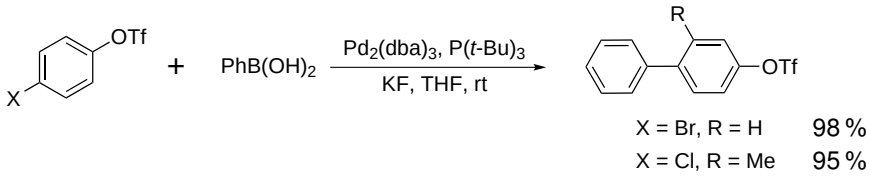
* In toluene, oxidative insertion of an aryltriflate under the same conditions resulted in a tightly-bound ion pair.

competition experiment using *B*-octyl-9-BBN (Scheme 3.5, top). By contrast, almost complete selectivity was achieved with 4-bromophenyl triflate under the same conditions (Scheme 3.5, bottom) due to accelerated C–Br oxidative insertion *para* to the electron withdrawing triflate group.



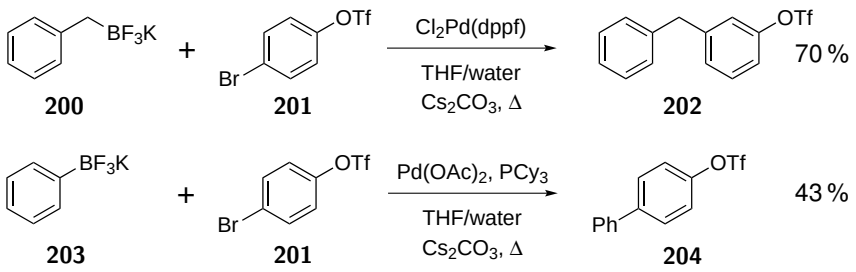
Scheme 3.5 Intra- and intermolecular Br/OTf selectivities.[191]

Later, Fu and Littke discovered that tri-*tert*-butylphosphine in combination with a palladium(0) source (a catalyst system previously found effective for challenging arylchlorides[192]) gave complete selectivity for the bromide in *para*-bromophenyl triflate in a high-yielding Suzuki coupling (Scheme 3.6).[193] A similar reactivity could be achieved even for the *para*-chlorophenyl triflate. Their best results were obtained with only a slight excess of ligand with respect to palladium and $PdP(t\text{-Bu})_3$ was proposed as the active catalytic species.



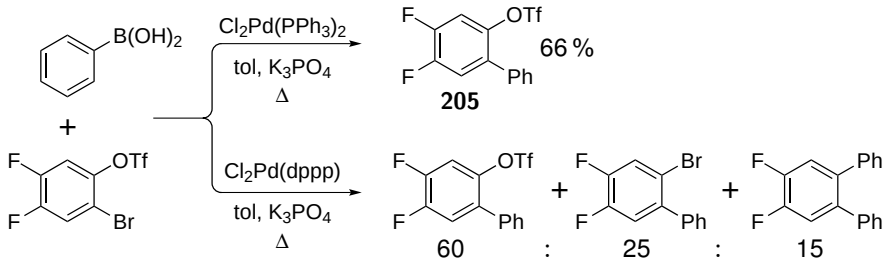
Scheme 3.6 Selective reaction at halides catalysed by $Pd_2(dba)_3/P(t\text{-Bu})_3$.[193]

While studying the reaction of potassium trifluoroborate salts with triflates, Molander and co-workers showed that the benzyl organoboron substrate **200** (Scheme 3.7) also coupled preferentially at the bromide of *para*-bromophenyl triflate. Aryliodides were poor substrates in this reaction and selectivity was reversed for the *para*-chlorophenyl triflate, favouring reaction at triflate over the halide. Similar results were achieved with potassium phenyltrifluroborate (**203**) although the yield for biphenyl **204** was somewhat diminished.[194]



Scheme 3.7 Selectivity for bromide with potassium trifluoroborate salts.[187,194]

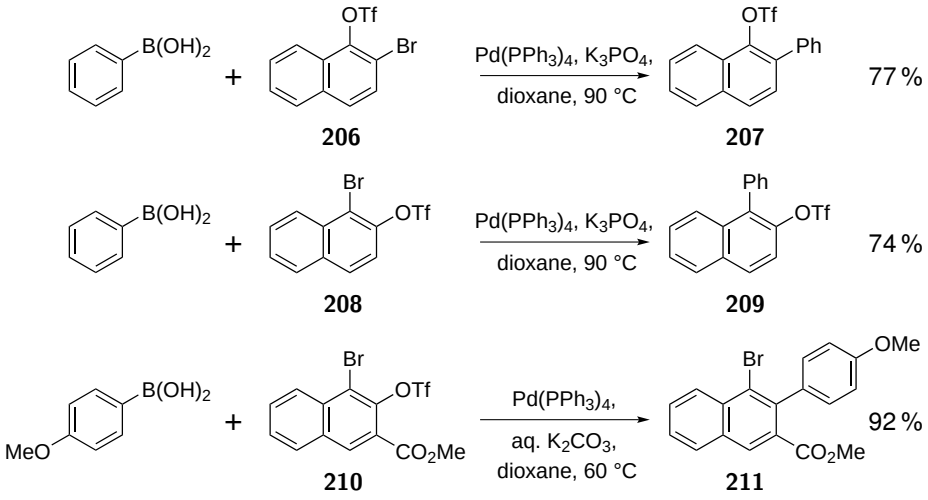
Brown and co-workers observed selectivities for insertion at bromide ranging from 2 : 1 to complete, according to the conditions and substrates employed (Scheme 3.8).[195] Citing a general preference for reaction at triflate groups in other cross-coupling reactions, they made two proposals to account for their results. First, that the boronic acid aids oxidative insertion at the halide through a B–Br interaction. Alternatively, and in their opinion more plausibly, that the coordination of a boronate species to the palladium provides a more active insertion pathway. However, this fails to account for condition-dependent selectivity previously noted in Stille reactions, where insertion at bromide was preferred in dioxane and at triflate in DMF with added lithium chloride.[196]



Scheme 3.8 Selectivity for *ortho*-bromo(difluorophenyl) triflates by Brown and co-workers.[195]

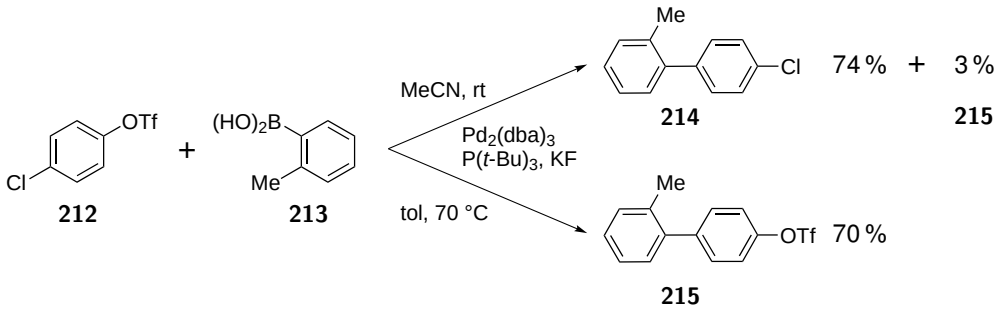
Lager and co-workers have explored the chemoselectivity of Suzuki coupling on several naphthalenes[197–199] and a polysubstituted quinoline.[200] In general they obtained a preference for reaction at bromide regardless of any inherent site-selectivity (giving **207** and **209**, Scheme 3.9). However, this may be altered by additional substitution, with **210** favouring reaction *ortho* to an electron withdrawing (and potentially palladium coordinating) ester group. They stress the importance of heating at only 90 °C and using precisely 1 eq. of boronic acid for monoarylation to occur.

Computational investigation has also been undertaken concerning the chemoselectivity of halide and triflate groups during Suzuki reactions. Schoenebeck and Houk used an



Scheme 3.9 Chemoselectivity for Br/OTf overrides site-dependence for naphthalenes unless additional functionality is present.[197–199]

activation strain model on *para*-chlorophenyl triflate, finding a lower energy barrier for oxidative insertion with a $PdPMe_3$ catalytic species at the chloride.[201] Reaction at triflate, which requires distortion of the stronger C–O bond, was less favourable. The energetic preference was reversed when the catalyst was modelled as $Pd(PMe_3)_2$, indicating an important role for the ligand in site selectivity.



Scheme 3.10 Solvent dependent chemoselectivity.[202]

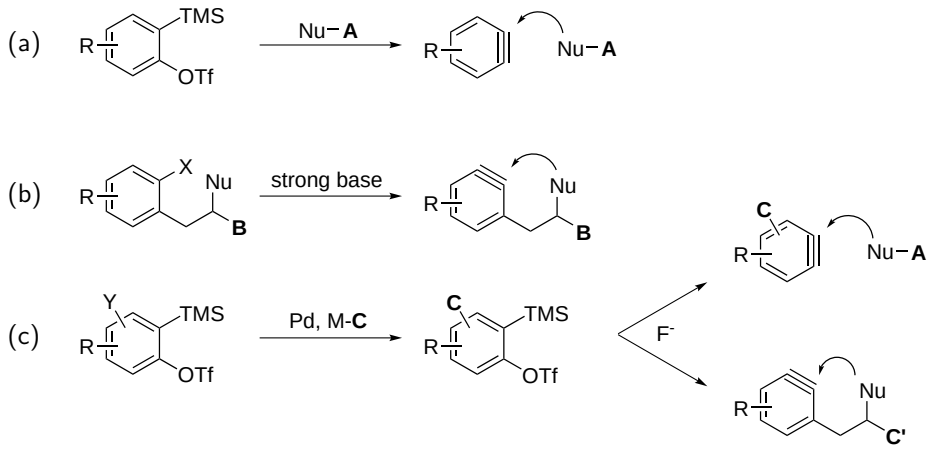
More recently Schoenebeck and Proutiere demonstrated that chloride/triflate selectivity, again using *para*-chlorophenyl triflate, is reversed in a polar solvent such as acetonitrile (Scheme 3.10).[202] Computational investigations concluded that solvent effects at a mono-ligated $[PdP(t\text{-}Bu)_3]$ catalyst could not account for this discrepancy. Instead an anionic $[PdP(t\text{-}Bu)_3X]^-$ complex, which would be more stable in a polar medium, was considered. The calculated energy barrier for C–OTf insertion with this catalytic species was more favourable than for reaction at chloride.

3.2 Aims

Aryne chemistry has undergone considerable expansion in popularity and scope in recent years, due in large part to the development of 1,2-(trimethylsilyl)aryl triflate precursors by Kobayashi. Although benzyne precursor **4** and a few other simple derivatives are commonly employed, the availability of more complex reagents remains limited.

Kobayashi precursors are applied to the vast majority of metal-catalysed aryne methodologies and although larger polyaromatic examples have been prepared, each must be designed and synthesised individually. Similarly, benzyne precursors of this type bearing additional functionality and capable of useful transformations have been reported, but their preparations are typically laborious and narrow in scope (see Section 1.4).

Intermolecular aryne reactions have been used to construct more complex molecules, including the early stages of natural product syntheses. However, the large-scale application *ortho*-(trimethylsilyl)phenyl triflates might be disfavoured on grounds of atom efficiency or cost, especially if the aryne contributes only a small and unfunctionalised fragment (Scheme 3.11, (a)).



Scheme 3.11 Functionalised arynes: a) Complexity of aryne is limited, b) functional group compatibility on **B** restricted, c) wide range of functionality on **C**.

Although highly reactive, arynes may often exhibit good chemoselectivity. However, haloarenes are used almost exclusively for larger aryne fragments due to their relative ease of preparation, despite necessitating harsh conditions and thus limiting the range of compatible functionality (Scheme 3.11, (b)). The ability to introduce a pre-existing

aryne precursor motif by an alternative route could therefore substantially increase the complexity of structures available for this chemistry.

This project aims to find a new method to prepare 2-(trimethylsilyl)phenyl triflates from a common and easily obtained substrate. It was envisaged that a pre-formed aryne precursor, while retaining the key triflate and trimethylsilyl groups, would react selectively at a third site. If sufficiently general, a broadly applicable cross-coupling route could introduce diverse functionality at this site, giving access to a far greater range of Kobayashi-type precursors. In combination with mild, fluoride induced generation of the reactive intermediate, these substrates would permit new aryne reactions to be developed.

Such precursors could be incorporated later in a synthesis, where functionality sensitive to strongly basic conditions or organometallic reagents may also be present on a molecule and where mild, high-yielding steps are particularly desirable.

3.3 Optimisation

Selective ring functionalisation is problematic if (trimethylsilyl)aryl triflates are to be employed as substrates for a cross-coupling reaction. The triflate leaving group may also act as a pseudohalide, undergoing oxidative insertion with low valent transition metals, and has been used extensively in Suzuki and other cross-coupling protocols. Additionally, triflates are prone to hydrolysis in basic conditions, a trimethylsilyl group may also undergo transmetallation in some circumstances, while benzyne formation from 1,2-elimination of these two groups is of course well known. Replacement of the leaving group with a more stable species (such as an imidazolylsulfonate or tosylate) might overcome some of these issues but would inevitably alter the aryne forming properties to some extent.

It was assumed that the key difficulty would be achieving selective oxidative insertion at a desired site whilst leaving the triflate group untouched. Aryl iodides undergo rapid oxidative insertion and so an iodo-(trimethylsilyl)phenyl triflate would be an attractive choice to achieved chemoselective reaction. However, iodophenols are not readily accessible (neither 2,6- nor 2,4-diiodophenol are commercially available, for example), are less atom-economic and may have stricter storage and disposal requirements. By contrast dibromophenols, from which the desired halide-substituted Kobayashi-type aryne precursors can be synthesised, are far more easily accessed and were therefore adopted as the substrate of choice.

As discussed earlier in Section 3.1.4, a number of examples exist in which oxidative insertion at a bromide had been achieved in the presence of triflate groups. It was therefore anticipated that such a coupling could be performed on a bromo-2-(trimethylsilyl)phenyl triflate if optimal conditions were found.

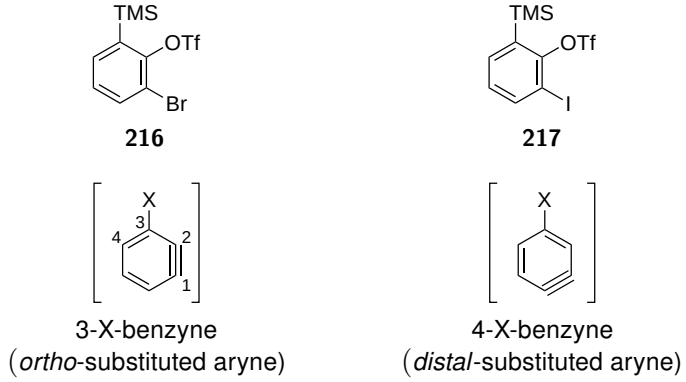
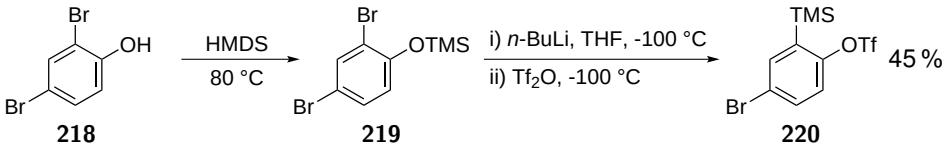


Fig. 3.3 Halo-aryne precursors: known precursor **216**, inaccessible **217**.

3.3.1 *distal*-Bromo aryne precursor



Scheme 3.12 Preparation of aryne precursor **220** from the dibromophenol. Silylation of **218** occurred quantitatively with 1.1 eq. HMDS. Reaction conditions for preparation of **220**: i) crude **219** (1 eq.) *n*-Bu-Li (1.1 eq., 1.6 M in hexane), in THF (0.14 M); ii) Tf_2O (1.2 eq.), −100 °C, 20 min.

Initial work focussed on the *distal*-bromo aryne precursor **220**, which could be synthesised from the readily available 2,4-dibromophenol (**218**) using a route already established for other substituted *ortho*-bromophenols (Scheme 3.12).[75] In addition, separating the site of intended oxidative insertion (the bromine) from a potential leaving group might reduce the likelihood of possible side reactions or triflate elimination and be more amenable to reaction than at a hindered *ortho*-substituted position.

Beginning with conditions based on those described by Fu[193] (see Scheme 3.6, section 3.1.4) the 4-bromo aryne precursor **220** was treated with phenylboronic acid (**223**) and potassium fluoride in tetrahydrofuran for 5 h at room temperature with $Pd_2(dba)_3$ and tri-*tert*-butylphosphine (Fig. 3.4, (a)). Analysis of the crude reaction by LCMS indicated a degree of conversion had taken place. A second compound eluted soon

after the starting material and was ascribed to the coupling product **221**. Increasing the water content of the reaction mixture, achieved by replacement of KF with its hydrate $KF \cdot 2\,H_2O$, improved the reaction (Fig. 3.4, (b)).

The use of a fluoride base, although often employed in Suzuki reactions, was of some concern given the nature of the substrates and was considered a potential hurdle for further optimisation. Replacement of the fluoride base with caesium carbonate gave similar, if not qualitatively cleaner conversion by HPLC (Fig. 3.4, (c)), however potassium phosphate, even with added water, was less effective. (Fig. 3.4, (d)). **221** was isolated in 42 % using Cs_2CO_3 and confirmed as the desired product.

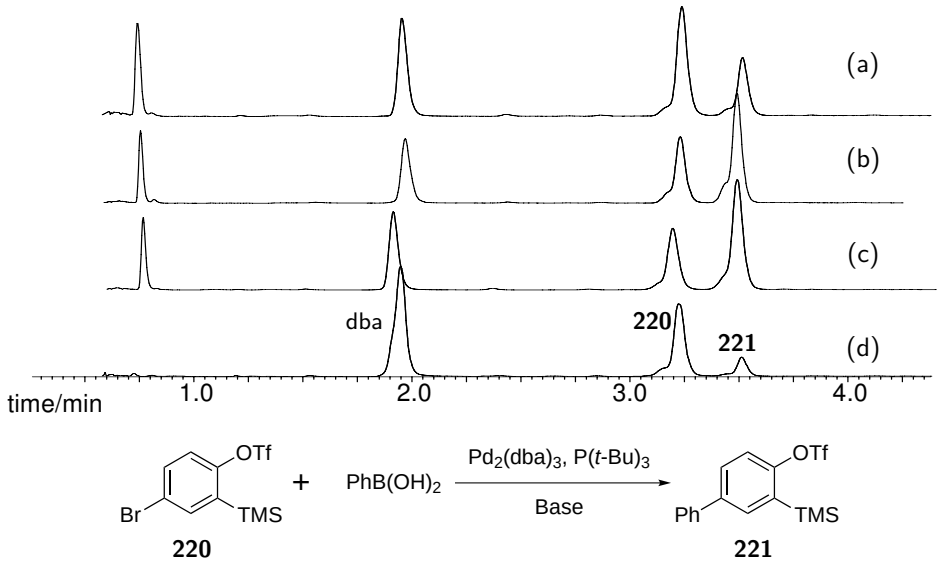


Fig. 3.4 HPLC traces for initial screening with **220**. Conditions: 1.1 eq. $PhB(OH)_2$ (**223**), Pd_2dba_3 (5 mol %) P*t*-Bu_3 (10 mol %), THF (0.1 M) and 3 eq. base; a) KF, b) $KF \cdot 2\,H_2O$, c) Cs_2CO_3, d) THF:Water 20:1 K_3PO_4, rt, 5 h. Separation was performed on a C-18 reverse phase column 50×2.1 mm, particle size 5 µm. Eluents were water (A), acetonitrile (B), and a 1:1 mixture of water : acetonitrile containing 0.1 % ammonium hydroxide (C). The flow rate was set to 1.1 ml min^{-1}. The gradient was increased linearly from 57.5 : 37.5 : 5.0 A : B : C to 2.5 : 92.5 : 5.0 A : B : C over 0–4 min after which it was set at 95 : 5 B : C from 4.01–4.50 min. Detection by UV was performed at 254 nm.

3.3.2 *ortho*-Bromo aryne precursor

Having demonstrated the feasibility of Suzuki cross-coupling on a 2-(trimethylsilyl)phenyl triflate motif, albeit in moderate yield, attention was switched to the more interesting 3-bromo aryne substrate **216**. While the *distal*-phenyl precursor **221** is known and has been used in aryne chemistry,[203] it offers little selectivity in most reactions. The *ortho*-phenyl benzyne precursor **44** by contrast can react with excellent regioselectivity, and could also permit intramolecular interaction with the aryne bond if additional functionality were introduced on the 2′-ring position.

Disappointingly, applying identical conditions to those for **220** resulted in only trace quantities of biphenyl **44** when using **216** (Fig. 3.5, (d)). Altering the nature of the base, which had led to pronounced changes with the previous substrate, was next attempted. Potassium phosphate tribasic (Fig. 3.5, (a)) and potassium carbonate (Fig. 3.5, (e)) were also unsuccessful, both displaying essentially no conversion of the starting halide. The stronger potassium hydroxide base led to a new peak with $m/z = 245.2$, consistent with hydrolysis of the triflate to the corresponding phenol.

However, in the presence of potassium phosphate hydrate, **216** did show an appreciable level of reactivity with a new peak, assigned as **44**, emerging shortly after the starting material (Fig. 3.5, (b)). Similar results were obtained when water was introduced as a co-solvent and K_3PO_4 used as the base (Fig. 3.5, (f)), this latter method being preferable for ease of handling. Increasing the temperature to reflux gave only a modest qualitative improvement in conversion.

Having recovered a degree of reactivity for the Suzuki coupling with the *ortho*-bromo precursor **216**, the optimisation of other parameters was required to achieve improved conversion.

To this end a screen of alternative solvents was then undertaken. The previously active potassium phosphate base was retained and the appropriate solvent used in a 5 : 1 ratio with water. Each reaction was run for 24 hours at room temperature prior to analysis and the results are displayed in Fig. 3.6. For ease of handling and improved purity of the phosphine ligand $[HP(t\text{-Bu})_3]BF_4$ replaced $P(t\text{-Bu})_3$ but conditions were otherwise unchanged.†

The ethereal solvents THF (Fig. 3.6, (a)) 1,4-dioxane (i), and dimethoxy ethane (j) all gave appreciable conversion but by-products also emerged. Very similar results were seen in the more polar solvent acetonitrile (e). In highly polar solvents dimethyl sulfoxide (c), *N,N*-dimethylformamide (d) and in particular methanol (f), consumption

† A small quantity of 1,1′-di-*tert*-butylbiphenyl was also added to each example.

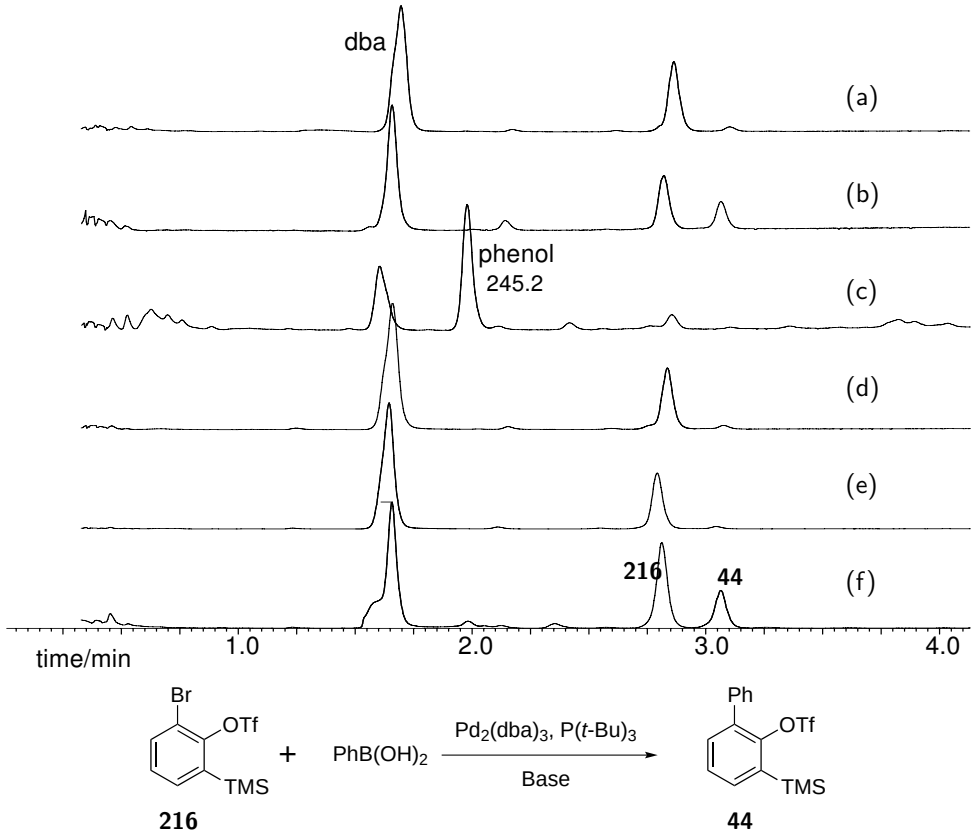


Fig. 3.5 HPLC traces for screening with **216**. 1.1 eq. $PhB(OH)_2$, Pd_2dba_3 (5 mol %) P(*t*-Bu)$_3$ (10 mol %), THF (0.1 M) and 3 eq. base; a) K_3PO_4, b) $K_3PO_4 \cdot H_2O$, c) KOH, d) Cs_2CO_3, e) K_2CO_3, f) THF:water 5:1 K_3PO_4, rt, 5 h. Separation was performed on a C-18 reverse phase column 50×2.1 mm, particle size 5 µm. Eluents were water (A), acetonitrile (B), and a 1:1 mixture of water : acetonitrile containing 0.1 % ammonium hydroxide (C). The flow rate was set to 1.1 ml min^{-1}. The gradient was increased linearly from 57.5 : 37.5 : 5.0 A : B : C to 2.5 : 92.5 : 5.0 A : B : C over 0–4 min after which it was set at 95 : 5 B : C from 4.01–4.50 min. Detection by UV was performed at 254 nm.

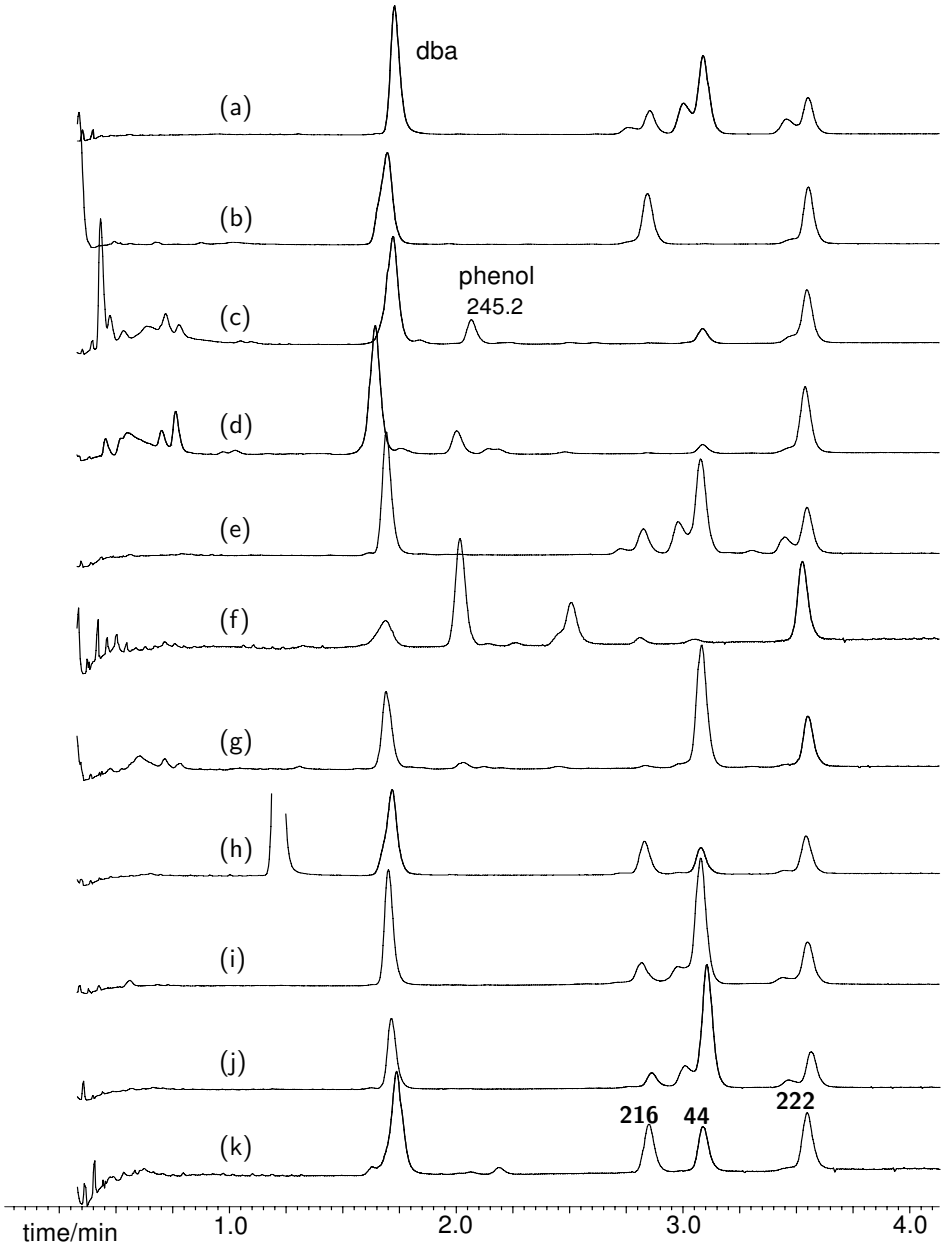


Fig. 3.6 HPLC traces for solvent screen with **216** and 1.1 eq. $PhB(OH)_2$, at rt for 24 h using Pd_2dba_3 (5 mol %) $[HP(t\text{-}Bu)_3]BF_4$ (10 mol %), K_3PO_4 3 eq. in solvent:water 5:1 (0.1 M). a) THF, b) NMP, c) DMSO, d) DMF, e) MeCN, f) MeOH, g) DMA, h) toluene, i) dioxane, j) DME, k) DCM. **44** is the desired product and **222** an inert internal standard (1,1′-di-*tert*-butylbiphenyl.) Separation was performed on a C-18 reverse phase column 50×2.1 mm, particle size 5 µm. Eluents were water (A), acetonitrile (B), and a 1:1 mixture of water : acetonitrile containing 0.1 % ammonium hydroxide (C). The flow rate was set to 1.1 ml min^{-1}. The gradient was increased linearly from 57.5 : 37.5 : 5.0 A : B : C to 2.5 : 92.5 : 5.0 A : B : C over 0–4 min after which it was set at 95 : 5 B : C from 4.01–4.50 min. Detection by UV was performed at 254 nm.

of the starting material did occur. However, the major product was a peak at $m/z = 245.2$, which appeared to be the phenol formed from hydrolysis of the triflate group. No trace of **44** was present after reaction in *N*-methylpyrrolidone (b).

The most promising result from this screening was the reactivity in DMA (Fig. 3.6, (g)), which indicated complete consumption of **216**. Although this is a relatively uncommon solvent for Suzuki reactions, DMF is used extensively. The encouraging conversion seen under these conditions allowed isolation of the desired product **44** in 49 % after purification by column chromatography. However, despite numerous attempts to optimise other reaction parameters using DMA/water as solvent, no improvement in the isolated yield could be found.

With only limited success in DMA, other solvent systems were re-examined. In the aprotic and poorly hydrogen bonding solvents DCM and toluene (Fig. 3.6, (h) and (k)), the HPLC traces also indicated clean reaction, though with substantially lower consumption of the starting material. By raising the reaction temperature to 90 °C in toluene and ensuring an inert nitrogen atmosphere, complete conversion of **216** could be observed, permitting the isolation of *ortho*-phenyl aryne precursor **44** in excellent 95 % yield (Fig. 3.7). Interestingly, applying these conditions to the *distal*-bromo aryne precursor **220** gave almost no conversion, illustrating a remarkable orthogonality of the 6- and 4-positions in bromo-2-(trimethylsilyl)phenyl triflate.

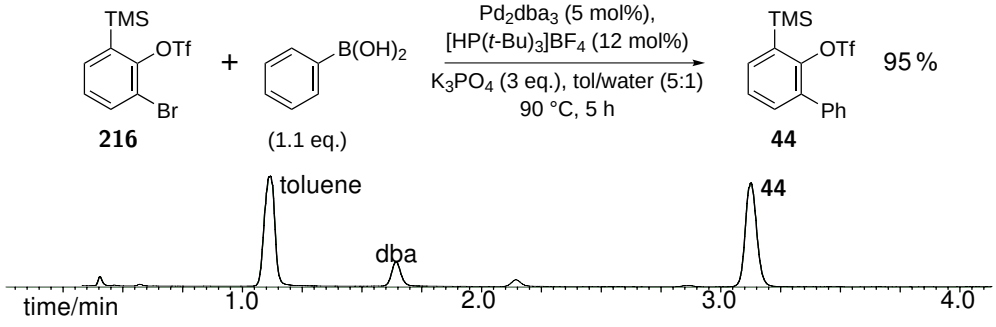


Fig. 3.7 Optimised Suzuki coupling conditions.

3.3.3 Control reactions

A number of control reactions were also undertaken, which are shown in Table 3.1 (the optimised conditions are given entry 1). $Pd(PPh_3)_4$ (Table 3.1, entry 2) was a less effective pre-catalyst (in line with earlier findings in DMA), giving a poorer (78 %) yield despite complete consumption of the starting material. A significant but unidentified by-product peak that eluted earlier than the starting material in this example may account for the discrepancy. Inert conditions were shown to be important, although not crucial, with 56 % product by GC still formed when the reaction vessel was left open to the atmosphere (entry 3).

Phenyl boronic acid pinacol ester was a poor substrate for the reaction, giving just 14 % of the product (entry 4). The MIDA boronate of *para*-tolylboronic acid was also tested and again showed incomplete conversion, the *para*-methyl substituted product **225** being isolated in just 28 %.

The starting material was stable to the reaction conditions in the absence of palladium (entry 5) and a base was necessary for appreciable conversion; only 10 % of **44** formed in the absence of potassium phosphate (entry 6) but sodium bicarbonate was also effective (entry 11).

The loading of palladium catalyst could be reduced with no loss in yield (entry 8) if the reaction time was also extended to 24 h. Increasing the stoichiometry of phosphine ligand with respect to palladium lowered efficiency slightly (entry 9) and it is of note that $Pd(P(t\text{-}Bu)_3)_2$, when examined during initial reaction optimisation, was also somewhat less effective.

Analysis of the reaction prior to the more typical 5 h time period indicated that, at least for the simplest case of phenylboronic acid, completion was achieved within 1 h (entry 12). The longer time period was used generally for convenience, because longer time periods were beneficial in earlier screening at room temperature, and to ensure completion with more demanding substrates.

It is assumed that scope remains for further optimisation or modification of the procedure. The catalyst loading may be lowered if inert conditions are ensured, and the time and temperature parameters could be adjusted according to the priorities of the operative. While the presence of water is clearly important, no attempts were made to determine the optimal levels and its content could most likely be reduced if desired. Sodium bicarbonate might allow increased functional group compatibility if used in place of the phosphate base.

Table 3.1 Control reactions for Suzuki coupling of **216** and phenyl boronic acid.[a]

entry	Pd	ligand	base	**216** [b]	**44** [b]
1	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	2 [c]	90 [c]
2	$Pd(PPh_3)_4$	-	K_3PO_4	0	78
3 [d]	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	47	56
4 [e]	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	86	14
5	-	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	100	0
6	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	-	89	10
7 [f]	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	dry K_3PO_4	68	28
8 [g]	1.25 % Pd_2dba_3	2.75 % $[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	0	95
9	Pd_2dba_3	22 % $[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	10	86
10 [h]	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	6	88
11	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	$NaHCO_3$	0	95
12 [i]	Pd_2dba_3	$[HP(t\text{-}Bu)_3]BF_4$	K_3PO_4	0	94

[a] Typical conditions: 10 mol % Pd, 2 eq. $PhB(OH)_2$, 3 eq. base, vessels inerted *via* 3× evacuation/N_2 backfill, 1.5 ml stock solution (**216** (0.106 M), dodecane (0.587 M) in toluene), 0.3 ml water, solvents degassed under N_2 flow and added through septum, 90 °C, 5 h. [b] % yield by GC compared to dodecane as an internal standard. [c] Average of three experiments. [d] Solvents not degassed, vessel left open to atmosphere. [e] Using phenylboronic acid pinacol ester in place of $PhB(OH)_2$. [f] No added water. [g] Reaction time 24 h. [h] Reaction temperature 50 °C. [i] Reaction time 1 h.

Throughout these investigations little evidence for double arylation of **216** was observed, although mixtures were not exhaustively analysed during optimisation. Even when a five-fold excess of *para*-methoxyphenylboronic acid (**226**) was employed, homocoupling and protodeboronation were responsible for excess boronic acid consumption. The presence of the *ortho*-trimethylsilyl group presumably helped to impede reaction at the triflate on steric grounds and inductive electron donation may have further disfavoured oxidative insertion at this site.

3.4 Scope of the selective Suzuki coupling

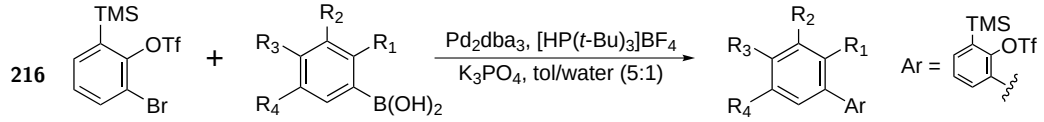
With the optimised conditions in hand, the scope of the reaction was next explored and the full extent of successful couplings between **216** and boronic acids is displayed in Table 3.2. Both electron rich *para*-methyl and *para*-methoxy phenylboronic acids (**224** and **226**) and the electron poor *para*-trifluoromethyl phenylboronic acid (**228**) were suitable substrates, furnishing their respective aryne precursors in high yields. The *para*-methyl ester substituted phenylboronic acid did not result in the desired product, presumably due to hydrolysis on the ester group.

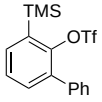
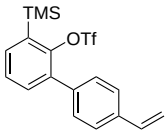
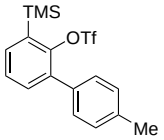
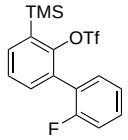
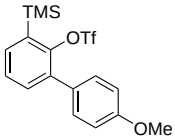
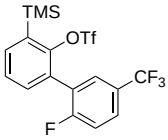
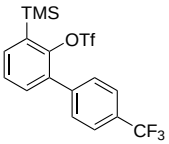
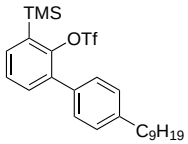
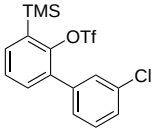
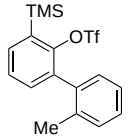
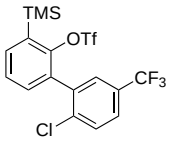
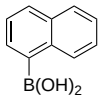
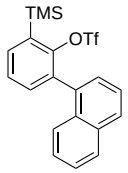
Unsurprisingly, the presence of a bromide in the boronic acid was not well tolerated but its replacement with a chloride did not lead to significant side reaction and the 3′-chlorobiphenyl aryne precursor **231** was obtained in 87 % yield. This substrate would permit elaboration of the biphenyl scaffold through additional cross-coupling steps after aryne generation. Alternatively, selectivity for chloride over triflate is known[193] and could allow opportunities for sequential aryne precursor construction. The *para*-vinyl functionalised product **235**, which was isolated in 89 % yield, also provides a site for elaboration *via* alkene cross-metathesis or other methods.

Phenylboronic acids with *ortho*-heterogroups proved more challenging. 2-(Methoxy)-phenylboronic acid and 2-(methylthio)phenylboronic acid did couple although incomplete reaction in both cases and challenging purifications made isolation of the product difficult. Phenylboronic acids with *ortho*-carboxyl, hydroxyl, formyl and cyano groups all performed poorly under the standard conditions, giving less than 10 % product.

Yields were slightly diminished when an *ortho*-fluorine substituent was present in the boronic acid (Table 3.2, entries 8 and 9) with incomplete conversion of the starting material **216**, although separation of the aryne precursor products was straightforward. The reduced yield of the *para*-nonyl precursor **241** reflects, in part, the slightly more troublesome separation of this compound, which was prepared on a larger scale. In general, however, the reactions could be performed with no alteration over a range of scales (0.1–0.7 mmol) with little effect on reproducibility.

Table 3.2 Suzuki coupling of boronic acids and **216**.[a]

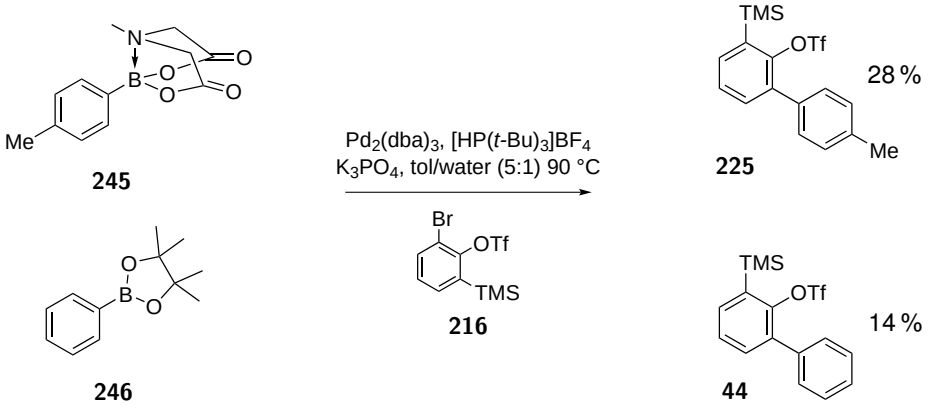


entry	boronic acid	product	yield (%)	entry	boronic acid	product	yield (%)
1 [b]	$R_{1–4}$ = H **223**	 **44**	95	7	R_1,R_2,R_4 = H R_3 = $CHCH_2$ **234**	 **235**	89
2 [b]	R_1,R_2,R_4 = H R_3 = Me **224**	 **225**	82	8	$R_{2–4}$ = H R_1 = F **236**	 **237**	66
3 [b]	R_1,R_2,R_4 = H R_3 = OMe **226**	 **227**	89	9	R_2,R_3 = H R_1 = F, R_4 = CF_3 **238**	 **239**	74
4 [b]	R_1,R_2,R_4 = H R_3 = CF_3 **228**	 **229**	82	10	R_1,R_2,R_4 = H R_3 = C_9H_{19} **240**	 **241**	70
5	R_1,R_3,R_4=H R_2 = Cl **230**	 **231**	87	11 [b]	$R_{2–4}$ = H R_1 = Me **213**	 **242**	92
6	R_2,R_3 = H R_1 = Cl, R_4 = CF_3 **232**	 **233**	82	12	 **243**	 **244**	98

[a] Conditions: 5 mol % $Pd_2(dba)_3$, 0.12 eq. $[HP(t\text{-}Bu)_3]BF_4$, 2 eq. $ArB(OH)_2$, 3 eq. K_3PO_4, 5 h, 90 °C.
[b] With 1.1 eq. of boronic acid.

3.4.1 Alternative coupling reagents

While the general protocol tolerated trifluoromethyl and halide substituents on a phenylboronic acid, the reaction with more electron deficient substrates did not prove successful. 2-Fluoro-5-nitro-, 2-chloro-5-nitro- and 2-fluoro-5-cyano-phenylboronic acids all failed to give appreciable conversion, for example. Given the poor reactivity of phenylboronic pinacol ester (**246**) and *para*-tolyl MIDA boronate (**245**), employing masked boronic acids more widely was not initially considered. However, having noted



Scheme 3.13 Coupling of masked boronic acids: MIDA boronate (isolated yield), and pinacol boronic ester (GC yield).

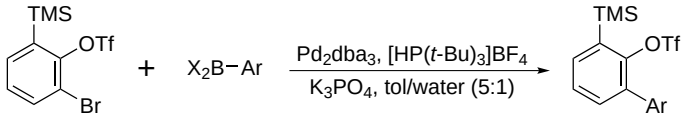
the findings of Urawa *et al.* who used phenylboronic esters containing an *ortho*-nitrile group for couplings where the free acid failed,[‡][204] the reaction of **216** and pinacol ester **247** was attempted. Pleasingly, the 2′-cyanobiphenyl aryne precursor **248** was obtained in excellent yield (Table 3.3, entry 1) under the standard cross-coupling conditions.

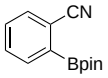
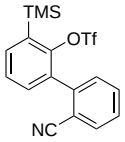
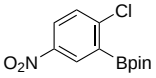
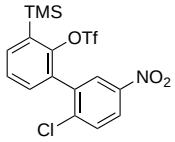
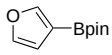
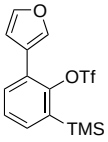
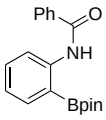
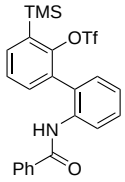
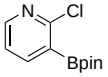
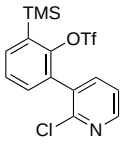
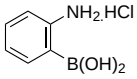
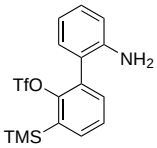
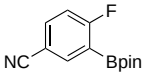
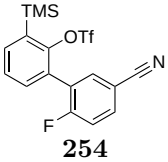
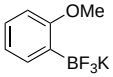
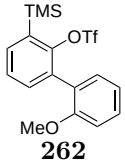
Supposing that the electron-withdrawing properties of the *ortho*-nitrile group increased the rate of transmetallation under the optimised conditions (by accelerated boronic ester hydrolysis or otherwise) and that the same effect might be in operation with electron-deficient rings more generally, several other pinacol esters were synthesised. This appeared to be the case and the results of coupling these substrates to **216** are given in Table 3.3.

The heterocyclic furan ring could be introduced in excellent 93 % (Table 3.3, entry 2) while the chloropyridyl substrate **251** also reacted to give **252** (entry 3) albeit in reduced yield. The 5′-nitrile- and 5′-nitro-compounds **254** and **256** could also be obtained in

‡ Urawa *et al.* attributed their success to the inhibition of boronic acid-assisted nitrile hydrolysis.

Table 3.3 Suzuki coupling of boronic acid precursors with **216**.[a]



entry	boronate species	product	yield (%)	entry	boronate species	product	yield (%)
1	 **247**	 **248**	87	5	 **255**	 **256**	42
2	 **249**	 **250**	93	6	 **257**	 **258**	41
3	 **251**	 **252**	45	7	 **259**	 **260**	49
4	 **253**	 **254**	60	8	 **261**	 **262**	27

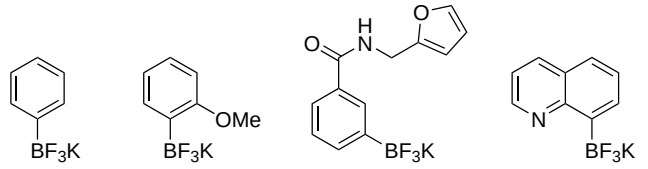
[a] Conditions: 5 mol % $Pd_2(dba)_3$, 0.12 eq. $[HP(t\text{-}Bu)_3]BF_4$, 2 eq. $ArB(OH)_2$, 3 eq. K_3PO_4, 5 h, 90 °C.

the same manner. The yields, while still moderate in some cases, represent a significant improvement over the free boronic acids.

Having found the pinacol esters well suited to electron poor substrates, the pinacol ester of *ortho*-methoxyphenylboronic acid was also considered. The free boronic acid had been prone to protodeboronation but it remained problematic in the protected form. During the investigation of alternative boronic acid precursors, the potassium trifluoroborate salt **203** was also subjected to the standard coupling conditions and, in contrast to the pinacol ester–protected phenyl boronic acid, gave the desired biphenyl product **44** in

essentially quantitative yield. Initial concerns over the expected liberation of fluoride in the course of this reaction appeared unfounded; presumably the basic and/or biphasic nature of the conditions protected the labile trimethylsilyl group from any accumulation of fluoride anions.

Since the potassium trifluoroborate salt appeared to be a suitable surrogate for the boronic acid irrespective of electron withdrawing functionality, it might be a suitable masking group for hindered substrates. However, when an *ortho*-methoxy group was introduced (substrate **261**) the conversion of **216** was once again incomplete and the product was obtained in only 28 % (Table 3.3, entry 8). The yield in this example is further lowered by its challenging isolation. Attempts using other available reagents of this type were also envisaged (**263** and **264**, Fig. 3.8) but none were capable of cross-coupling with **216** under the standard conditions.



203 (99 %) **261** (28 %) **263** (no reaction) **264** (no reaction)

Fig. 3.8 Potassium trifluoroborate salts attempted.

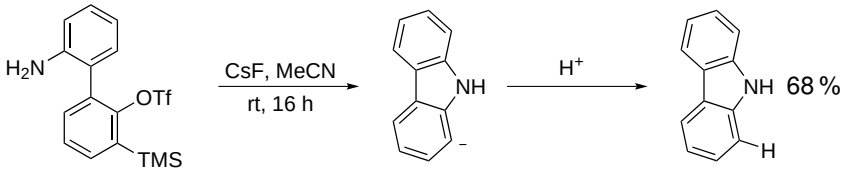
Further attempts at cross-coupling with *ortho*-substituted substrates were more successful. The benzamide-containing boronic ester **257** allowed the preparation of a biphenyl aryne precursor bearing *ortho*-amide functionality (Table 3.3, entry 6). A similar reaction with the aniline gave inferior results to 2-aminophenyl boronic acid when used directly as its hydrochloride salt (**259**), which gave **260** in 49 % yield (Table 3.3, entry 7).

3.5 Reactions of substituted aryne precursors

With reliable access to a range of aryne precursors having been established, the potential applications of these substrates was next investigated. A range of further reactions that have been attempted on 2-functionalised (trimethylsilyl)phenyl triflates are detailed in the following sections.

3.5.1 *ortho*-Nucleophilic groups

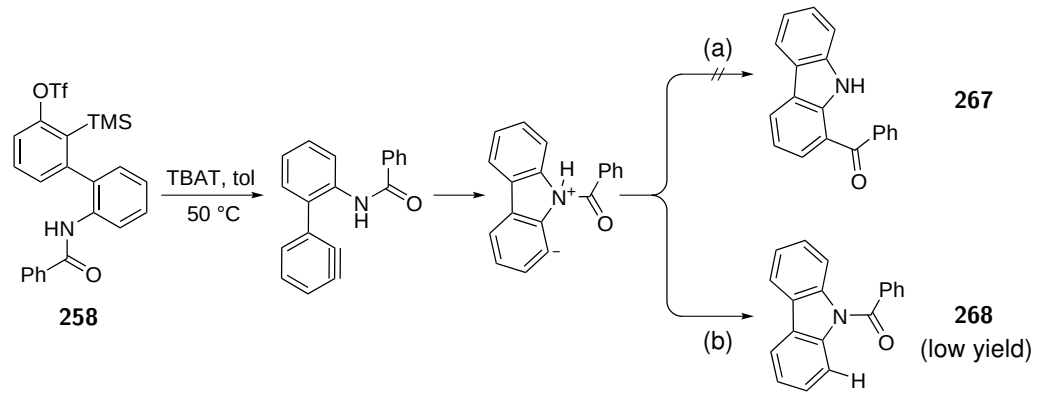
Anilines are known to be excellent nucleophiles for benzyne. Thus intramolecular cyclisation to the aryne generated from **260** should be trivial, giving carbazole (**265**) after protonation of the resulting aryl anion (Scheme 3.14). Indeed, after the addition of caesium fluoride to the precursor in acetonitrile on a small (25 mg) scale, carbazole was obtained in 68 % yield. This would most likely improve upon scale up or with minor adjustments to the protocol.



260 **265**

Scheme 3.14 Carbazole synthesis from **260**

Amides are also sufficiently nucleophilic to attack arynes but the resulting zwitterionic species may, in the absence of an α-proton, rearrange to give σ-insertion products.[146] Since the benzamide aryne precursor **258** was directly accessible *via* cross-coupling, the feasibility of such an amide insertion reaction was examined. **258** was subjected to conditions applicable to the intermolecular insertion of benzyne to *N*-phenyl benzamide, which would lead to **267** (Scheme 3.15, pathway (a)) by an analogous intramolecular process.



258 **267** **268** (low yield)

Scheme 3.15 Aryne generation with adjacent benzamide

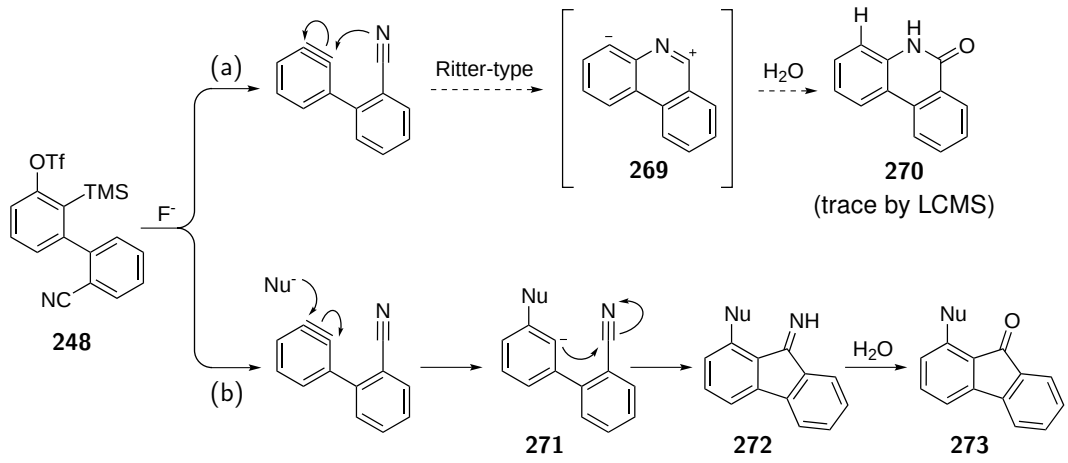
After purification, *N*-benzoyl carbazole, **268** (Scheme 3.15, pathway (b)) was detected as a minor component of the reaction mixture by ^{1}H NMR but no evidence for the amide-insertion product **267** was found. The carbazole zwitterion is presumably

more conformationally restrained than the analogous acyclic reactions, which may inhibit rearrangement, although a similar 1,3-benzoyl migration under photochemical conditions is known.[205] Optimisation towards the carbazole would probably be straightforward and might be synthetically useful if additional sensitive functionality were present.

3.5.2 Reactivity at a nitrile group

The *ortho*-nitrile aryne precursor **248** could be particularly useful for further studies due to its high-yielding synthesis and the potential chemistry of the *ortho*-group through both aryne-mediated reactions and other transformations.

Perhaps unsurprisingly, given the compatibility of *ortho*-(trimethylsilyl)phenyl triflate derived aryne chemistry with nitrile solvents, Ritter-type reactivity was not apparent as a major pathway. When the aryne was generated from TBAF in tetrahydrofuran in the absence of additional reactants (Scheme 3.16, (a)) only trace quantities of possible cyclisation products were observed.

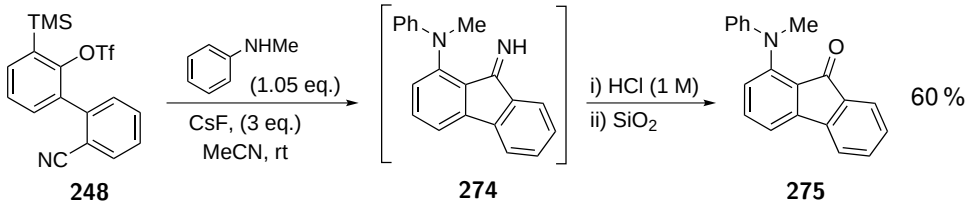


Scheme 3.16 a) Speculative Ritter-type reactivity, b) Cascade aryne–nitrile capture.

An alternative reaction mode in which the pendant nitrile acts as an electrophile was also considered. Nitriles are stable to attack from relatively weak nitrogen nucleophiles whereas arynes react readily with soft nucleophiles. Furthermore, hindered 2-substituted arynes such as **248** may do so with a good degree of regioselectivity. The resulting aryl anion **271** should be expected to react rapidly in an intramolecular fashion with the adjacent nitrile, furnishing a cyclic product **272**, from which hydrolysis would lead to a 1-substituted fluorenone (Scheme 3.16, (b)).

The reaction of *N*-methyl aniline with the aryne generated from **248** using 3 eq. of caesium fluoride was carried out at room temperature and on quenching with 1 M HCl, immediately gave a deep purple solution that was assumed to be the fluorenone **275**. After workup and purification on silica, however, a minor product could not be fully removed (Fig. 3.9, (a)).

It became apparent on further purification that the action of silica was slowly converting the initial major product to the expected fluorenone. This is well illustrated by the emergence of signals later confirmed as **275** (Fig. 3.9, (b)) at the expense of those ascribed to fluorenimine **274**.



Scheme 3.17 1-Amino fluorenone synthesis.

The overall reaction giving 60 % of a 2-amino-fluorenone is shown in Scheme 3.17. It is assumed that heating the crude product with acid and/or silica should simplify purification of **275** and improve the overall yield. The reliable isolation of **274** is unlikely to be viable given its instability towards silica but it could conceivably serve as a substrate for further elaboration if quenched with a nucleophile other than water.

A number of routes to fluoren-9-ones and similar motifs have been published that utilise arynes. Meyers and co-workers noted the dimerisation of an oxazoline-containing aryl-chloride *via* aryne and arylanion formation, giving **276** after hydrolysis (Scheme 3.18, (a)),[206] although the example would not be generally applicable. More recently Zhang and Larock used benzyne from 2-(trimethylsilyl)phenyl triflates with *ortho*-iodobenzaldehydes to prepare various fluorenones in a palladium catalysed process (Scheme 3.18, (b)).[207]

Friedel–Crafts type intramolecular attack of nitriles has been known for some time,[208] while C–H functionalisation routes to fluorenones have been recently reported, but such approaches generally require high temperatures and/or strongly acidic conditions.[209]

The intramolecular aryne route from **248** (Scheme 3.17) allows the incorporation of 1-amino groups, which are rarely present in other fluorenone syntheses, under especially mild conditions. The reaction is expected to be quite general with respect to aryne compatible nucleophiles and should permit the synthesis of a range of fluorenones with

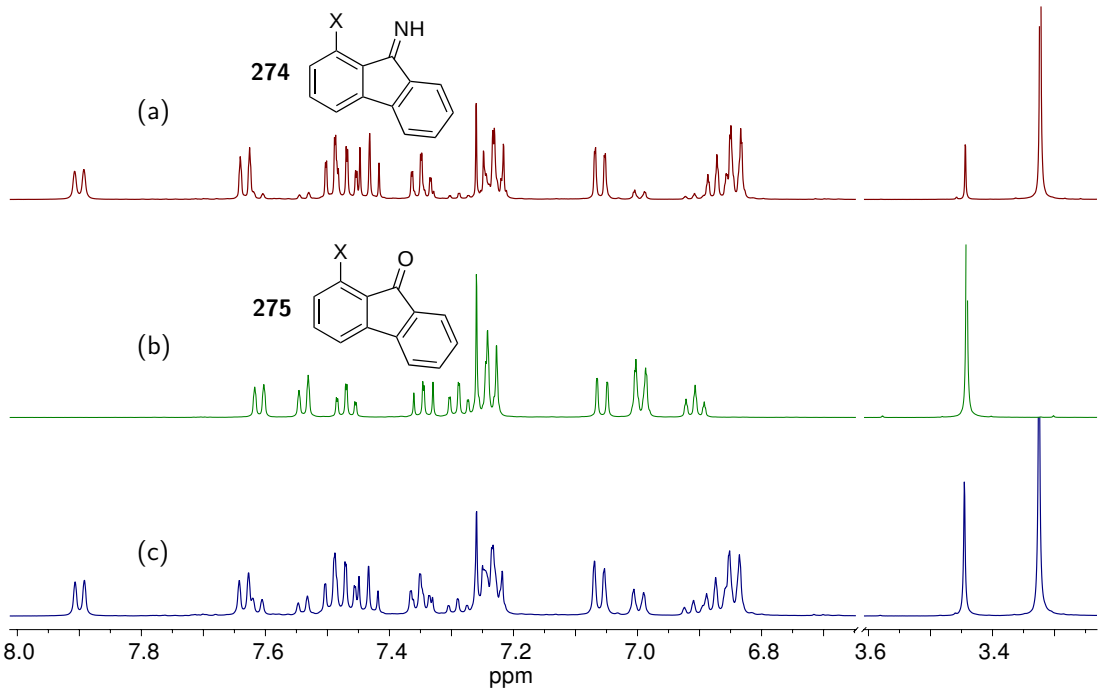
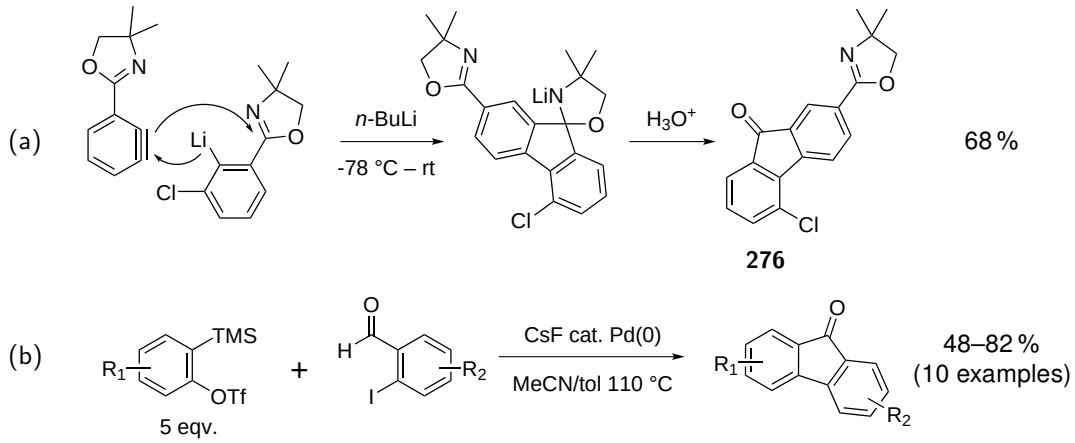


Fig. 3.9 ^{1}H NMR spectra for purification of **275**: a) Mixed fracton after initial column, mostly comprised of **274**, re-columned to give: b) pure **275** and c) second mixed fraction with a smaller proportion of **274**.

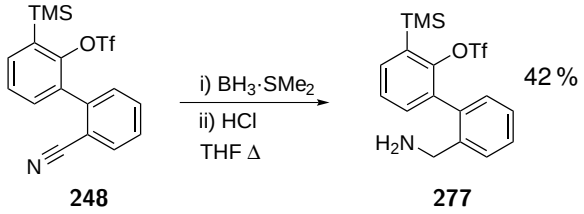
various functionality in the 1-position. The introduction of nucleophilic hetero-groups in a metal-free step is especially attractive as sulphur or nitrogen containing species can often interfere with palladium-mediated couplings. Analogues of **248** in which the nitrile is extended from the ring may also be of interest as a similar reaction would lead to phenanthrenone or larger ring structures.



Scheme 3.18 Synthesis of fluoren-9-ones by aryne methods: a) Meyers,[206] b) Zhang and Larock.[207]

Nitrile reduction

Borane–dimethylsulfide adduct, which is known to reduce nitriles in the presence of a triflate group,[210] was selected as a potential reducing agent for the nitrile-containing substrate **248**. Indeed, 1.1 eq. of $BH_3{\cdot}SMe_2$ in refluxing THF was sufficient to bring about the desired transformation (Scheme 3.19) and **277** was isolated in 42 % yield. It is assumed that dihydrophenanthridine could be trivially synthesised, as was the case for carbazole from the analogous aniline-containing aryne precursor, **260**.



Scheme 3.19 Reduction of **248** using $BH_3{\cdot}SMe_2$.

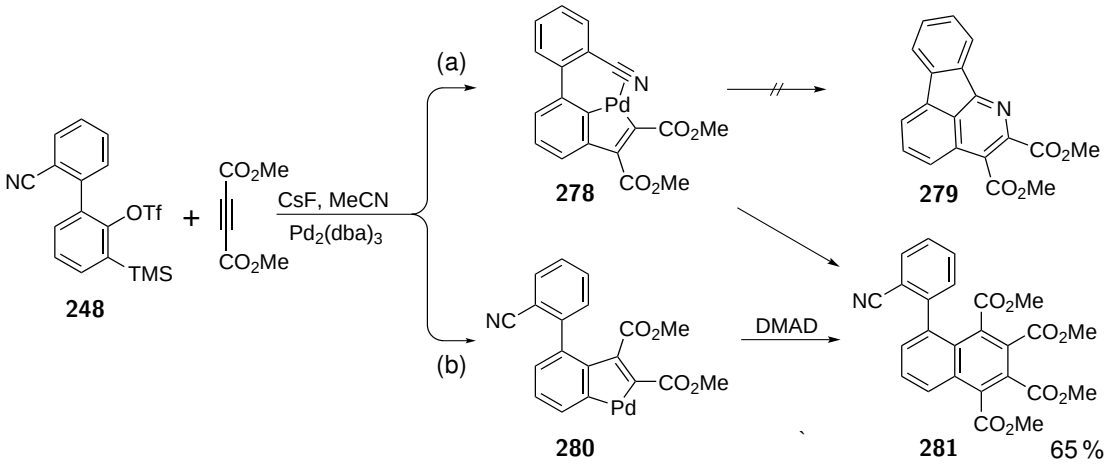
3.5.3 Metal catalysed [2+2+2] reactions

With the 2′-cyanophenyl benzyne precursor

Nitrile groups may also participate as a 2π component in transition-metal-catalysed reactions. If a cyclometalated species such as **278** (Scheme 3.20, pathway (a)) were to be formed with the aryne in the presence of a further intermolecular 2π species then

interaction with the C≡N bond might be possible. Subsequent insertion of the nitrile and reductive elimination would lead to **279**.

However, when DMAD (1.2 eq.) and **248** were mixed with caesium fluoride and catalytic $Pd_2(dba)_3$, the [2+2+2] product **281** was instead formed (in 65 % yield with respect to DMAD) as a mixture with a small quantity of DMAD-trimerisation product (hexamethyl-benzene hexacarboxylate). It is possible that steric repulsion of the benzonitrile ring resulted in the alternative palladacycle (Scheme 3.20, pathway (b)), precluding formation of **279**.



Scheme 3.20 [2+2+2] reaction of DMAD and **248**.

Among the transition metals used to catalyse formal [2+2+2] cycloadditions, cobalt is well known to be effective with a nitrile component. Thus pyridines may be synthesised from α,γ-cyanoalkynes and an additional acetylene.[211] However, cobalt-catalysed aryne reactions are rather rare.[212] Similar reactions have been performed under nickel catalysis and aryne–nitrile [2+2+2] reactions are also known.[213] Preliminary experiments with **248** using a nickel or cobalt source (NiI_2/dppe or $Co(dppe)Cl_2$ with an excess of zinc) gave only intractable mixtures.

Triphenylene synthesis

Triphenylenes are interesting polyaromatic benzenoid hydrocarbons, known to form discotic liquid crystals, which have potential applications as materials in organic electronics.[214] The palladium-catalysed trimerisation of arynes is an important route to strained triphenylenes, particularly for otherwise sterically challenging arrangements of substituted rings.[215] Its application to biphenylarynes, which has not been previously

reported, would be of considerable interest given the newly accessible range of precursors.

The *para*-methoxybiphenyl **227** was selected as a test substrate to ease characterisation and was stirred overnight with $Pd_2(dba)_3$ and CsF in acetonitrile (Scheme 3.21). The crude reaction mixture was complex by ^1H NMR but isolation of a single component using silica column chromatography revealed a simple, symmetric compound that was confirmed as the triphenylene **283** by mass spectroscopy and X-ray crystallography (Fig. 3.10).

The unit cell for the crystal structure contains six distinct molecules of **283** in addition to co-crystallised solvent. In each case the triphenylene core is distorted from planarity and the methoxyphenyl groups are rotated to varying extents. The reaction is assumed to proceed *via* palladacycle **282c** with the alternative intermediates **282a** or **282b**, which would lead to an asymmetric triphenylene, being disfavoured on steric grounds.

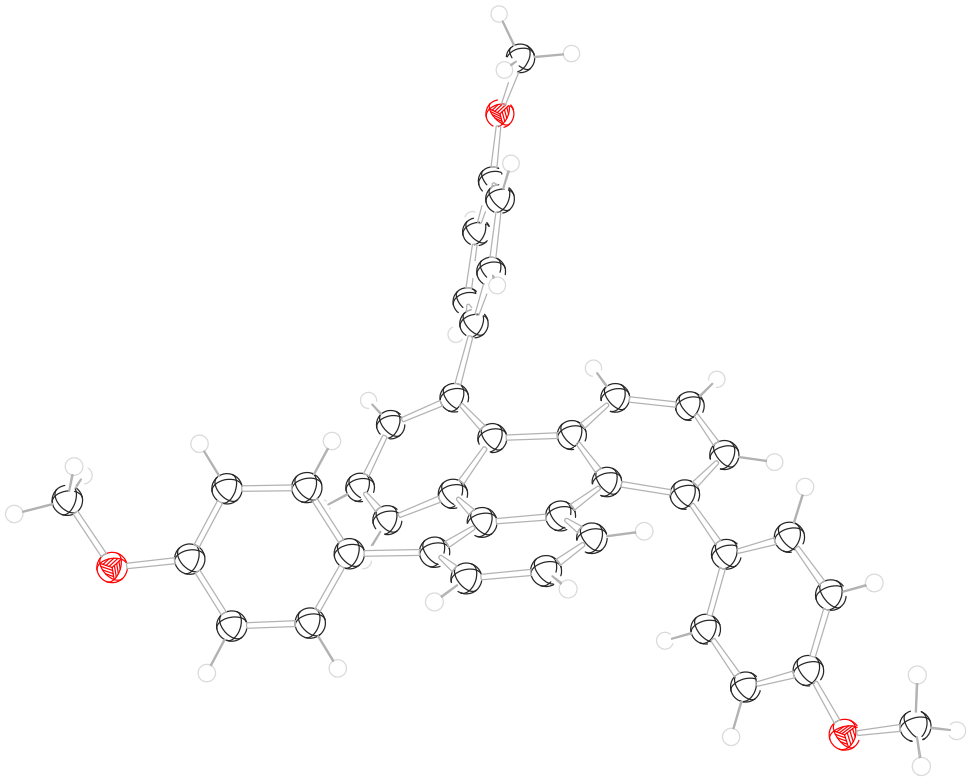
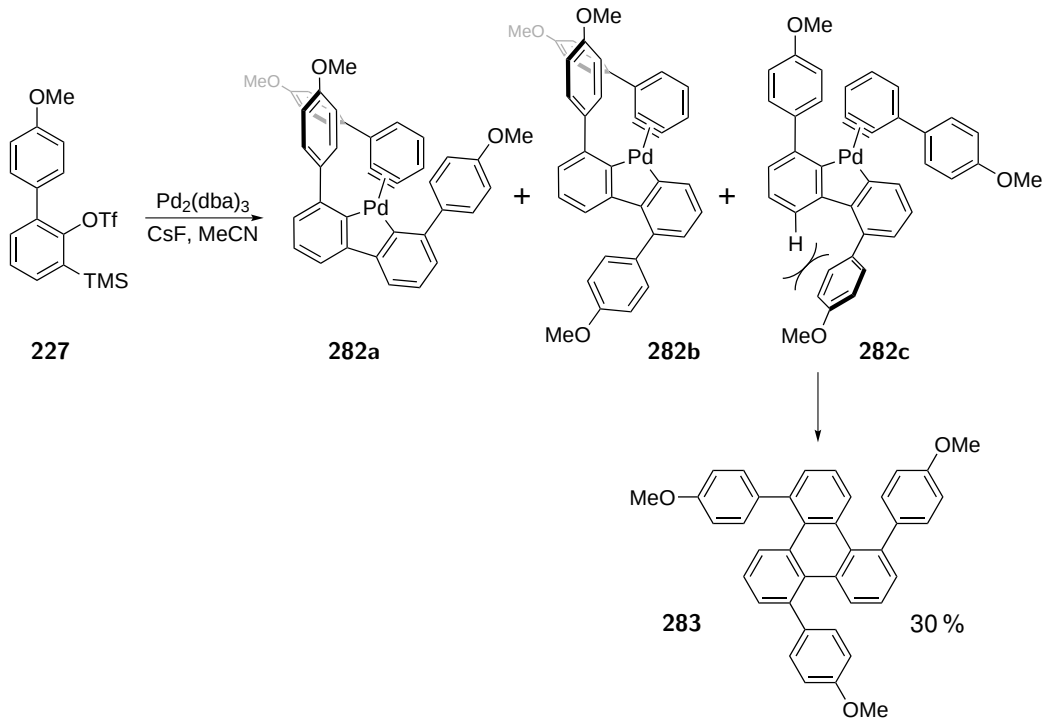


Fig. 3.10 X-ray crystal structure of triphenylene **283** with displacement ellipsoids at the 50 % probability level. Only a single molecule is shown for clarity.



Scheme 3.21 Palladium catalysed [2+2+2] cyclotrimerisation reaction to give triphenylene **283**

Peña *et al.* have performed analogous aryne cyclisations with the polycyclic 3,4-phenanthryne[216] or 1,2-triphenylyne,[84] also generated from Kobayashi-type precursors. Interestingly, with these substrates they obtained only asymmetric triphenylenes (**285** and **286**, Fig. 3.11), seeing no evidence of the symmetric products.

These triphenylenes are thought to arise from the symmetric metallocycle intermediate **284**, which necessitates an asymmetric final product. Presumably the additional rotational degrees of freedom available in **282c** limits any 1,4-strain between the highlighted proton and the adjacent ring.

It should be noted that no triphenylene could be isolated when the same procedure was applied to the *para*-nonyl-substituted aryne precursor, **241**.§ It was not possible to determine whether trimerisation had failed or if the symmetrical triphenylene was present in a mixture of highly lipophilic polyaromatic structures that could not be separated.

§ Long alkyl chains are often incorporated into discotic liquid crystal monomers to alter their supramolecular (and sometimes handling) characteristics.

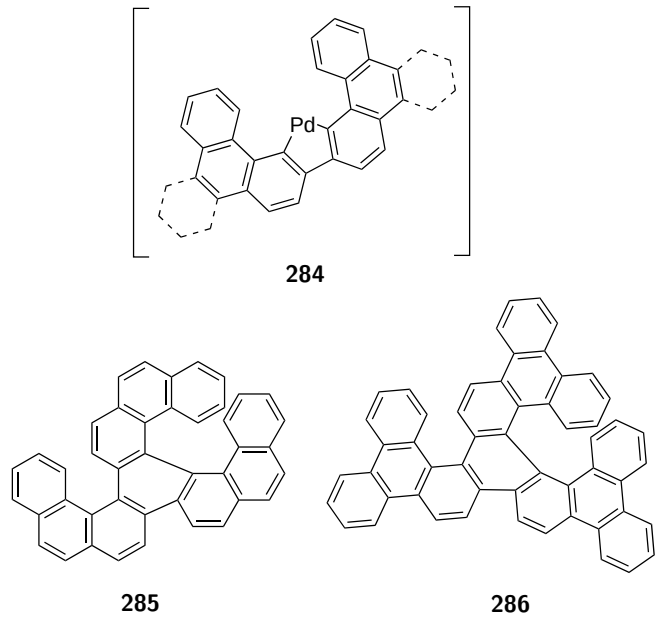


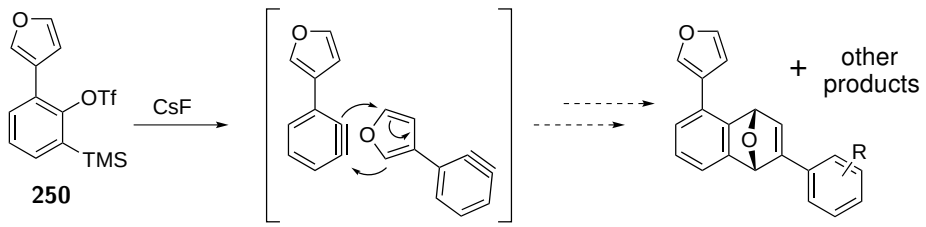
Fig. 3.11 Triphenylenes synthesised by Pẽna *et al.*[216,84]

Nevertheless it is believed that a range of symmetric triphenylenes would be attainable more generally, when functionality on the terminal rings facilitates isolation. Oxidative cyclodehydrogenation of **283** with, for example, $FeCl_3$ should result in a formally C_3 symmetric tribenzocoronene, as has been demonstrated with triaryl triphenylenes previously,[217] and might provide a useful extension.

3.6 Further attempts and leads

3.6.1 Benzyne–furan reactions

With the furan functionalised aryne precursor in hand, the well known [4+2] reaction of benzyne and furan was addressed in an intramolecular manner. Simply stirring **250** in acetonitrile (0.1 M) overnight with caesium fluoride led to a brown solid that was fully soluble in $CDCl_3$ but gave only broad peaks by ^1H NMR. This is assumed to be a mixture of oligomeric products with a varying number of cycloadduct units, but mass spectrometry experiments did not aid characterisation and further investigations were not pursued. Since this aryne precursor is easily synthesised in high yield, however, additional study may be worthwhile. In particular, varying concentrations and aryne generation rates may give different results.



Scheme 3.22 Aryne formation from **250** in the absence of additional reactants.

3.6.2 Further reactions on the 2′-ring

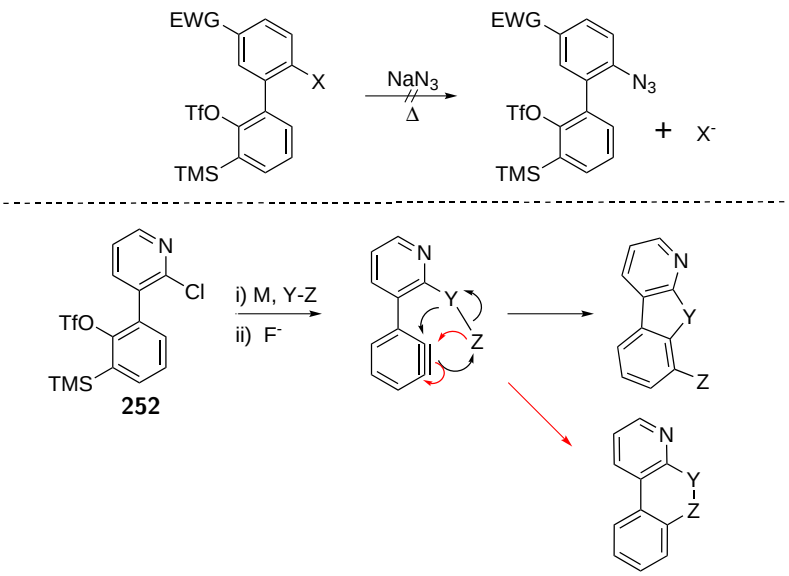
The ability to incorporate leaving groups at the 2′-position of a biphenyl aryne raises the possibility of further functionalisation that would be well placed to interact with a subsequently generated aryne bond. Chloride and fluoride substituents, which can be easily introduced at this site, may undergo S_NAr displacement on electron-poor rings. If the displaced group were fluoride, autogeneration of the aryne might also be feasible without the requirement for an external fluoride source.

Initial attempts were undertaken with the trifluoromethyl-containing aryne precursors, **233** and **239**, (Scheme 3.23, top; EWG = CF_3, X = Cl or F). 3 eq. of sodium azide in acetonitrile or in acetone/water at 70 °C failed to give any new products and the starting materials were recovered untouched. Smith has shown that 2-(trimethylsilyl)phenyl triflates may withstand Grignard reagents or metal azides under more forcing conditions (in DMF with 18-crown-6)[98] and these may be applicable here. Furthermore, a 2′-halo-5′-nitro-biphenyl such as **256** should be more amenable to S_NAr reactivity although no reaction was attempted on this substrate.

Alternatively, bond-forming reactions at an activated halide such as **252** might be more readily facilitated by a transition metal (Scheme 3.23, bottom). If a difunctionalised nucleophile were introduced in this way then tricyclic scaffolds could be easily accessed by aryne insertion reactions or arylation, on the introduction of a fluoride source.

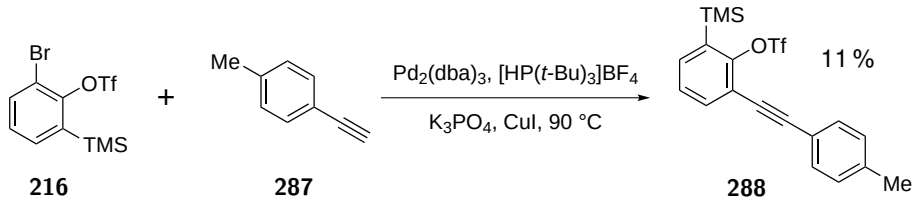
3.6.3 Sonogashira coupling

In the Sonogashira coupling a copper acetylide, generated *in situ* from a second catalytic cycle, takes the place of the organometallic species.[218] An attempt was made to apply the general cross-coupling procedure to the functionalisation of **216** using *para*-methyl phenylacetylene (**287**) as the nucleophilic component. The only modification was the addition of 10 mol % copper(I) iodide.



Scheme 3.23 S_NAr attempts on electron deficient arenes.

However, just 11 % of the *ortho*-ethynyl functionalised product **288** could be recovered under the conditions previously optimised for Suzuki coupling, with some minor consumption of the acetylene starting material through homocoupling also evident (Scheme 3.26). No improvement could be found when the reaction was conducted under anhydrous conditions or with an amine base (triethylamine or *N*,*N*-diisopropylethylamine) as are often employed in Sonogashira couplings,[218b] and further attempts at optimisation were not pursued.



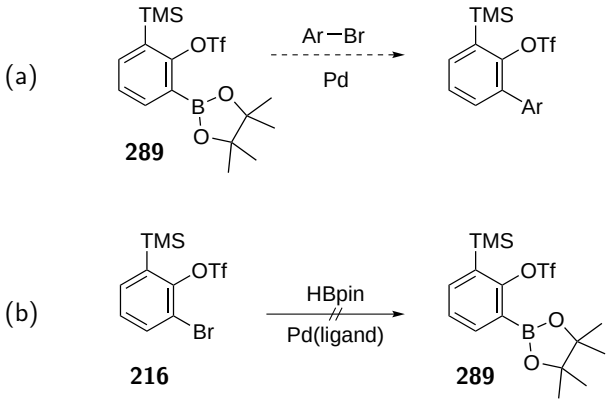
Scheme 3.24 Sonogashira coupling of aryne precursor **216** conducted under standard conditions with 10 mol % CuI.

3.6.4 Boryl-substituted aryne precursors

Given the success of Suzuki coupling on bromo-aryne precursor **216**, it would be interesting to subject a boryl-containing analogue such as **289** to the same optimised conditions but with an arylbromide coupling partner (Scheme 3.25, (a)). If successful this would permit biphenyl aryne precursor synthesis from a wider range of substrates, perhaps even with **216**.

Conversion of the *ortho*-bromo substrate **216** to a boronic pinacol ester by palladium catalysed Masuda borylation[219] would be an efficient route to *ortho*-boryl-functionalised Kobayashi-type aryne precursors. A brief investigation of conditions typical for the reaction of aryl halides with pinacolborane (Pd/SPhos or Pd/dppf with triethylamine in dioxane) did not, however, result in the desired product (**289**), with only starting material being recovered (Scheme 3.25, (b)).

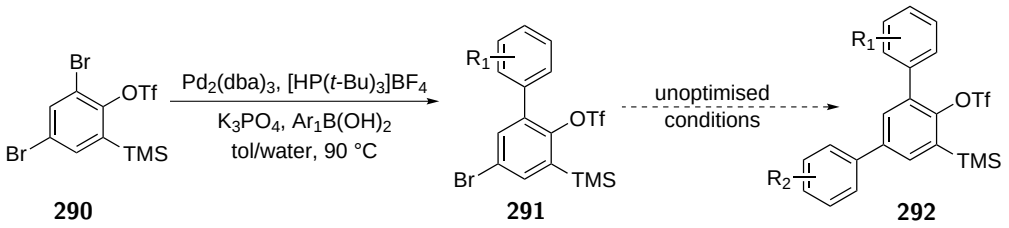
289 has since been prepared, albeit over several steps from the iodophenol.[71] Given the arduous preparation of these borylaryne precursors and the recent progress in Miyaura borylation[220] with hindered substrates,[221] it may also be of interest to reinvestigate a more direct preparation with $B_2(pin)_2$.



Scheme 3.25 Boron-substituted aryne precursors: a) Proposed alternative cross-coupling b) attempted Masuda borylation of **216**.

3.6.5 More highly functionalised aryne precursors

Early in this project it was noted that no reaction occurred at the 2-bromo site of the *ortho*-(trimethylsilyl)phenyl triflate **216** under conditions suitable for the 4-bromo analogue **220**. It may therefore be possible to exploit these apparently orthogonal reactivities in a sequential functionalisation of the known substrate **290** (Scheme 3.26). The 2-aryl-4-bromo aryne precursor **291** should be readily accessible assuming the 4-bromo site remains inert under the typical reaction conditions. Further optimisation would presumably be necessary to achieve the second arylation step in acceptable yield.



Scheme 3.26 Potential elaboration of dibromo(trimethylsilyl)phenyl triflate by sequential coupling reactions.

3.6.6 Conclusions

Palladium catalysed cross-coupling methodology has been developed to selectively arylate bromo(trimethylsilyl)phenyl triflates with boronic acids. Thus 3-aryl-2-(trimethylsilyl)phenyl triflates may be easily prepared in high yields *via* a simple 1-step protocol from a single precursor. The reaction is quite general and electron deficient species may be introduced using boronic acid pinacol esters. *ortho*-Substituents are tolerated, although those with strongly coordinating groups remain problematic. Potassium trifluoroborate salts could also be used as substrates.

Fluoride induced elimination of the labile groups results in *ortho*-biphenyl arynes and these reactive intermediates have been utilised in a number of further reactions. The methodology facilitates new routes to several heterocycles and a novel type of 1,5,9-triaryl triphenylene has also been obtained.

With the expanding availability of boronic acids and other boron species, many new aryne precursors could be produced in this way. A wide range of functionalities may now easily be incorporated allowing previously challenging aryne reactions to be envisaged, and it is expected that this methodology will be useful for organic materials and heterocycle syntheses. Further work to investigate intramolecular aryne chemistry is ongoing in the Greaney group.

Chapter 4

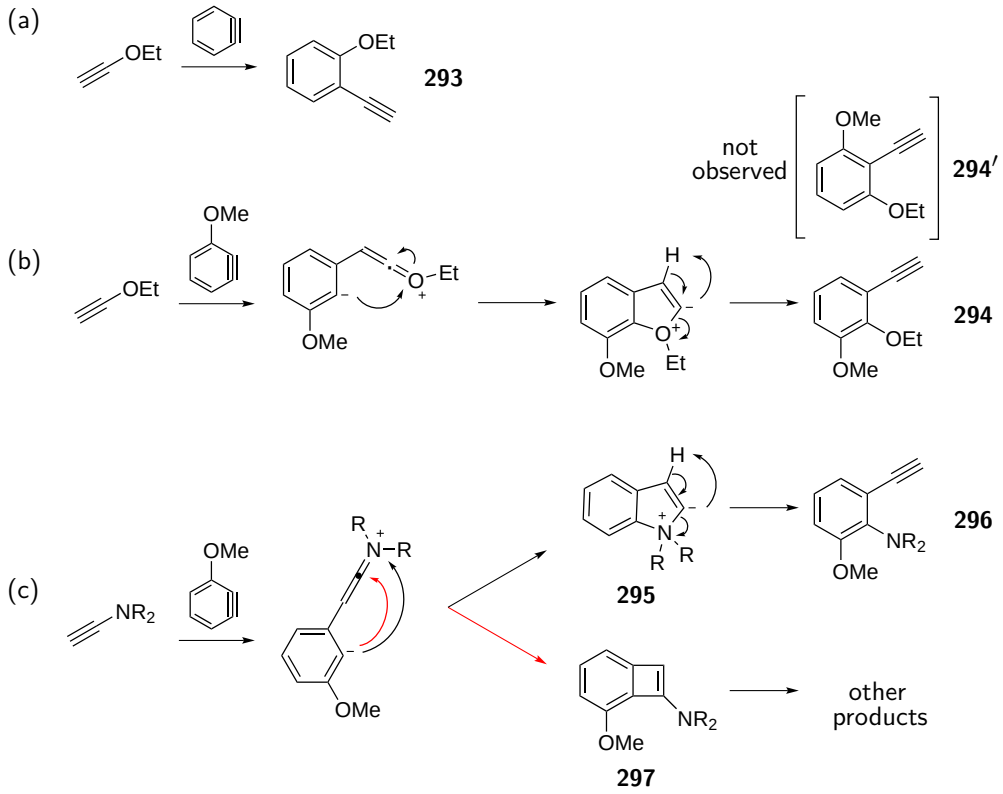
Benzyne σ-Insertions

4.1 Introduction

In 1962 Stiles and co-workers observed that the reaction of ethoxyacetylene and benzyne, generated from benzenediazonium-2-carboxylate, led to the insertion product **293** (Scheme 4.1, (a)).[222] More recently Łązkowski, Peña and co-workers expanded the scope of this reaction to several other substituted arynes using *ortho*-(trimethylsilyl)phenyl triflates as aryne precursors.[223] In the course of this work they discovered that with *ortho*-methoxy benzyne the reaction gave the 2,3-dialkoxyphenyl acetylene product **294**. This displayed a regioselectivity opposite to that predicted if ethoxyacetylene were nucleophilic at oxygen (as proposed by Hoffmann[10]). The 1,3-relationship between the *meta*-directing methoxy group and the acetylene in **294**, and not the ethoxy species, favoured a revised mechanism in which attack first occurs from the ethoxyacetylene carbon (Scheme 4.1, (b)). This was corroborated by computational studies.

Aryne σ-insertions are a useful route to *ortho*-difunctionalisation and there are many examples involving C(sp^2)–heteroatom or C(sp^2)–C bonds. The insertion of arynes at an sp-hybridised carbon, however, remains relatively under explored (see Section 1.2.2). This project aimed to investigate and expand the scope of such reactions. In particular, if a C(sp)–N species were to react with 3-methoxybenzyne in similar fashion to ethoxyacetylene then it would grant straightforward access to 2-amino-3-ethynyl anisoles (**296**), which would be difficult to obtain directly by other means.

The insertion of an aryne into a C–N bond typically proceeds by nucleophilic attack from the heteroatom followed by cyclisation into an electrophilic, often carbonyl carbon.



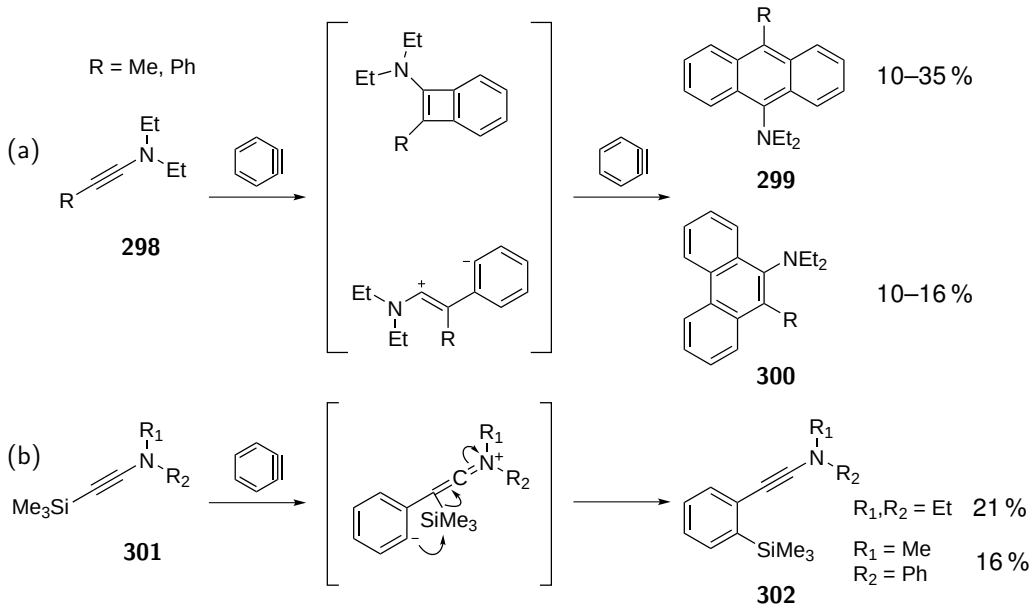
Scheme 4.1 Insertion of benzyne into C–X bonds: a) Stiles *et al.*,[222] b) Łązkowski *et al.*,[223] c) anticipated C–N insertion.

However protected enamines, like vinyl ethers, add to benzyne at carbon and both may then cyclise to give benzocylobutenes.[27,224] Other examples of *C*-arylation with enamines and anilines also exist.[225,226]

It seemed reasonable, therefore, that a tertiary amine with an acetylene in place of a vinyl group should attack arynes though the β-carbon in an analogous manner to ethoxyacetylene. After initial C–C bond formation, two modes of rearrangement are available (Scheme 4.1, (c)). 4-*Exo* cyclisation, which is known for enamines, must be less favourable for the strained, antiaromatic benzocyclobutadiene intermediate **297**. Alternatively, 5-*endo* cyclisation onto nitrogen leading to **295** also becomes possible (the analogous unstabilised enamine-derived zwitterion would be implausible). Neither route gives stable products; the former must undergo dimerisation or other further reactions while the latter may rearrange to give the desired product, **296**.

Indeed at least two examples of ynamine benzyne reactions have been reported. In 1968 Ficini and Krief found that *N*,*N*-diethylynamines bearing a 2-methyl or 2-phenyl group

react with two equivalents of benzyne (generated from *ortho*-bromo-fluorobenzene and magnesium) to give multiple products. The reaction is assumed to proceed *via* the benzocyclobutadiene and a series of further rearrangements and is generally low yielding (Scheme 4.2, (a)).[227] Later, Sato and co-workers discovered that a similar reaction of 2-(trimethylsilyl)ynamines and benzyne resulted in a net C–Si insertion, attributed to a 1,3-silyl shift from the initially formed zwitterionic intermediate (Scheme 4.2, (b)).[228] In neither of these examples was cyclisation onto the ynamine nitrogen reported.



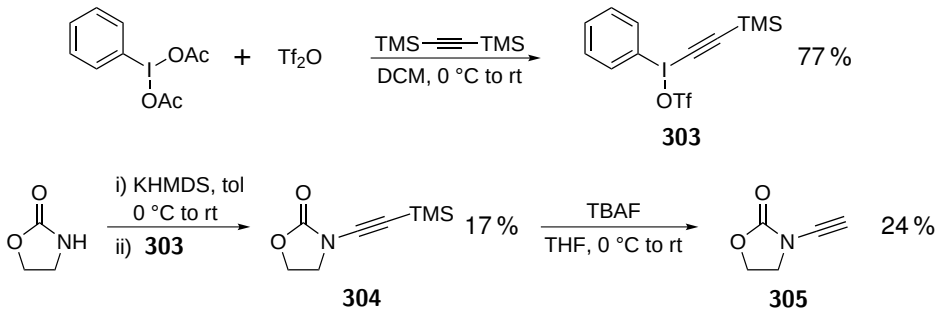
Scheme 4.2 Reactions of ynamines with benzyne: a) Ficini,[227] b) Sato.[228]

Unlike ynamines, the more electron-poor ynamides are relatively stable and their study and use in synthesis has increased significantly in recent years.[229,230] Improved preparations of the reagents are also continuing to be developed. Ynamides remain nucleophilic at the β-carbon and can react *via* keteniminium cations in the presence of a strong acid or other powerful electrophiles. As such, they were considered appropriate substrates to initiate the study of aryne C(sp)–N insertion reactions with benzyne.

4.2 Aryne ynamide insertions

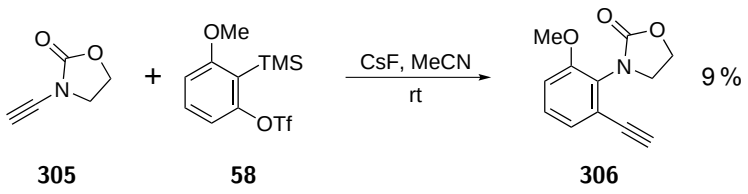
4.2.1 Insertions with oxazolidinone–acetylene

Investigations began with *N*-ethynyloxazolidinone (**305**), which was prepared by the transfer of an ethynyl(trimethylsilyl) unit onto 2-oxazolidinone using the hypervalent iodine(III) species, phenyl((trimethylsilyl)ethynyl)iodonium triflate (**303**, Scheme 4.4). Subsequent deprotection with TBAF gave a terminal acetylene.



Scheme 4.3 Preparation of terminal ynamide **305**.

Stirring ynamide **305** and the 3-methoxy benzyne precursor **58** in acetonitrile with caesium fluoride gave a complex mixture of products from which the anticipated product **306** could be isolated, albeit in only 9 % yield (Scheme 4.4). The regioselectivity of the reaction mirrored that of the ethoxyacetylene insertion, being confirmed by two-dimensional NMR experiments and X-ray crystallography (Fig. 4.1). No evidence for the alternative regioisomer was found. The starting material (26 %) was also recovered although other components of the reaction product mixture were not identified.

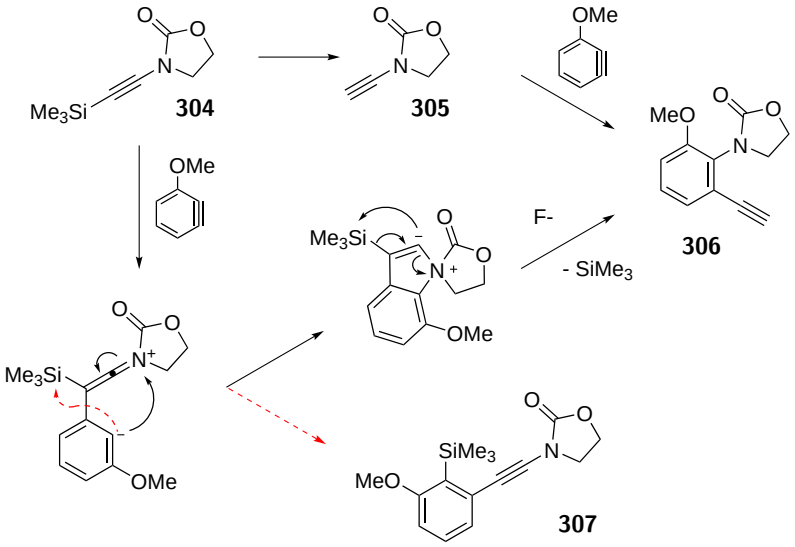


Scheme 4.4 Insertion of 3-methoxybenzyne into a terminal oxazolidinone ynamide. Conditions: **305** (0.175 mmol), **58** (1 eq.) in MeCN (0.5 M) with CsF (2.5 eq.), rt, 16 h.

Since the 2-(trimethylsilyl)ynamide **304** was also available from the preparation of **305**, this protected form of the substrate could be used directly (Scheme 4.5). Subjecting it to identical conditions gave the same insertion product (**306**) in a slightly higher 16 % yield. It is not clear whether desilylation occurs first to form **305** *in situ* or if the

(trimethylsilyl)ynamide itself attacks the aryne, with the silyl group being lost at a later stage. The similar reaction of Sato gives a precedent for the latter and indicates that a TMS group is no impediment to the nucleophilic action of an ynamine. However the side product **307**, which might also be expected from this pathway, was not detected. The protected ynamide starting material may be less susceptible to hydration or other breakdown pathways than a terminal ynamide.

Although these initial results did confirm that the net insertion of benzyne into a nitrogen–acetylene bond was feasible and that it occurred with the desired regioselectivity, it was felt that the complexity of reaction mixture, the challenging isolation of **306** and the low overall yield were significant impediments to further optimisation with **304** or **305**.



Scheme 4.5 *Insitu* desilylation-insertion product.

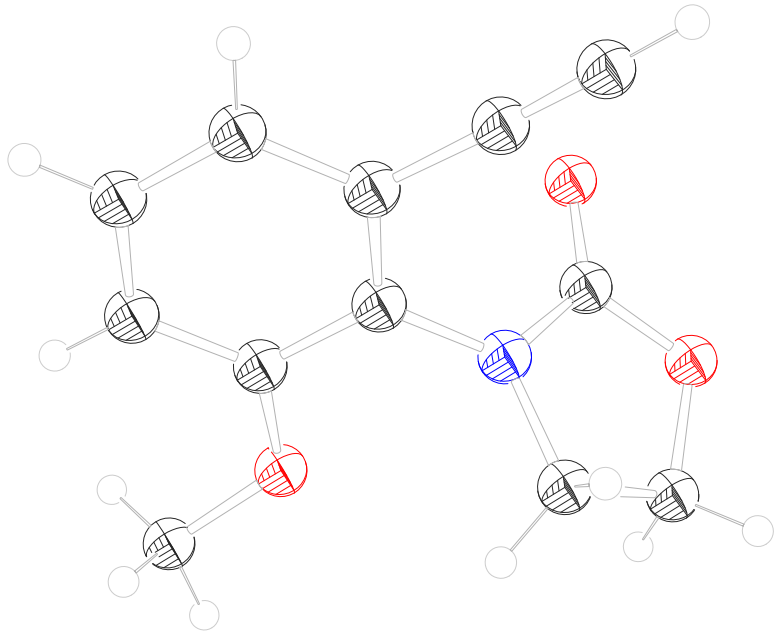
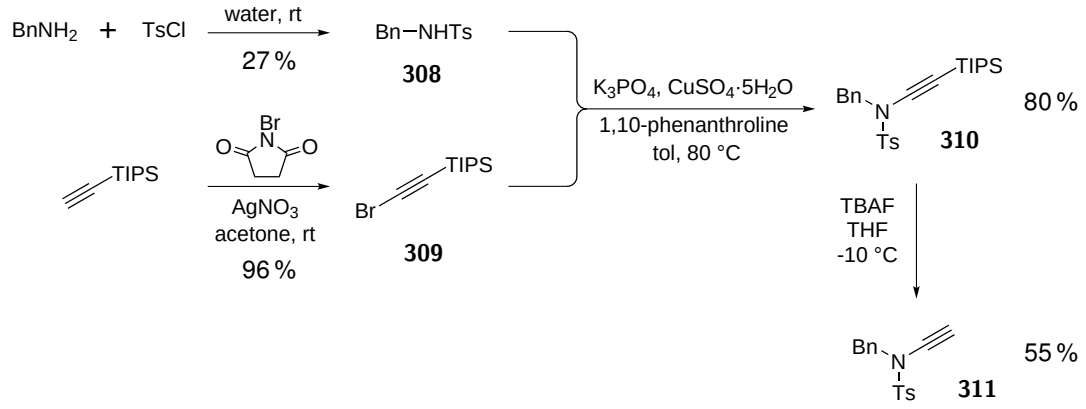


Fig. 4.1 The molecular structure of **306** with displacement ellipsoids at the 50 % probability level.

4.2.2 Insertions with *N*-ethynyl sulfonamides

Given the potential for aryne reactions at amide derived functionality and the known insertion pathways for oxazolidinones,[148] it was thought this heterocyclic based substrate might be in part responsible for the low yielding C(sp)–insertion. Having had success with tosyl protecting groups in aryne syntheses (Chapter 2) these were considered as an alternative. Like amide-containing ynamides, *N*-ethynyl sulfonamides have improved stability over ynamines, and are often crystalline solids. They also have increased nucleophilicity at the β-carbon relative to more conjugated amides.[231] With this in mind, *N*-tosyl ynamide **311** was prepared and the benzyl group chosen as a third *N*-substituent to provide orthogonal protection to the amine (Scheme 4.6).

Initial attempts to insert benzyne from **4** by subjecting *N*-tosyl ynamide **311** to conditions similar to those used with **305** were encouraging. The apparently much simpler reaction mixture had a significant component corresponding to the mass of a single arylation event, with other peaks being less evident by HPLC than for earlier substrates. After isolation a new acetylene terminal ^{1}H peak was seen, confirming



Scheme 4.6 Preparation of terminal ynamide **311**.

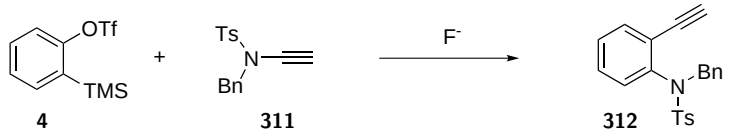
that the major product was not the result of simple arylation at this position. Furthermore the spectra, when recorded in deuterated benzene, was indicative of an *ortho*-difunctionalised ring system consistent with **312**.

The hydrolysis product **313** could also be obtained in 20 % yield, raising concerns that **311** might be unstable under the reaction conditions. However, an acid catalysed pathway (Scheme 4.7, top) would be unlikely in the presence of caesium fluoride and other keteniminium derived products such as **316** were not detected. Hydrolysis could be induced by the addition of zinc chloride, which gave substantially elevated levels of **313** and inhibited the formation of **312** to a large extent. In the absence of the Lewis acid and under anhydrous conditions, little of this side product could be detected in the crude reaction mixture by NMR.

A brief screen of aryne generating conditions was next conducted and is shown in Table 4.1. Conversion of the starting material was poor at room temperature with only 6 % (NMR yield) of product formed in acetonitrile. Changing the solvent to THF and using potassium fluoride/18-crown-6 to generate benzyne gave an improved yield of 25 % but side products became more apparent. Running the reaction at higher temperature under a variety of conditions gave consistently increased amounts of **312**. The cleanest conversion was observed in 3 : 1 toluene/acetonitrile with caesium fluoride, which allowed isolation of the product in 40 % yield.

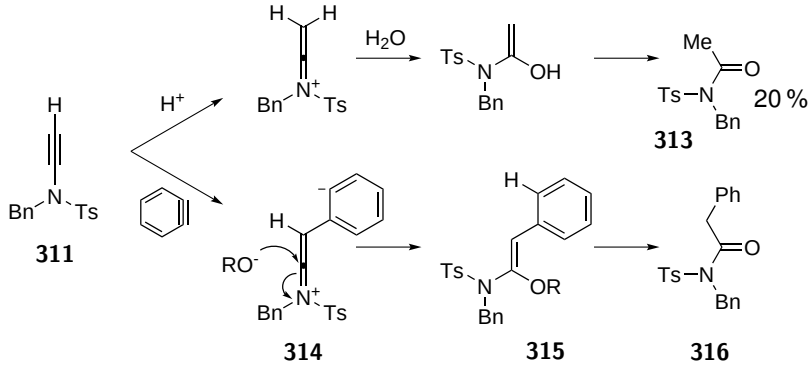
While only moderate, the yields of **312** achieved here are comparable to those obtained by Stiles (37 %) and Łązkowski *et al.* (51 %) for the analogous C–O insertions. The reaction of 3-methoxybenzyne with **311** would provide the 1,2,3-trifunctionalised sulfonamide analogue of **306**.

Table 4.1 Conditions for C–N insertion with **311** [a]



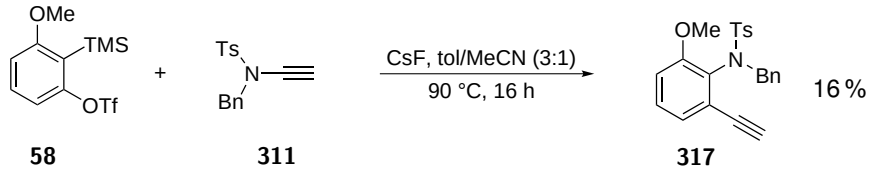
No.	Fluoride Source	Solvent	Temp (°C)	Time	Yield (%)[b]
1	CsF	MeCN	rt	16 h	6
2	KF/18-C-6	THF	rt	5 h	25
3	CsF	MeCN/Tol	90	16 h	40[c]
4	TBAT	Tol	120	10 min[d]	42
5	CsF	MeCN	90	5 h	43

[a] Conditions: **311** (0.100 mmol) and **4** (1.5 eq.) in solvent (0.1 M) with fluoride source (3 eq.). [b] NMR yield. [c] Isolated yield. [d] Microwave heating.



Scheme 4.7 Hydrolysis of ynamide **311**

However, when using **58** in place of **4** under the optimised conditions the reaction progressed only to a limited extent, with starting materials being the major components of the crude reaction mixture after heating overnight (56 % of limiting reagent **311** remained). Only 15 % of the presumed insertion product **317** (Scheme 4.8) was observed (NMR yield) with which by-product formation became competitive. The methoxy group may limit C–N bond formation at its *ortho*-position on steric grounds and is presumably a greater obstacle when using **311** than with the smaller oxazolidinone group.



Scheme 4.8 Tosylynamide with 3-methoxybenzyne

4.3 Conclusions and further work

Ynamide addition to arynes has been demonstrated for the first time. The reaction proceeds *via* nucleophilic attack from the terminal β-carbon followed by rearrangement to give a C(sp)–N insertion product. When an *N*-tosylynamide is employed the reaction proceeds in reasonable yield with benzyne. A 3-methoxy substituent on the aryne resulted in lower conversion. Although trifunctionalised arenes with a 1-oxy-2-amino--3-acetyl relationship could not be prepared effectively, further optimisation of this reaction should be possible. In particular, the careful choice of an ynamide that is both sufficiently nucleophilic and sufficiently stable to undergo arylation but that does not present steric or electronic impediments to rearrangement may allow a useful insertion reaction to be developed.

Replacement of the benzyl group in **311** with a methyl (**318**, Fig. 4.2) would be a straightforward means to reduced hindrance at the nitrogen while cyclic *N*-sulfonylynamide such as **319** might also be of interest. More speculatively, ynimines based on **320** (TMS-**320** is known[232]) may be capable of a similar aryne insertion reaction and lack the second *N*-substituent of ynamides or ynamines.

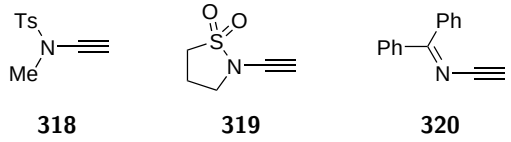
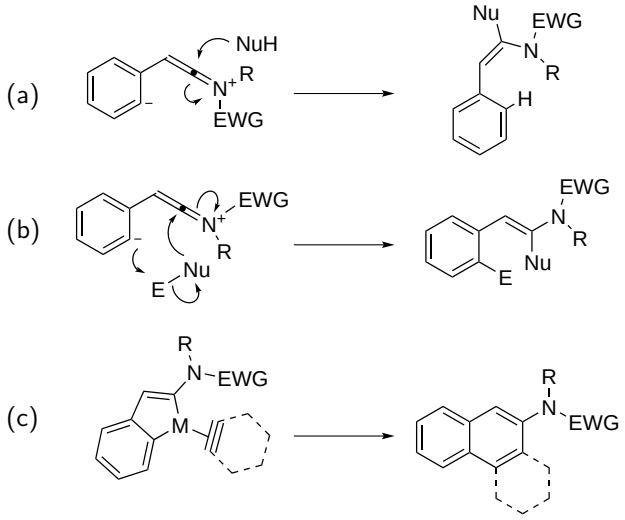


Fig. 4.2 Possible substrates for further aryne–ynamide insertion reactions.

There has been a recent surge of interest in ynamide chemistry. These reagents undergo a wide range of transformations including cycloadditions and reactions with electrophiles at either site while being compatible with transition-metal-catalysed processes. In some ways their initial nucleophilicity is complementary to that of electrophilic arynes with both species capable of a second bond forming process from a zwitterionic intermediate.

Since ynamides are activated towards nucleophiles by strong electrophiles then arynes may serve this role (Scheme 4.9, (a)). Ynamides may also be able to participate as the nucleophile in aryne three component reactions (Scheme 4.9, (b)) or in transition-metal-mediated [2+2+2] chemistry (c). Such reactions might be useful alternatives to C–N insertion, which is slow at low temperature, particularly with hindered substrates.



Scheme 4.9 Further pathways for aryne-ynamide reactivity.

Chapter 5

Conclusions

The previous chapters describe studies that advance the chemistry and availability of arynes derived from 2-(trimethylsilyl)phenyl triflates. Methodology for the arylation of tosylhydrazones has been developed and the resulting *N*-aryl-*N*-tosyl hydrazones serve as intermediates in a Fischer indole reaction. Thus *N*-tosyl indoles may be prepared in a one-pot protocol from accessible starting materials. In the course of this work, a novel reaction between benzyne and an *N*-*tert*-butoxycarbonyl-protected hydrazone was also discovered, which may be of interest in future heterocycle synthesis.

It has been found that both *N*-ethynyl oxazolidinone and an *N*-tosyl ynamide undergo a C(sp)–N bond insertion reaction with arynes. Although the yields of such reactions are at present only moderate, scope exists for further optimisation with alternative ynamides and the route permits the aryne-mediated synthesis of *ortho*-ethynyl anilines.

These projects and many other recent developments in aryne methodology have been enabled by Kobayashi-type aryne precursors, which allow the generation of arynes under easily controlled and mild conditions. Work aimed at expanding the availability of these reagents has therefore also been undertaken.

It was shown that the Suzuki reaction may be performed chemoselectively at the bromine substituent of 2-bromo-6-(trimethylsilyl)phenyl triflate, leaving the key triflate and trimethylsilyl functionalities untouched. This method allows *ortho*-biphenyl aryne precursors incorporating a wide range of functionality to be prepared.

Several reactions that utilise biphenyl arynes derived from this procedure have been demonstrated and further development of these initial findings will allow the preparation of diverse products including *ortho*-substituted fluorenones or symmetric

triphenylenes. The increased accessibility of aryne precursors with otherwise unavailable substituents should allow further new aryne-based methodology to be developed in addition to expanding the scope of existing aryne chemistry.

Chapter 6

Experimental

^{1}H NMR spectra were recorded on a 300, 400 or 500 MHz instrument and ^{13}C spectra recorded at 75, 101 or 126 MHz and calibrated to residual solvent peaks as the internal standard; proton signals in $CDCl_3$ 7.26 ppm, DMSO-d_6 2.50 ppm and C_6D_6 7.16 ppm and carbon signals in $CDCl_3$ 77.16 ppm, DMSO-d_6 39.52 ppm. ^{19}F NMR spectra were recorded at 377 MHz or 471 MHz and ^{11}B spectra at 160 MHz and are referenced to an external standard. The ^{1}H data are presented as follows: chemical shift (in ppm on the δ scale) or chemical shift range for a multiplet, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and app. indicating apparent multiplicity), the coupling constant (J, in Hz) and integration. The assignment of components in a mixture of isomers is reported where possible, with integrations given as proportion of the sample. The ^{13}C, ^{19}F and ^{11}B data are reported as the ppm on the δ scale with multiplicity from non-decoupled nuclei noted where appropriate for the ^{13}C spectra. High resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, or by the University of Manchester School of Chemistry Mass Spectrometry Service. The data are recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on silica 60 F_{254} glass or aluminium backed plates and visualised by UV light and/or anisaldehyde, vanillin, ninhydrin or potassium permanganate stains. Flash column chromatography was performed using a wet silica slurry (particle size 35–70 µm or 40–63 µm) or on pre-packed disposable silica columns (particle size 40–60 µm) under a positive pressure. Melting points were obtained on a Griffin or Gallenkamp melting point apparatus. Acetonitrile was dried before use (alumina column) or purchased as such and stored under nitrogen. All reagents were purchased from chemical suppliers and used as received unless otherwise noted.

6.1 The benzyne Fischer indole reaction

6.1.1 Hydrazone precursor syntheses

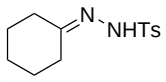
General procedure for hydrazone synthesis A

The *N*-protected hydrazine (1 eq.) and ketone (1.1 eq.) were dissolved in ethanol (0.3 M) with a few drops of cat. acetic acid and the mixture heated at reflux for 1 h. After cooling, the crude material was collected by filtration, being washed with cold diethyl ether, recrystallised once from hot ethanol (unless otherwise stated) and dried *in vacuo*.

General procedure for hydrazone synthesis B

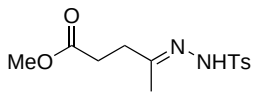
The *N*-protected hydrazine (1 eq.) and ketone (1.1 eq.) were dissolved in ethanol (0.3 M) and the mixture heated at reflux for 1 h. After cooling, the crude material was collected by filtration, being washed with cold diethyl ether, recrystallised from hot ethanol and dried *in vacuo*.

N′-Cyclohexylidene-4-methylbenzenesulfonohydrazide, 139



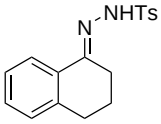
Prepared according to general procedure A but with three rounds of recrystallisation. Isolated 3.9 g (12 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H), 7.73–7.70 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H), 2.30–2.21 (m, 2H), 2.11–2.02 (m, 2H), 1.48–1.55 (br s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 143.0, 136.5, 129.4, 127.5, 34.7, 27.4, 26.7, 25.5, 24.9, 21.0.[233]

(*E*)-Methyl-4-(2-tosylhydrazono)pentanoate, 145



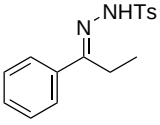
Prepared according to general procedure A. Isolated 3.32 g (87 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.74–7.70 (m, 2H), 7.43–7.37 (m, 2H), 3.49 (s, 3H), 2.38 (s, 3H), 2.43–2.34 (m, 4H), 1.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5, 157.1, 143.0, 136.2, 129.2, 127.5, 51.2, 32.5, 29.2, 21.0, 17.0.

(*E*)-*N*′-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-4-methylbenzenesulfonohydrazide, 147



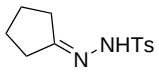
Prepared according to general procedure B. Isolated 2.60 g (79 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.77 (dd, J = 7.8, 0.7 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.25 (app. td, J = 7.4, 1.3 Hz, 1H), 7.21–7.08 (m, 2H), 2.72–2.61 (m, 2H), 2.54 (t, J = 6.6 Hz, 2H), 2.36 (s, 3H), 1.81–1.68 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 152.8, 143.3, 139.8, 136.3, 131.6, 129.4, 129.3, 128.6, 127.6, 126.2, 124.0, 28.7, 25.9, 21.2, 21.0.[234]

(*E*)-4-Methyl-*N*′-(1-phenylpropylidene)benzenesulfonohydrazide, 149



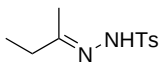
Prepared according to general procedure A. Isolated 2.11 g (84 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.64 (s, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.65–7.52 (m, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.38–7.27 (m, 3H), 2.69 (q, J = 7.6 Hz, 2H), 2.36 (s, 3H), 0.97 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 156.2, 142.3, 135.3, 135.2, 128.5, 128.3, 127.4, 126.5, 125.1, 20.0, 18.9, 9.4.[234]

N′-Cyclopentylidene-4-methylbenzenesulfonohydrazide, 151



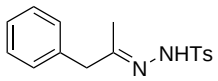
Prepared according to general procedure A but without recrystallisation. Isolated 1.66 g (60 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.95 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 2.39 (s, 3H), 2.23 (t, J = 7.4 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 1.70 (app. p, J = 7.1 Hz, 2H) , 1.66–1.58 (m, 2H).[235]

(*E*)-*N*′-(Butan-2-ylidene)-4-methylbenzenesulfonohydrazide, 153



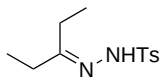
Prepared according to general procedure B. Isolated 1.36 g (47 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.90 (s, 1H), 7.75 (s, J = 8.2 Hz, 2H) , 7.38 (d, J = 8.2 Hz, 2H), 2.37 (s, 3H), 2.10 (d, J = 7.4 Hz, 2H), 1.76 (s, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 159.9, 143.0, 136.3, 129.2, 127.6, 31.1, 21.0, 16.3, 10.3.[236]

(*E*)-4-Methyl-*N*′-(1-phenylpropan-2-ylidene)benzenesulfonohydrazide, 155



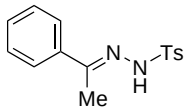
Prepared according to general procedure A. Isolated 0.481 g (55 %) as a pale yellow crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.03 (s, 1H), 7.75–7.69 (m, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.25–7.14 (m, 3H), 7.00–6.95 (m, 2H), 3.38 (s, 2H), 2.41 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 157.5, 143.1, 136.9, 136.3, 129.3, 128.8, 128.3, 127.6, 126.5, 44.2, 21.0, 16.0.[237]

4-Methyl-*N*′-(pentan-3-ylidene)benzenesulfonohydrazide, 157



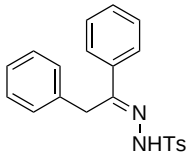
Prepared according to general procedure A. Isolated 1.80 g (25 %) as a white crystalline solid ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.95 (s, 1H), 7.77–7.68 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H), 2.19 (q, J = 7.6 Hz, 2H), 2.12 (q, J = 7.3 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 163.6, 143.0, 136.3, 129.2, 127.5, 28.3, 22.6, 21.0, 10.3, 9.4.[238]

(*E*)-4-Methyl-*N*′-(1-phenylethylidene)benzenesulfonohydrazide, 159



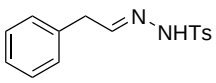
Prepared according to general procedure B. Isolated 1.11 g (37 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.50 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.65–7.58 (m, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.39–7.34 (m, 3H), 2.36 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 153.1, 143.3, 137.4, 136.2, 129.5, 129.4, 128.4, 127.6, 125.9, 21.0, 14.3.[239]

(*E*)-*N*′-(1,2-Diphenylethylidene)-4-methylbenzenesulfonohydrazide, 162



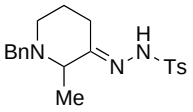
Prepared according to general procedure A. Isolated 2.53 g (61 %) as a pale yellow crystalline solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.97 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.64–7.60 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.34–7.27 (m, 3H), 7.22 (app. t, J = 7.4 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 7.1 Hz, 2H), 4.16 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 153.1, 143.5, 136.6, 136.2, 135.9, 129.6, 129.3, 128.5, 128.4, 128.1, 127.5, 126.4, 126.3, 32.2, 21.0.[240]

(*E*)-4-Methyl-*N*′-(2-phenylethylidene)benzenesulfonohydrazide, 185



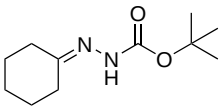
Prepared according to general procedure B. Isolated 1.39 g (23 %) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.72–7.62 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 5.8 Hz, 1H), 7.27–7.18 (m, 3H), 7.05–6.94 (m, 2H), 3.41 (d, J = 5.8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.1, 143.3, 136.3, 136.1, 129.6, 128.7, 128.5, 127.3, 126.6, 38.0, 21.0.[241]

(*E*)-*N*′-(1-Benzyl-2-methylpiperidin-3-ylidene)-4-methylbenzenesulfonohydrazide, 187



Isolated 0.64 g (41 %) as a brown crystalline solid. Synthesised according to general procedure A but with recrystallisation from EtOH/Et_2O. The parent ketone was prepared according to the protocol of Zhao *et al.*[242] ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.30–7.18 (m, 3H), 7.15 (d, J = 7.0 Hz, 2H), 3.46, 3.50 (ABq, J_{AB} = 13.6 Hz, 2H), 3.15 (q, J = 6.8 Hz, 1H), 2.81–2.68 (m, 1H), 2.55–2.52 (m, 1H), 2.42 (dt, J = 12.4, 4.2 Hz, 1H), 2.38 (s, 3H), 2.24–2.14 (m, 1H), 1.64–1.49 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.9, 143.0, 139.0, 136.3, 129.3, 128.4, 128.1, 127.5, 126.8, 59.1, 56.5, 45.5, 23.0, 22.8, 21.0, 12.9.

tert-Butyl 2-cyclohexylidenehydrazine-1-carboxylate, 143

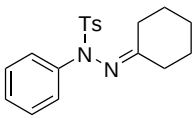


Prepared according to general procedure A. Isolated 3.18 g (71 %) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 2.36–2.32 (m, 2H), 2.22–2.16 (m, 2H), 1.73–1.56 (m, 6H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 153.3, 80.9, 35.6, 28.4, 26.9, 26.2, 25.9, 25.7. IR (thin film, cm^{-1}): 3239 (w), 2937 (w), 1677 (s).[243]

6.1.2 Arylation of protected hydrazones

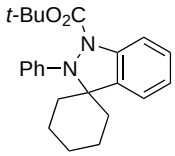
In general *N*-aryl hydrazone intermediates were not isolated as the crude reaction mixture could undergo Fischer cyclisation in one pot. **140** is given as an example:

N′-Cyclohexylidene-4-methyl-*N*-phenylbenzenesulfonohydrazide, 140



2-(Trimethylsilyl)phenyl triflate (1.5 eq.) and caesium fluoride (3 eq.) were added to *N*-tosyl cyclohexanone hydrazone (**139**, 0.200 mmol, 1 eq.) in acetonitrile (0.1 M) and stirred at rt overnight under nitrogen. The mixture was then quenched with water, extracted twice with diethyl ether, the combined organic layers dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by recrystallisation from hot methanol to give a pale brown crystalline solid, 41 mg (61 %) m.p. 127–130 °C (lit. 130 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 7H), 7.05–6.98 (m, 2H), 2.38 (s, 3H), 2.37–2.29 (m, 4H), 1.68–1.57 (m, 2H), 1.53–1.45 (m, 2H), 1.39–1.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 144.0, 142.8, 131.5, 129.0, 128.9, 128.7, 127.1, 125.2, 35.1, 29.9, 26.8, 25.5, 24.7, 21.1. HRMS (ES^+) cald. for $C_{19}H_{23}N_2O_2S$ $(M+H)^+$: 343.1475, found: 343.1477.[244]

Compound 144, proposed structure: *tert*-Butyl 2′-phenylspiro[cyclohexane-1,3′-indazole]-1′(2′*H*)-carboxylate, 144″



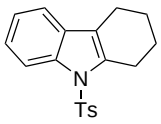
Prepared as with **140** but from Boc-protected hydrazone **143** using 2.4 eq. 2-(trimethylsilyl)phenyl triflate and 6 eq. caesium fluoride and columned with hexane : diethyl ether (15 : 1) to give a colourless oil, 41 mg (50 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (br s, 1H, Ar-H), 7.29 (td, J = 7.8, 1.2 Hz, 1H), 7.22–7.09 (m, 6H), 7.08 (td, J = 7.4, 0.9 Hz, 1H), 2.11–1.34 (br m, 19H). 7.63 peak assignment confirmed with the aid of HSQC spectroscopy. ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5 (C), 147.9 (C), 141.7 (C), 138.7 (C), 128.3, 128.0, 126.7, 126.6, 123.5, 122.3, 114.9, 81.3 (C), 69.9 (C), 28.4 (CH_3), 25.5 (CH_2), 22.3 (CH_2). Assignments made with the aid of DEPT-135 spectroscopy. The 152.5 peak was at the limit of detection. IR (thin film, cm^{-1}): 2930 (w), 1723 (w), 1698 (s), 1598 (w). HRMS (ES^+) cald. for $C_{23}H_{28}N_2NaO_2$ $(M+Na)^+$: 387.2048, found: 387.2050.

6.1.3 *N*-Tosyl indole synthesis

General procedure for the one-pot preparation of *N*-tosyl indoles

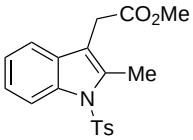
To a mixture of the appropriate *N*-tosyl hydrazone (0.2–0.3 mmol, 1 eq.), (trimethylsilyl)aryl triflate (1.5 eq.) and caesium fluoride (3 eq.), was added dry acetonitrile (0.1 M). The tube was then flushed briefly with nitrogen, sealed and stirred at rt for 12 h. On consumption of starting material, boron trifluoride etherate (2 eq. unless otherwise stated) was added and the mixture heated at 90 °C (external temperature) for 5 h. After cooling, the reaction was quenched with sat. aq. $NaHCO_3$, extracted with ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (dry loading on silica, eluted with hexane/diethyl ether) and dried *in vacuo* to afford the desired product.

9-Tosyl-2,3,4,9-tetrahydro-1*H*-carbazole, 141



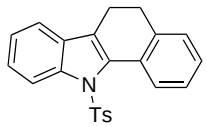
Isolated 30.2 mg (80 %) as a pale yellow crystalline solid, m.p. 116–118 °C (lit. 118.5–119.3 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.11 (m, 1H), 7.70–7.62 (m, 2H), 7.36–7.31 (m, 1H), 7.31–7.14 (m, 4H), 3.02 (tt, J = 6.2, 1.6 Hz, 2H), 2.60 (tt, J = 6.0, 1.9 Hz, 2H), 2.33 (s, 3H), 1.93–1.85 (m, 2H), 1.83–1.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 136.4, 136.4, 135.5, 130.5, 129.9, 126.5, 124.0, 123.3, 118.7, 118.1, 114.5, 24.8, 23.4, 22.2, 21.6, 21.2. HRMS (ES^+) calcd. for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.12093, found: 326.120868.[245]

Methyl 2-(2-methyl-1-tosyl-1*H*-indol-3-yl)acetate, 146



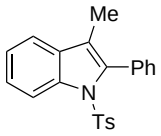
Isolated 58.2 mg (66 %) as a pale yellow crystalline solid, m.p. 96–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 7.4 Hz, 1H), 7.35–7.20 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 3.63 (s, 3H), 3.61 (s, 2H), 2.58 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 144.8, 136.4, 136.3, 134.8, 130.0, 130.0, 126.4, 124.3, 123.6, 118.5, 114.6, 113.3, 52.2, 30.2, 21.6, 13.0. HRMS (ES^+) calcd. for $C_{19}H_{23}N_2O_4S^+$ $(M+NH_4)^+$: 375.13730, found: 375.1377

11-Tosyl-6,11-dihydro-5*H*-benzo[*a*]carbazole, 148



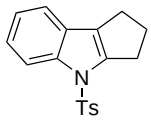
Isolated 38.0 mg (76 %) as a pale brown crystalline solid, m.p. 172–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.39–7.16 (m, 8H), 6.93 (d, J = 8.2 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 2.60 (t, J = 7.4 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 140.4, 137.7, 136.1, 132.3, 131.5, 129.0, 128.8, 128.5, 127.9, 127.4, 127.2, 127.2, 126.4, 125.5, 125.1, 118.8, 118.5, 29.5, 21.6, 20.8. HRMS (ES^+) calcd. for $C_{23}H_{23}N_2O_2S^+$ $(M+NH_4)^+$: 391.1475, found: 391.1465

3-Methyl-2-phenyl-1-tosyl-1*H*-indole, 150



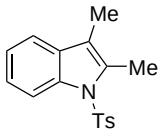
As with the general procedure but with 2 eq. aryne precursor. Isolated 47.6 mg (67 %) as a pale brown crystalline solid, m.p. 152–157 °C (lit. 163–164 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.3 Hz, 1H), 7.49–7.27 (m, 10H), 7.05 (d, J = 8.1 Hz, 2H), 2.30 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 137.3, 136.8, 135.2, 131.9, 131.7, 131.5, 129.3, 128.5, 127.5, 126.9, 125.1, 124.0, 119.9, 119.1, 116.4, 21.7, 9.6. HRMS (ES^+) calcd. for $C_{22}H_{23}N_2O_2S^+$ $(M+NH_4)^+$: 379.1475, found: 379.147413.[246]

4-Tosyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole, 152



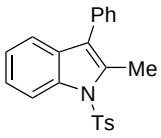
Isolated 46.3 mg (54 %) as a pale brown crystalline solid, m.p. 158–162 °C (lit. 155–157 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.25–7.18 (m, 4H), 3.15 (t, J = 7.2 Hz, 2H), 2.77–2.69 (m, 2H), 2.50 (app. p, J = 7.2 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 143.7, 140.3, 135.9, 129.9, 127.3, 126.6, 126.6, 123.3, 123.2, 119.0, 114.4, 28.1, 27.5, 24.1, 21.6. HRMS (ES^+) calcd. for $C_{18}H_{18}NO_2S^+$ $(M+H)^+$: 312.10528, found 312.1056.[247]

2,3-Dimethyl-1-tosyl-1*H*-indole, 154



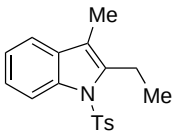
Isolated 56.5 mg (69 %) as a pale brown crystalline solid, m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.38–7.32 (m, 1H), 7.30–7.18 (m, 2H), 7.15 (d, J = 8.1 Hz, 2H), 2.51 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 136.5, 136.4, 132.4, 131.4, 129.9, 126.4, 124.0, 123.3, 118.4, 116.1, 114.6, 21.6, 12.8, 9.0. HRMS (ES^+) calcd. for $C_{17}H_{21}N_2O_2S^+$ $(M+NH_4)^+$: 317.13183, found: 317.131946.

2-Methyl-3-phenyl-1-tosyl-1*H*-indole, 156



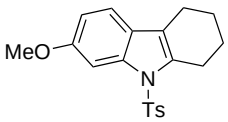
As with the general procedure but with 2 eq. aryne precursor. Isolated 91.6 mg (66 %) as a pale orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.48–7.39 (m, 3H), 7.39–7.33 (m, 3H), 7.31 (ddd, J = 8.4, 7.3, 1.2 Hz, 1H), 7.29–7.18 (m, 3H), 2.61 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 136.4, 136.4, 133.2, 133.1, 130.1, 130.0, 130.0, 128.6, 127.4, 126.5, 124.3, 123.6, 122.6, 119.3, 114.6, 21.6, 13.6. HRMS (ES^+) calcd. for $C_{22}H_{20}NO_2S^+$ $(M+H)^+$: 362.12093, found: 362.1213.[246]

2-Ethyl-3-methyl-1-tosyl-1*H*-indole, 158



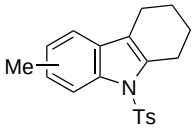
Isolated 26.9 mg (68 %) as a pale orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23–8.10 (m, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.38 (dd, J = 7.5, 0.8 Hz, 1H), 7.30–7.21 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 3.02 (q, J = 7.3 Hz, 2H), 2.31 (s, 3H), 2.15 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 138.9, 136.6, 136.3, 131.6, 129.7, 126.2, 124.0, 123.3, 118.4, 116.1, 115.1, 21.5, 19.8, 15.0, 8.8. HRMS (ES^+) calcd. for $C_{18}H_{20}NO_2S^+$ $(M+H)^+$: 314.12093, found: 314.1212.[248]

7-Methoxy-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazole, 167



The major regioisomer was isolated to give 52.0 mg (61 %) as a pale yellow crystalline solid, m.p. 113–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.23–7.15 (m, 3H), 6.85 (dd, J = 8.5, 2.2 Hz, 1H), 3.88 (s, 3H), 2.96 (tt, J = 6.4, 1.9 Hz, 2H), 2.54 (tt, J = 5.9, 1.7 Hz, 2H), 2.33 (s, 3H), 1.95–1.79 (m, 2H), 1.79–1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 144.5, 137.3, 136.4, 134.1, 129.9, 126.4, 124.4, 118.6, 118.4, 111.8, 99.6, 56.0, 24.8, 23.4, 22.2, 21.7, 21.2. HRMS (ES^+) calcd. for $C_{20}H_{22}NO_3S^+$ $(M+H)^+$: 356.1315, found: 356.1318.

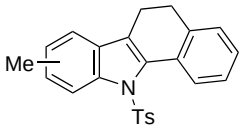
Methyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazole, 168



Isolated 61.0 mg (72 %) as a mixture of three possible regioisomers in a 0.22 : 0.3 : 0.48 ratio, as a pale orange solid. Full assignment of the ^{1}H spectra was aided by NOE experiments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (app. d, J = 8.4 Hz, 0.7H, **168c** and **168b**), 8.01 (s, 0.3H, **168a**), 7.71–7.62 (m, 2H), 7.26–7.17 (m, 2.3H), 7.17–7.04 (m, 1.48H), 6.95 (d, J = 7.3 Hz, 0.22H, **168a**), 3.13–2.95 (m, 2H), 2.90 (tt, J = 6.0, 2.0 Hz, 0.44H, **168a**, CH_2), 2.66–2.55 (m,

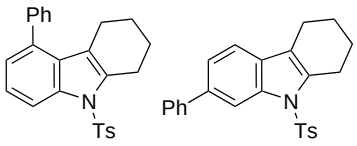
2.22H), 2.51 (s, 1.4 eq. 0.9H, **168b**, CH_3), 2.44 (s, 1.44H, **168c**, CH_3), 2.35–2.36 (3× s, 3H, Ts-H), 1.93–1.74 (m, 4H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 144.4, 144.4, 136.8, 136.6, 136.5, 136.5, 136.4, 135.6, 135.0, 134.7, 134.6, 133.9, 132.9, 130.7, 130.5, 129.8 (three signals), 129.0, 128.2, 126.5, 126.4, 126.4, 125.2, 125.1, 124.6, 123.7, 119.3, 118.6, 118.1, 117.7, 114.8, 114.2, 112.3, 25.1, 24.8, 24.8, 24.5, 23.4 (two signals), 22.9, 22.8, 22.2 (two signals), 22.1, 21.6 (three Me signals), 21.4, 21.2 (two signals), 20.1. The unlisted peak is believed to come at 126.4. HRMS (ES^+) calcd. for $C_{20}H_{22}NO_2S^+$ $(M+H)^+$: 340.1366, found: 340.1370.

Methyl-7-tosyl-6,7-dihydro-5*H*-benzo[*c*]carbazole, 169



Isolated 72.3 mg (73 %) as a mixture of three possible isomers in a 0.18 : 0.33 : 0.48 ratio as a pale orange crystalline solid, m.p. 138–143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 0.48H), 8.11 (d, J = 8.3 Hz, 0.18H), 8.07 (br s, 0.33H, **169b**), 8.03–7.94 (m, 1H), 7.36 (app. t, J = 7.4 Hz, 1H), 7.27–7.13 (m, 5H), 7.09–6.92 (m, 0.81H), 2.87–2.76 (m, 2.34H), 2.58 (app. t, J = 7.4 Hz, 1.62H), 2.52 (s, 0.99H, **169b**, CH_3), 2.46 (s, 0.54H, **169a**, CH_3), 2.39 (s, 1.44H, **169c**, CH_3), 2.25–2.24 (3× s, 3H, Ts-Me). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 144.2, 144.2, 140.8, 140.5, 138.5, 137.7, 137.3, 137.0, 136.1, 135.9, 135.6, 135.4, 134.8, 132.3, 132.2, 131.6, 131.0, 130.1, 129.3, 129.2, 129.1, 129.1, 128.7, 128.6, 128.5, 127.9, 127.7, 127.5, 127.4, 127.4, 127.2, 127.2, 127.2, 127.1, 127.0, 126.9, 126.8, 126.4, 126.3, 126.3, 126.2, 125.1, 118.9, 118.8, 118.4, 118.1, 116.1, 29.8, 29.5, 29.5, 23.4, 22.2, 21.6, 21.4, 20.8, 20.7, 20.1. HRMS (ES^+) calcd. for $C_{24}H_{22}NO_2S^+$ $(M+H)^+$: 388.1366, found: 388.1364.

6- and 7-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole, 170

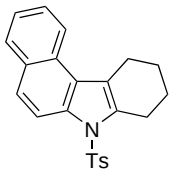


170a **170b**

Isolated 45.5 mg (57 %) as a mixture of the two major products in a 1.6 : 1 ratio as a pale brown crystalline solid, m.p. 57–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 1.4 Hz, 0.6H), 8.21 (dd, J = 8.4, 0.9 Hz, 0.4H), 7.72–7.64 (m, 3.2H), 7.50–7.42 (m, 1.8H), 7.40–7.27 (m, 3.6H), 7.20 (d, J = 8.1 Hz, 0.8H, **170a** TsAr-H), 7.17 (d, J = 8.1 Hz, 1.2H, **170b** TsAr-H), 7.06 (dd, J = 7.3, 0.9 Hz, 0.4H), 3.06–2.96 (m, 2H), 2.60 (tt, J = 6.0, 2.0 Hz, 1.2H, **170b** CH_2), 2.34 (s, 1.2H, **170a** CH_3), 2.31 (s, 1.8H, **170b** CH_3), 1.95 (tt, J = 6.1, 2.0 Hz, 0.8H, **170a** CH_2), 1.92–1.83 (m, 1.2H), 1.83–1.72 (m, 2H), 1.53–1.45 (m, 0.8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 141.9, 141.0, 137.4, 137.0, 136.6, 136.5, 136.1, 135.9, 135.3, 129.9, 129.8, 129.7, 129.5, 128.9, 128.0, 127.6, 127.6, 127.2, 127.1, 126.6,

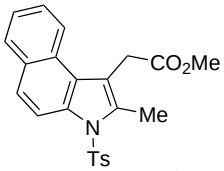
126.5, 125.1, 123.3, 122.8, 118.7, 118.6, 118.3, 113.4, 113.1, 25.2, 24.9, 24.5, 23.4, 22.9, 22.7, 22.2, 21.7, 21.6, 21.3. HRMS (ES^+) calcd. for $C_{25}H_{24}NO_2S^+$ $(M+H)^+$: 402.1528, found: 402.1531.

7-Tosyl-8,9,10,11-tetrahydro-7*H*-benzo[*c*]carbazole, 172



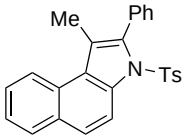
Isolated 48.8 mg (51 %) as a pale yellow crystalline solid, m.p. 170–173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 9.1 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.73–7.64 (m, 3H), 7.56–7.49 (m, 1H), 7.48–7.42 (m, 1H), 7.16 (d, J = 8.2 Hz, 2H), 3.12 (br s, 4H), 2.31 (s, 3H), 1.90 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 136.5, 134.7, 133.3, 131.1, 129.9, 128.7, 128.2, 126.4, 126.0, 124.5, 124.5, 124.4, 123.9, 120.1, 114.7, 25.2, 25.2, 22.9, 22.8, 21.6. HRMS (ES^+) calcd. for $C_{23}H_{22}NO_2S^+$ $(M+H)^+$: 376.13658, found: 376.1365.

Methyl 2-(2-methyl-3-tosyl-3*H*-benzo[*e*]indol-1-yl)acetate, 173



Prepared as with general procedure but an additional equivalent of boron trifluoride etherate was added and a further 1 h of heating required for complete consumption of hydrazone intermediate. The major regioisomer was isolated to give 41.0 mg (68 %) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.55 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.49–7.42 (m, 1H), 7.18 (d, J = 8.4 Hz, 2H), 4.05 (s, 2H), 3.67 (s, 3H), 2.67 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 144.9, 136.5, 134.2, 133.7, 131.2, 130.0, 129.0, 127.5, 126.4, 126.3, 125.2, 124.6, 123.9, 123.2, 114.7, 114.7, 52.4, 32.6, 21.6, 12.8. HRMS (ES^+) calcd. for $C_{23}H_{22}NO_4S^+$ $(M+H)^+$: 408.12641; found 408.1266

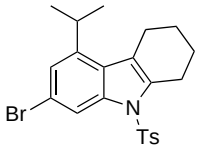
1-Methyl-2-phenyl-3-tosyl-3*H*-benzo[*e*]indole, 174



The major product was isolated 28.8 mg (27 %) as a pale brown crystalline solid, m.p. 138–142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 9.1 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.00–7.90 (m, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.56 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.53–7.42 (m, 4H), 7.42–7.35 (m, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 2.45 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 136.4, 135.6, 134.6, 132.1, 131.7, 131.5, 129.4, 128.9, 128.6, 128.6, 127.6, 126.8, 126.3, 125.8, 125.5, 124.7, 123.8, 121.0,

115.9, 21.6, 13.9. HRMS (ES^+) calcd. for $C_{26}H_{22}NO_2S^+$ $(M+H)^+$: 412.1366, found: 412.1368.

7-Bromo-5-isopropyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazole, 183b



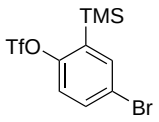
Isolated 3 mg (6 %) as a brown crystalline solid, 57–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 1.7 Hz, 1H), 7.68–7.62 (m, 2H), 7.26–7.19 (m, 3H), 3.51 (hept, J = 6.8 Hz, 1H), 2.97 (tt, J = 6.1, 2.0 Hz, 2H), 2.82 (tt, J = 5.7, 1.9 Hz, 2H), 2.36 (s, 3H), 1.86–1.71 (m, 4H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 143.7, 137.3, 136.3, 135.8, 130.1, 126.7, 126.6, 123.2, 118.0, 117.8, 115.0, 29.1, 25.1, 24.5, 24.2, 22.8, 22.7, 21.7. MS (ES^+) calcd. for $C_{22}H_{24}{}^{79}BrNO_2S$ $(M+H)^+$: 446.1, and for $C_{22}H_{24}{}^{81}BrNO_2S$ $(M+H)^+$: 448.1; found: 446.1, 448.1.

6.2 Biphenyl aryne precursors *via* palladium-mediated cross-coupling

6.2.1 Starting material synthesis

Aryne precursor **216** was synthesised according to the protocol of Peña *et al.*[75] from 1,6-dibromophenol and is known in the literature.[249] Purification by distillation under high vacuum was used in addition to column chromatography.

4-Bromo-2-(trimethylsilyl)phenyl trifluoromethanesulfonate, 220



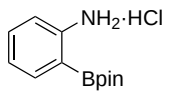
2,6-Dibromophenol (**218**, 8.10 g, 32.2 mmol) was dissolved in HMDS (7.4 ml, 35.4 mmol) and heated at reflux for 2 h. The volatile components were removed *in vacuo* to leave 10.4 g (100 %) of the intermediate (2,6-dibromophenyl)trimethylsilane (**219**). Crude **219** (6.42 g, 19.8 mmol) was dissolved in THF (130 ml), the solution cooled to −100 °C (internal temperature, liquid N_2/Et_2O bath) and *n*-butyl lithium in hexane (13.6 ml, 1.6 M, 1.1 eq.) was added dropwise. The mixture was stirred for 20 min while the temperature warmed to approx. −80 °C. The mixture was again cooled to −100 °C, triflic anhydride (6.7 g, 23.8 mmol 1.2 eq.) added dropwise and the mixture then warmed to −70 °C over 20 min. Cold sat. aq. sodium bicarbonate (120 ml) was added, the phases separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (heptane) gave a white solid (3.4 g, 45 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 2.6 Hz,

1H), 7.54 (dd, J = 8.8, 2.6 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 0.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 139.0, 135.9, 134.2, 121.8, 121.5, 118.6 (q, J_{CF} = 320.1 Hz), -0.9.[250]

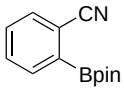
General procedure for the synthesis of pinacol boronic esters from the free boronic acid

To a solution of pinacol (~3 mmol, 1 eq.) in dichloromethane (0.5 M) was added the boronic acid (1 eq.) and the reaction mixture stirred for 2 h at rt. The solvent was removed *in vacuo* to give the respective pinacol boronic esters in high yields.

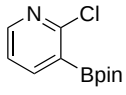
247,[204] **251**[251] and **321**[252] were synthesised according to the general procedure and are known in the literature.



321

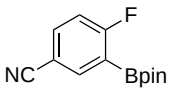


247



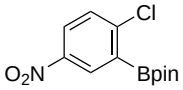
251

4-Fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile, 253



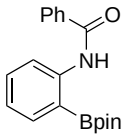
Synthesised according to the general procedure. Isolated 485 mg (93 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, J = 5.3, 2.3 Hz, 1H), 7.67 (ddd, J = 8.5, 5.0, 2.3 Hz, 1H), 7.07 (app. t, J = 8.6 Hz, 1H), 1.30 (s, 12H). ^{11}B NMR (160 MHz, $CDCl_3$) δ 29.6. ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2 (d, J_{CF} = 261.2 Hz), 141.8 (d, J_{CF} = 9.9 Hz), 137.2 (d, J_{CF} = 10.4 Hz), 118.2 (s), 116.9 (d, J_{CF} = 25.0 Hz), 108.4 (d, J_{CF} = 3.6 Hz), 84.8 (s), 24.9 (s). The *C*-B peak was not observed.[253]

2-(2-Chloro-5-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 255



Synthesised according to the general procedure. Isolated 863 mg (96 %) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 2.9 Hz, 1H), 8.17 (dd, J = 8.8, 2.9 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 1.38 (s, 12H). ^{11}B NMR (128 MHz, $CDCl_3$) δ 22.5. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 146.1, 131.5, 130.6, 126.6, 85.1, 24.9. The *C*-B peak was not observed.

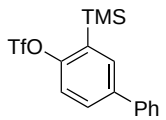
N-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide, 257



To a solution of **321** (630 mg, 2.46 mmol) in dichloromethane (110 ml) was added triethylamine (1.0 ml, 7.2 mmol) and benzoyl chloride (0.36 ml, 3.1 mmol) and the mixture stirred for 10 min at rt. Water (100 ml) was then added and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was recrystallised from toluene, before being redissolved in dichloromethane and washed with water and dil. HCl. The organic layer was then dried ($MgSO_4$), the solvent removed, and the product again recrystallised from toluene to give a white solid, 450 mg (57 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.74 (dd, J = 8.4, 1.0 Hz, 1H), 8.07–8.01 (m, 2H), 7.82 (dd, J = 7.5, 1.7 Hz, 1H), 7.67–7.44 (m, 4H), 7.11 (app. td, J = 7.4, 1.0 Hz, 1H), 1.41 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 145.1, 136.4, 135.5, 133.2, 131.8, 128.6, 127.4, 123.2, 119.3, 84.6, 25.1. The *C*-B peak was not observed.[254]

6.2.2 Biphenyl synthesis

3-(trimethylsilyl)-[1,1′-biphenyl]-4-yl trifluoromethanesulfonate, 221



Aryne precursor **220** (80 mg, 0.21 mmol), phenylboronic acid (**223**, 28.4 mg, 1.1 eq.) and caesium carbonate (207 mg, 3 eq.) were added to a tube, which was flushed with nitrogen. $Pd_2(dba)_3$ (9.7 mg, 5 mol %) and tri-*tert*-butylphosphine (30 µl of a ~0.83 M solution in tetrahydrofuran, 12 mol %) were dissolved in tetrahydrofuran (2 ml), which was added through a septum and the mixture stirred at rt for 5 h. The contents were then filtered through Celite, being rinsed with diethyl ether, and the solvents removed *in vacuo*. The crude product was purified by column chromatography, eluting with heptane. Isolated 33.4 mg (42 %) as an off-white, crystalline solid, m.p. 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2.5 Hz, 1H), 7.62 (dd, J = 8.6, 2.5 Hz, 1H), 7.59–7.51 (m, 2H), 7.50–7.44 (m, 2H), 7.45–7.37 (m, 2H), 0.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 140.7, 139.9, 135.1, 133.1, 130.1, 129.1, 128.0, 127.4, 119.9, 118.7 (q, J_{CF} = 320.2 Hz), -0.65.[255]

General procedure for biphenyl aryne precursor synthesis A

Aryne precursor **216** (1 eq., ~ 0.2 mmol), the appropriate boronic acid (1.1 eq.), $Pd_2(dba)_3$ (5 mol %), $[HP(t\text{-}Bu)_3]BF_4$ (12 mol %) and potassium phosphate tribasic (3 eq.) were weighed to a tube which was evacuated and refilled with nitrogen three times. Toluene and water (5 : 1, 1 ml toluene for every 0.1 mmol of **44**), which had been degassed under a flow of nitrogen for at least 5 min, were added sequentially through a septum and the mixture stirred at 90 °C (external heating-block temperature) for 5 h. On cooling, the contents were filtered through Celite, being rinsed with diethyl ether, and the solvents removed *in vacuo*. The crude product was purified by column chromatography, elution was performed with neat heptane or with ethyl acetate/heptane (1–5 %).

General procedure for biphenyl aryne precursor synthesis B

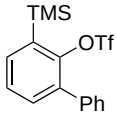
Aryne precursor **216** (1 eq.), the appropriate boronic acid or pinacol boronic ester (2 eq. unless otherwise stated), a mixture of $Pd_2(dba)_3$ and $[HP(t\text{-}Bu)_3]BF_4$ (palladium : phosphine 1 : 1.2, 10 % Pd), which had been previously mixed in a pestle and mortar, and potassium phosphate tribasic (3 eq.) were weighed to a tube which was evacuated and refilled with nitrogen three times. Toluene and water (5 : 1, 1 ml toluene for every 0.1 mmol of **44**), which had been degassed under a flow of nitrogen for at least 5 min, were added sequentially through a septum and the mixture stirred at 90 °C (external heating-block temperature) for 5 h. On cooling, the contents were filtered through Celite, being rinsed with diethyl ether, and the solvents removed *in vacuo*. The crude product was purified by column chromatography, elution was typically performed with diethyl ether/hexane or ethyl acetate/hexane (0–5 %). In some cases hexane/toluene gave superior separation.

General procedure for biphenyl aryne precursor synthesis C

The appropriate boronic acid or pinacol boronic ester (2 eq.), a mixture of $Pd_2(dba)_3$ and $[HP(t\text{-}Bu)_3]BF_4$ (palladium : phosphine 1 : 1.2, 10 % Pd), which had been previously mixed in a pestle and mortar, and potassium phosphate tribasic (3 eq.) were weighed to a tube which was evacuated and refilled with nitrogen three times. A stock solution of aryne precursor **216** (1 eq., 0.106 M) and dodecane (0.058 M) in degassed toluene was added through a septum followed by water (volume to give 5 : 1 ratio of stock solution : water), which had been degassed under a flow of nitrogen for at least 5 min, and the mixture stirred at 90 °C (external heating-block temperature) for 5 h. On cooling, the contents were filtered through Celite, being rinsed with diethyl ether, and the solvents removed *in vacuo*. The crude product was purified by column

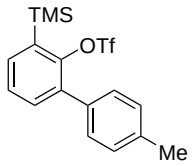
chromatography, elution was typically performed with diethyl ether/hexane or ethyl acetate/hexane (0–5 %). In some cases hexane/toluene gave superior separation.

3-(Trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 44



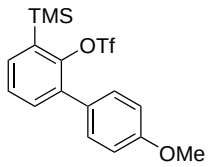
Prepared according to general procedure A from boronic acid **223**. Isolated 77 mg (97 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.52 (m, 1H), 7.47–7.33 (m, 7H), 0.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 137.0, 136.4, 136.0, 135.9, 133.7, 129.8, 128.5, 128.2, 128.1, 118.1 (q, J_{CF} = 320.7 Hz), 0.35.[67]

4′-Methyl-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 225



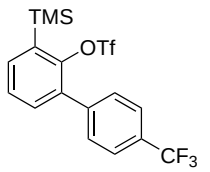
Prepared according to general procedure A from boronic acid **224**. Isolated 67.9 mg (82 %) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 1H), 7.48–7.41 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H), 0.48 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.0, 138.0, 136.4, 135.9, 135.7, 134.2, 133.8, 129.6, 129.2, 128.2, 118.2 (q, J_{CF} = 320.7 Hz), 21.4, 0.39. HRMS (EI^+) calcd. for $C_{17}H_{19}F_3O_3SSi$ $(M)^+$: 388.0776, found: 388.0765.

4′-Methoxy-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 227



Prepared according to general procedure A from boronic acid **226**. Isolated (89 %) as a white crystalline solid, m.p. 72–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.50 (m, 1H), 7.44–7.40 (m, 2H), 7.37 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H), 0.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 149.0, 135.0, 134.9, 134.5, 132.7, 129.9, 128.4, 127.2, 117.8 (q, J_{CF} = 320.6 Hz), 112.9, 54.4, -0.62. HRMS (EI^+) calcd. for $C_{17}H_{19}F_3O_4SSi$ $(M)^+$: 404.0720, found: 404.072838

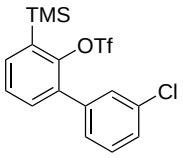
4′-(Trifluoromethyl)-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 229



Prepared according to general procedure A from boronic acid **228**. Isolated 76.7 mg (82 %) as a white crystalline solid, m.p. 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 7.3, 2.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.47 (app. t, J = 7.4 Hz, 1H), 7.42 (dd, J = 7.5, 2.0 Hz, 1H), 0.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4,

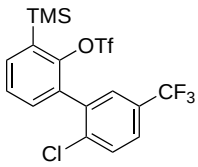
139.7, 135.8, 135.5, 134.1, 132.4, 129.6 (q, $J_{CF} = 32.4$ Hz), 129.2, 127.4, 124.4 (q, $J_{CF} = 3.7$ Hz), 123.2 (q, $J_{CF} = 272.1$ Hz), 117.1 (q, $J_{CF} = 320.5$ Hz) -0.69. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6, -74.0. HRMS (EI^+) calcd. for $C_{17}H_{16}F_6O_3SSi$ $(M)^+$: 442.0488, found: 442.0470.

3′-Chloro-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 231



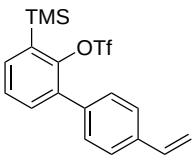
Prepared according to general procedure B from boronic acid **230**. Isolated 75.8 mg (87 %) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 6.8, 2.5 Hz, 1H), 7.50–7.27 (m, 6H), 0.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 137.8, 135.5, 135.4, 134.0, 133.4, 132.5, 128.8, 128.8, 127.4, 127.3, 127.0, 117.2 (q, $J_{CF} = 320.8$ Hz), -0.68. HRMS (EI^+) calcd. for $C_{16}H_{16}{}^{35}ClF_3O_3SSi$ $(M)^+$: 408.0225, found: 408.0216

2′-Chloro-5′-(trifluoromethyl)-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 233



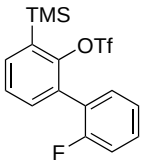
Prepared according to general procedure C from boronic acid **232**. Isolated 260 mg (82 %) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.5, 1.9 Hz, 1H), 7.65–7.58 (br m, 3H), 7.48 (app. t, J = 7.5 Hz, 1H), 7.40 (dd, J = 7.5, 1.9 Hz, 1H), 0.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 137.8, 137.5, 136.5, 136.1, 133.8, 132.3, 130.3, 129.4 (q, J_{CF} = 33.4 Hz), 129.4 (q, $J_{CF} = 3.6$ Hz), 128.2, 126.4 (m), 123.7 (q, $J_{CF} = 270.0$ Hz), 118.1 (q, J_{CF} = 320.0 Hz), 0.11. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.7, -74.4. HRMS (EI^+) calcd. for $C_{17}H_{15}{}^{35}ClF_6O_3SSi$ $(M)^+$: 476.0104, found: 476.0089

3-(Trimethylsilyl)-4′-vinyl-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 235



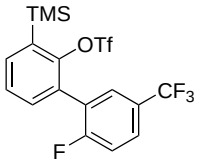
Prepared according to general procedure B from boronic acid **234**. Isolated 75.9 mg (89 %) as an off-white crystalline solid, m.p. 56–59 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 5.2, 4.1 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.46–7.38 (m, 4H), 6.77 (dd, J = 17.6, 10.9 Hz, 1H), 5.83 (d, J = 17.7 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 0.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 137.4, 136.5, 136.5, 136.1, 136.1, 136.0, 133.6, 129.9, 128.2, 126.3, 118.2 (q, $J_{CF} = 320.6$ Hz), 114.6, 0.38. HRMS (EI^+) calcd. for $C_{18}H_{19}F_3O_3SSi$ $(M)^+$: 400.0771, found: 400.0772.

2′-Fluoro-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 237



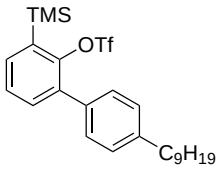
Prepared according to general procedure B from boronic acid **236**. Isolated 172 mg (66 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 6.7, 2.5 Hz, 1H), 7.50–7.35 (m, 4H), 7.23 (app. td, J = 7.5, 1.2 Hz, 1H), 7.20–7.10 (m, 1H), 0.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (d, J_{CF} = 248.7 Hz), 150.0, 136.8, 135.7, 134.0, 132.2 (d, J_{CF} = 2.8 Hz), 130.5, 130.3 (d, J_{CF} = 10.7 Hz), 128.2, 124.6 (d, J_{CF} = 15.4 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 118.1 (q, J_{CF} = 320.3 Hz), 115.8 (d, J_{CF} = 22.3 Hz), 0.23. ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.3, -115.2. HRMS (EI^+) calcd. for $C_{15}H_{13}F_4O_3SSi$ $(M\text{ -Me})^+$: 377.0285, found: 377.0274.

2′-Fluoro-5′-(trifluoromethyl)-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 239



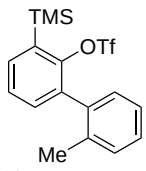
Prepared according to general procedure C from boronic acid **238**. Isolated 227 mg (74 %) as a white crystalline solid, m.p. 53–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.62 (m, 3H), 7.49 (app. t, J = 7.4 Hz, 1H), 7.44 (ddd, J = 7.4, 1.8, 0.8 Hz, 1H), 7.27 (app. t, J = 8.8 Hz, 1H), 0.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6 (d, J_{CF} = 254.9 Hz), 149.4, 137.5, 136.3, 133.8, 129.9–129.4 (m), 128.9, 128.4, 127.9–127.5 (m), 127.1 (dd, J_{CF} = 33.5, 3.8 Hz), 125.6 (d, J_{CF} = 16.7 Hz), 123.8 (q, J_{CF} = 272.1 Hz), 118.1 (q, J_{CF} = 320.1 Hz), 116.6 (d, J_{CF} = 23.7 Hz), 0.17. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.1, -74.3, -109.4.HRMS (EI^+) calcd. for $C_{16}H_{12}F_7O_3SSi$ $(M\text{ -Me})^+$: 445.0159, found: 445.0155.

4′-Nonyl-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 241



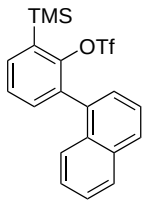
Prepared according to general procedure C from boronic acid **240**. Isolated 229 mg (71 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.48 (m, 1H), 7.48–7.37 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 2.72–2.53 (m, 2H), 1.64 (p, J = 6.9, 6.5 Hz, 2H), 1.42–1.18 (m, 12H), 1.07–0.79 (m, 3H), 0.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 143.1, 136.4, 135.9, 135.7, 134.2, 133.7, 129.6, 128.6, 128.2, 35.8, 32.1, 31.6, 29.7, 29.7, 29.5, 29.3, 22.8, 14.3, 0.38. The triflate q was not resolved. HRMS (EI^+) calcd. for $C_{25}H_{35}F_3O_3SSi$ $(M)^+$: 500.2023, found: 500.2022.

2′-Methyl-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 242



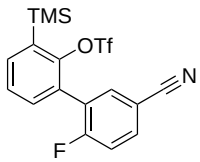
Prepared according to general procedure A from boronic acid **213**. Isolated 75.6 mg (92 %) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.4, 1.9 Hz, 1H), 7.43 (app. t, J = 7.4 Hz, 1H), 7.33 (dd, J = 7.5, 1.9 Hz, 1H), 7.32–7.19 (m, 4H), 2.17 (s, 3H), 0.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 136.6, 136.3, 136.0, 135.9, 135.3, 134.2, 130.9, 130.2, 128.4, 128.0, 125.7, 118.06 (q, J_{CF} = 320.5 Hz), 19.8, 0.17. HRMS (EI^+) calcd. for $C_{17}H_{19}F_3O_3SSi$ $(M)^+$: 388.0776, found: 388.0769.

2-(Naphthalen-1-yl)-6-(trimethylsilyl)phenyl trifluoromethanesulfonate, 244



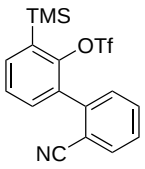
Prepared according to general procedure C from boronic acid **243**. Isolated 66.3 mg (98 %) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.87 (m, 2H), 7.70–7.66 (m, 1H), 7.62 (br d, J = 8.5 Hz, 1H), 7.57–7.43 (m, 6H), 0.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 136.4, 135.6, 135.1, 134.7, 134.3, 133.7, 131.7, 128.9, 128.8, 128.4, 128.1, 126.4, 126.0, 125.5, 125.2, 117.54 (q, J_{CF} = 320.5 Hz), 0.21. HRMS (EI^+) calcd. for $C_{20}H_{19}F_3O_3SSi$ $(M)^+$: 424.0771, found: 424.0753.

5′-Cyano-2′-fluoro-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 254



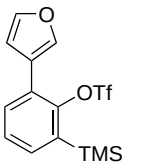
Prepared according to general procedure C from pinacol boronic ester **253**. Isolated 160 mg (60 %) as a pale yellow crystalline solid, m.p. 84–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.58 (m, 3H), 7.43 (app. t, J = 7.5 Hz, 1H), 7.33 (dd, J = 7.4, 1.8 Hz, 1H), 7.25–7.15 (m, 1H), 0.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (d, J_{CF} = 259.1 Hz), 149.2, 137.9, 136.5 (d, J_{CF} = 4.7 Hz), 136.4, 134.5 (d, J_{CF} = 9.7 Hz), 133.6, 128.5, 128.1, 126.7 (d, J_{CF} = 17.2 Hz), 118.1 (d, J_{CF} = 319.9 Hz), 117.8, 117.4 (d, J_{CF} = 24.0 Hz), 108.9 (d, J_{CF} = 3.9 Hz), 0.14. ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.3, -104.7. HRMS (EI^+) calcd. for $C_{16}H_{12}F_4NO_3SSi$ (M -Me)$^+$: 402.0238, found: 402.0223.

2′-Cyano-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 248



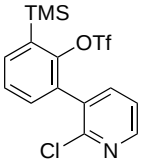
Prepared according to general procedure B from pinacol boronic ester **247**. Isolated 55.5 mg (87 %) as a colourless oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (ddd, J = 7.9, 1.3, 0.7 Hz, 1H), 7.72–7.62 (m, 2H), 7.55–7.48 (m, 3H), 7.44 (dd, J = 7.5, 1.9 Hz, 1H), 0.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 140.7, 137.7, 136.5, 133.6, 133.1, 132.8, 132.7, 131.6, 128.7, 128.4, 118.12 (q, J_{CF} = 320.3 Hz), 117.8, 113.4, 0.15. HRMS (EI^+) calcd. for $C_{17}H_{16}F_3NNaO_3SSi^+$ $(M+Na)^+$: 422.0464, found: 422.0465 IR (thin film, cm^{-1}): 2956 (w), 2228 (w), 1601 (w), 1393 (m).

2-(Furan-3-yl)-6-(trimethylsilyl)phenyl trifluoromethanesulfonate, 250



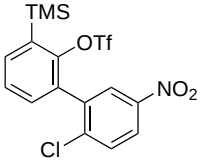
Prepared according to general procedure B from pinacol boronic ester **249**. Isolated 71.9 mg (93 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 7.51 (dd, J = 7.3, 2.0 Hz, 1H), 7.49 (app. t, J = 1.7 Hz, 1H), 7.44 (dd, J = 7.5, 2.0 Hz, 1H), 7.39 (app. t, J = 7.4 Hz, 1H), 6.64–6.53 (m, 1H), 0.43 (br s 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 142.3, 140.2, 135.1, 134.8, 131.5, 127.2, 126.4, 120.3, 117.4 (q, J_{CF} = 320.6 Hz), 110.2, -0.58. HRMS (EI^+) calcd. for $C_{14}H_{15}F_3O_4SSi$ $(M)^+$: 364.0407, found: 364.0390.

2-(2-Chloropyridin-3-yl)-6-(trimethylsilyl)phenyl trifluoromethanesulfonate, 252



Prepared according to general procedure B from pinacol boronic ester **251**. Isolated 48.5 mg (56 %) as a white crystalline solid, m.p. 118–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, J = 4.8, 2.0 Hz, 1H), 7.72 (dd, J = 7.6, 2.0 Hz, 1H), 7.66 (dd, J = 7.5, 1.8 Hz, 1H), 7.47 (app. t, J = 7.5 Hz, 1H), 7.36 (dd, J = 7.5, 1.8 Hz, 1H), 7.33 (dd, J = 7.6, 4.8 Hz, 1H), 0.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 149.6, 149.2, 141.1, 137.5, 136.0, 133.6, 132.5, 132.0, 128.3, 122.3, 118.1 (q, J_{CF} = 320.4 Hz), 0.06. HRMS (EI^+) calcd. for $C_{15}H_{16}{}^{35}ClF_3NO_3SSi^+$ $(M+H)^+$: 410.0255, found: 410.0261.

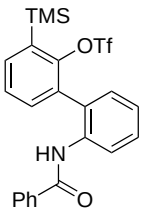
2′-Chloro-5′-nitro-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 256



Prepared according to general procedure C from pinacol boronic ester **255**. Isolated 101 mg (42 %) as a pale-blue crystalline solid, m.p. 74–77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 8.8, 2.8 Hz, 1H), 7.71 (dd, J = 7.4, 1.9 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.51 (app. t, J = 7.5 Hz, 1H), 7.41 (dd, J = 7.5, 1.9 Hz, 1H), 0.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 146.5, 140.9, 137.9, 137.4, 136.3, 133.6,

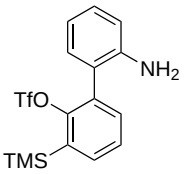
131.7, 130.7, 128.4, 127.5, 124.4, 118.1 (q, J_{CF} = 320.3 Hz), 0.07. HRMS (EI^+) calcd. for $C_{15}H_{12}{}^{35}ClF_3NO_5SSi$ $(M\text{ -Me})^+$: 437.9841, found: 437.9835.

2′-Benzamido-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 258



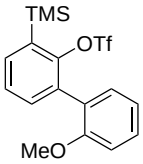
Prepared according to general procedure B from pinacol boronic ester **257**. Isolated 31.9 mg (41 %) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 1H), 7.72 (br s, 1H), 7.68–7.58 (m, 3H), 7.53–7.36 (m, 6H), 7.26–7.21 (m, 2H), 0.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 149.6, 137.2, 136.3, 135.6, 134.7, 134.5, 132.9, 132.0, 131.2, 129.6, 128.9, 128.7, 128.6, 127.1, 125.1, 123.9, 0.15. The triflate q was not resolved. HRMS (EI^+) calcd. for $C_{23}H_{23}F_3NO_4SSi^+$: 494.1064, found: 494.1052.

2′-Amino-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 260



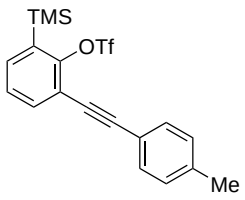
Prepared according to general procedure B with 2.5 eq. of the boronic acid amine hydrochloride salt **259**. Isolated 25 mg (49 %) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.2, 2.0 Hz, 1H), 7.51 (dd, J = 7.5, 2.0 Hz, 1H), 7.43 (app. t, J = 7.4 Hz, 1H), 7.18 (app. td, J = 7.7, 1.6 Hz, 1H), 7.05 (dd, J = 7.6, 1.6 Hz, 1H), 6.93–6.73 (m, 2H), 3.19 (br s, 2H), 0.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 144.3, 136.4, 136.0, 134.5, 133.6, 131.5, 129.6, 128.4, 122.2, 118.7, 118.2 (q, J_{CF} = 320.1 Hz), 116.3, 0.20. HRMS (ES^+) calcd. for $C_{16}H_{19}F_3NO_3SSi^+$ $(M+H)^+$: 390.0802, found: 390.0801.

2′-Methoxy-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 262



Prepared according to general procedure B from the potassium trifluoroborate salt **261**. Isolated 17.2 mg (27 %) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.44 (m, 1H), 7.37–7.32 (m, 2H), 7.30 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H), 7.21 (dd, J = 7.5, 1.7 Hz, 1H), 6.95 (app. td, J = 7.5, 1.1 Hz, 1H), 6.88 (br d, J = 8.3 Hz, 1H), 3.71 (s, 3H), 0.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 150.7, 135.9, 134.9, 134.3, 132.8, 131.9, 130.0, 127.9, 125.9, 120.7, 118.2 (q, J_{CF} = 320.5 Hz), 111.0, 55.5, 0.22.

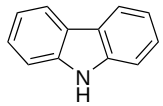
2-(*p*-Tolylethynyl)-6-(trimethylsilyl)phenyl trifluoromethanesulfonate, 288



Aryne precursor **44** (60 mg, 0.16 mmol), *p*-methyl-phenylacetylene (29 mg, 1.5 eq.), $Pd_2(dba)_3$ and $[HP(t\text{-}Bu)_3]BF_4$ (12.8 mg of the premixed catalyst, 5 mol % and 12 mol %), copper iodide (3 mg, 10 mol %) and potassium phosphate tribasic (3 eq.) were weighed to a tube which was evacuated and refilled with nitrogen three times. Toluene and water (5 : 1, 1.6 ml and 0.3 ml) were added sequentially through a septum and the mixture stirred at 90 °C (external heating-block temperature) for 5 h. On cooling, the contents were filtered through Celite, being rinsed with diethyl ether, and the solvents removed *in vacuo*. The crude product was purified by column chromatography (hexane, 1 % Et_2O in hexane). Isolated 9.3 mg (11 %) as a thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.6, 1.8 Hz, 1H), 7.51 (dd, J = 7.5, 1.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.34 (app. t, J = 7.5 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H), 0.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2, 139.3, 136.4, 135.8, 135.4, 131.7, 129.3, 127.7, 119.6, 118.8 (q, J_{CF} = 320.6 Hz), 118.7, 95.8, 83.1, 21.7, 0.13. HRMS (ES^+) calcd. for $C_{19}H_{23}F_3NO_3SSi^+$ $(M+NH_4)^+$: 430.1115, found: 430.1110.

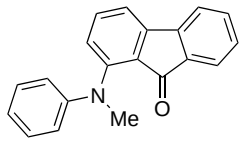
6.2.3 Reactions with substituted biphenyl aryne precursors

Carbazole, 265



2′-amino aryne precursor **260** (24 mg, 0.062 mmol) and caesium fluoride (28 mg, 3 eq.) were dissolved in acetonitrile (0.8 ml) and the reaction stirred overnight. The mixture was then diluted with ethyl acetate, washed with water – which was extracted with another portion of ethyl acetate – and the combined organic layers dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product purified by column chromatography (hexane : ethyl acetate 9 : 1) to give carbazole, 7 mg (68 %) as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2H), 8.05 (s, 1H), 7.51–7.36 (m, 4H), 7.30–7.18 (m, 2H).[256]

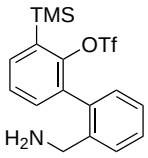
1-(Methyl(phenyl)amino)-9*H*-fluoren-9-one, 275



Aryne precursor **248** (47 mg, 0.118 mmol), *N*-methylaniline (13 mg, 0.123 mmol) and caesium fluoride (56 mg, 0.37 mmol) were added to a vial, which was briefly flushed with nitrogen before acetonitrile (1.2 ml) was added. The mixture was stirred overnight at rt after which the reaction was quenched with HCl (3 ml, 1 M), being stirred for 10 min. The solution was then made basic with sat. aq. $NaHCO_3$, extracted three times

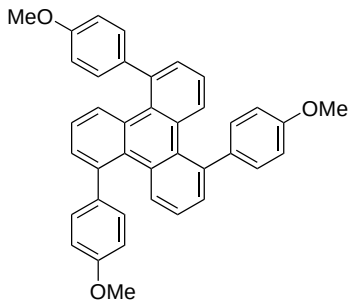
with diethyl ether, dried ($MgSO_4$), the solvent removed *in vacuo* and the crude product purified by column chromatography (hexane : ethyl acetate 7 : 1). The mixed fraction was recolumned (hexane : ethyl acetate 10 : 1) and the new mixed fraction from this second purification stirred in wet ethyl acetate with silica gel for 1 h. After subjecting this to a final round of chromatography the combined upper fractions gave the desired product as a red solid, 21.1 mg (60 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.47 (app. td, J = 7.4, 1.1 Hz, 1H), 7.35 (dd, J = 8.3, 7.1 Hz, 1H), 7.29 (app. td, J = 7.4, 1.0 Hz, 1H), 7.27–7.20 (m, 3H), 7.06 (d, J = 8.3 Hz, 1H), 7.03–6.96 (m, 2H), 6.91 (tt, J = 7.4, 1.0 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 148.3, 148.3, 146.7, 143.4, 135.3, 134.7, 134.0, 129.2, 129.1, 126.6, 125.1, 124.0, 120.8, 120.0, 118.4, 115.2, 41.1. HRMS (ES^+) calcd. for $C_{20}H_{15}NONa^+$ $(M+H)^+$: 308.1051, found: 308.1050. IR (thin film, cm^{-1}): 1698 (s).

2′-(Aminomethyl)-3-(trimethylsilyl)-[1,1′-biphenyl]-2-yl trifluoromethanesulfonate, 277



Borane-dimethyl sulfide (62 µl, 2.0 M in tetrahydrofuran, 1.1 eq.) was added to a solution of aryne precursor **248** (44.9 mg, 0.112 mmol) in tetrahydrofuran (1.1 ml) under nitrogen, the vessel sealed and heated to 60 °C for 3 h. HCl (3 ml, 1.5 M) was added and the mixture heated for a further 30 min at the same temperature after which it was made basic with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layers were dried (Na_2SO_4), the solvent removed *in vacuo* and the crude product purified by column chromatography (10 : 1 hexane : ethyl acetate followed by ethyl acetate and then acetonitrile) to isolate the reduced product, 19.1 mg (42 %) as a thick yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.3, 1.7 Hz, 1H), 7.52 (br d, J = 7.6 Hz, 1H), 7.46–7.37 (m, 2H), 7.35 (br d, J = 7.1 Hz, 1H), 7.30 (app. td, J = 7.6, 1.1 Hz, 1H), 7.23 (br d, J = 7.5 Hz, 1H), 3.75, 3.67 (ABq, J_{AB} = 14.6 Hz, 2H), 1.93 (br s, 2H), 0.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 141.2, 136.4, 135.7, 135.2, 135.1, 134.3, 131.2, 129.0, 128.1, 127.9, 126.8, 118.1 (q, J_{CF} = 320.5 Hz), 43.7, 0.19. HRMS (ES^+) calcd. for $C_{17}H_{21}F_3NO_3SSi^+$ $(M+H)^+$: 404.0958, found: 404.0952.

1,5,9-Tris(4-methoxyphenyl)triphenylene, 283

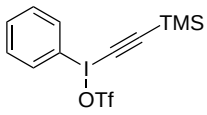


Aryne precursor **227** (0.667 mmol 271 mg), tris(dibenzylideneacetone)dipalladium (30.1 mg, 5 mol %) and caesium fluoride (305 mg, 2.0 mmol) were added to a flask which was flushed with nitrogen. Acetonitrile (2 ml), which had been degassed under a flow of nitrogen, was added and the mixture stirred overnight at rt. The reaction was then diluted with ethyl acetate, filtered through Celite, being flushed with ethyl acetate, and the solvents removed *in vacuo*. The crude product was purified by column chromatography (hexane/toluene) to give 40.3 mg (33 %) as a white crystalline solid, m.p. 209 °C. Recrystallisation from diethyl ether gave white needles that were suitable for X-ray diffraction studies. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.3, 1.4 Hz, 3H), 7.36–7.20 (m, 9H), 7.04 (dd, J = 8.3, 7.3 Hz, 3H), 7.00–6.90 (m, 6H), 3.88 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 139.5, 137.8, 131.7, 130.8, 130.5, 130.2, 128.3, 124.5, 114.4, 55.5. HRMS (EI^+) calcd. for $C_{39}H_{30}O_3$ $(M)^+$: 546.2195, found: 546.2165

6.3 Benzyne σ-insertion reactions

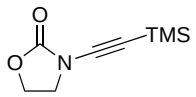
6.3.1 Ynamide synthesis

Phenyl((trimethylsilyl)ethynyl)iodonium trifluoromethanesulfonate, 303



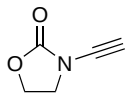
(Diacetoxyiodo)benzene (**303**, 6.32 g, 19.6 mmol) in dry DCM (30 ml) was cooled to 0 °C and trifluoromethanesulfonic acid (5.60 g, 37.3 mmol) added slowly. The mixture was stirred at 0 °C for 30 min after which bis(trimethylsilyl)acetylene (3.16 g, 18.5 mmol) was added. The reaction was then warmed slowly to rt and stirred for a further 2 h before being concentrated *in vacuo*. The resulting oily residue was poured dropwise into stirred hexane (100 ml) and the precipitate collected by filtration, being washed with diethyl ether, and dried *in vacuo* to give a white solid, 6.82 g (77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.04 (m, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.59–7.52 (m, 2H), 0.25 (s, 9H).[257]

3-((Trimethylsilyl)ethynyl)oxazolidin-2-one, 304



Oxazolidin-2-one (1 eq., 571 mg, 6.56 mmol) in dry toluene under nitrogen was cooled to 0 °C. KHMDS (1.2 eq., 15.7 ml, 0.5 M in toluene) was added dropwise and the mixture stirred for 2 h before being warmed to rt. Phenyl((trimethylsilyl)ethynyl)iodonium triflate, **303**, (1.3 eq., 3.82 g, 8.48 mmol) was then added portionwise and the reaction stirred overnight at rt. After filtration through a plug of silica, which was washed twice with diethyl ether, the solvent was removed *in vacuo* and the crude product purified by column chromatography to give a white solid, 199 mg (17 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50–4.30 (m, 2H), 4.03–3.74 (m, 2H), 0.20 (s, 9H).[258]

3-Ethynyloxazolidin-2-one, 305

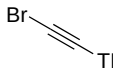


To 3-((trimethylsilyl)ethynyl)oxazolidin-2-one (**304**, 116 mg, 0.638 mmol) in THF (1.5 ml) was added TBAF (1.2 eq., 1 M in THF, 0.75 ml) at 0 °C. The reaction was warmed to rt and stirred for a further 30 min before being quenched with water and extracted with ethyl acetate followed by DCM. The combined organic layers were dried (Na_2SO_4), the solvent removed *in vacuo* and the crude product purified by column chromatography (hexane : ethyl acetate 2 : 1) to give a pale yellow solid, 17 mg (24 %). The procedure was not optimised. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59–4.32 (m, 2H), 4.06–3.83 (m, 2H), 2.85 (s, 1H).[258]

N-Benzyl-4-methylbenzenesulfonamide, 308

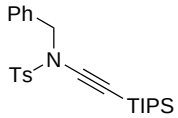
Tosyl chloride (7 g, 36.7 mmol) was added to a solution of benzyl amine (3.58 g, 33.4 mmol) in water (240 ml) and the reaction stirred at rt for 3 h. The mixture was extracted with ethyl acetate, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography (ethyl acetate/heptane) gave a pale yellow solid, 2.37 g (27 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.73 (m, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.30–7.27 (m, 2H), 7.22–7.18 (m, 2H), 4.56 (t, J = 6.1 Hz, 1H), 4.13 (d, J = 6.1 Hz, 2H), 2.44 (s, 3H).[259]

(Bromoethynyl)triisopropylsilane, 309



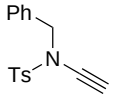
To a solution of triisopropylsilyl acetylene (5.00 g, 27.4 mmol) under nitrogen in dry acetone (275 mL) was added *N*-bromosuccinimide (5.37 g, 30.2 mmol) and silver nitrate (465 mg, 2.74 mmol). The mixture was stirred for 3 h at rt after which the solution was concentrated *in vacuo*, water (200 ml) added and the residue extracted with heptane (3 × 200 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a colourless oil, 6.87 g (96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.6, 61.9, 18.6, 11.4.[260]

N-Benzyl-4-methyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide, 310



A suspension of *N*-benzyl-4-methylbenzenesulfonamide (**308**, 2.29 g, 8.76 mmol), (bromoethynyl)triisopropylsilane (**309**, 2.29 g, 8.76 mmol), potassium phosphate tribasic (3.72 g, 17.5 mmol), $CuSO_4 \cdot 5\ H_2O$ (438 mg, 1.75 mmol) and 1,10-phenanthroline (632 mg, 3.51 mmol) in toluene (10 ml) was stirred for 60 h at 80 °C. On cooling, the mixture was filtered through Celite, which was washed with hexane, and the solvents removed *in vacuo*. The residue was purified by column chromatography (20 : 1 hexane : ethyl acetate) to give a pale yellow solid (3.10 g, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 2H), 7.31–7.26 (m, 7H), 4.49 (s, 2H), 2.44 (s, 3H), 0.94 (s, 21H).[261]

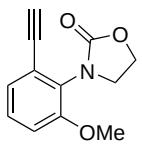
N-Benzyl-*N*-ethynyl-4-methylbenzenesulfonamide, 311



N-Benzyl-4-methyl-N-((triisopropylsilyl)ethynyl)benzenesulfonamide (**310**, 1.58 g, 3.58 mmol) in dry THF (40 ml) under nitrogen was cooled to approx. −10 °C ($CaCl_2 \cdot 6\ H_2O$/ice) and TBAF (1 M in THF, 7.2 ml, 7.2 mmol,) was added. The reaction mixture was stirred for 45 min and then warmed to rt. After quenching with sat. aq. ammonium chloride (25 ml) the reaction mixture was extracted three times with diethyl ether, the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallised from hot diethyl ether, purified by column chromatography (hexane : diethyl ether 10 : 1) and recrystallised a second time from hot diethyl ether to give a white crystalline solid, 556 mg (55 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.35–7.27 (m, 7H), 4.50 (s, 2H), 2.68 (s, 1H), 2.45 (s, 3H).[262]

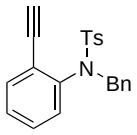
6.3.2 Insertion reaction products

3-(2-Ethynyl-6-methoxyphenyl)oxazolidin-2-one, 306



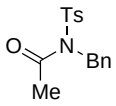
N-((Trimethylsilyl)ethynyl)-oxazolidinone (**305**, 32 mg, 0.175 mmol) and 2-(trimethylsilyl)-5-methoxy-phenyl triflate, **58** (60 mg, 0.175 mmol) in acetonitrile (3.5 ml, 0.05 M) along with caesium fluoride (67 mg, 0.438 mmol) were stirred overnight at rt. The mixture was then diluted with diethyl ether, poured into sat. brine and extracted twice with diethyl ether. The organic layers were then dried ($MgSO_4$), the solvent removed *in vacuo* and the crude product was purified by column chromatography (hexane : ethyl acetate 2 : 1) to give 5.1 mg (13 %) as a brown solid. Recrystallisation from $CDCl_3$ gave material suitable for X-ray diffraction studies. The same compound was obtained in 9 % yield from the unprotected *N*-(ethynyl)oxazolidinone, **304**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (app. t, J = 8.1 Hz, 1H), 7.15 (dd, J = 7.8, 1.2 Hz, 1H), 6.98 (dd, J = 8.4, 1.1 Hz, 1H), 4.59–4.46 (m, 2H), 3.96–3.90 (m, 2H), 3.86 (s, 3H), 3.27 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 156.3, 129.3, 127.7, 125.3, 123.5, 112.9, 82.0, 79.5, 62.8, 56.0, 46.2.

N-Benzyl-*N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide, 312



N-Benzyl-*N*-ethynyl-*N*-tosylamide (**311**, 28.5 mg, 0.100 mmol, 1 eq.) 2-(trimethylsilyl)phenyl triflate, **4** (45 mg, 1.5 eq.) and caesium fluoride (46 mg, 3 eq.) in tolunene : acetonitrile (3 : 1, 1 ml total volume, 0.1 M) were stirred overnight at 90 °C. The mixture was then diluted with water, extracted twice with ethyl acetate, the organic layers dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (hexane : ethyl acetate 20 : 1) to give 25.5 mg (40 %) as a brown solid. ^{1}H NMR (400 MHz, C_6D_6) δ 7.73–7.65 (m, 2H, Ts-H), 7.39–7.29 (m, 2H), 7.19–7.16 (m), 7.05–6.94 (m, 3H), 6.76–6.72 (m, 2H Ts-H), 6.69 (td, J = 7.8, 1.7 Hz, 1H), 6.60 (td, J = 7.6, 1.3 Hz, 1H), 5.02 (s, 2H), 2.48 (s, 1H), 1.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 140.4, 137.1, 136.2, 134.3, 132.4, 129.6, 129.4, 129.1, 128.4, 128.1, 128.1, 127.8, 123.0, 82.1, 80.4, 54.3, 21.7. HRMS (ES^+) calcd. for $C_{22}H_{19}NO_2SNa^+$ $(M+Na)^+$: 384.1034, found: 384.1033.

N-(2-Acetylphenyl)-*N*-benzyl-4-methylbenzenesulfonamide, 313



N-Benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (**311**, 29.0 mg, 0.101 mmol, 1 eq.), 2-(trimethylsilyl)phenyl triflate (1.5 eq.) caesium fluoride (3 eq.) were stirred overnight at rt in acetonitrile (0.1 M). The mixture was then diluted with water, extracted twice with ethyl acetate, the organic layers dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (hexane : ethyl acetate 20 : 1 to 10 : 1) and the minor component isolated, 7.6 mg (20 %), as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.42–7.22 (m, 7H), 5.08 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 145.0, 136.8, 136.8, 129.9, 128.7, 128.2, 127.9, 49.7, 25.1, 21.7.[263]

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Appendix 1: list of abbreviations

Ac	Acetyl
18-C-6	18-crown-6; 1,4,7,10,13,16-hexaoxacyclooctadecane
9-BBN	9-Borabicyclo(3.3.1)nonane
Ad	adamantyl
aq.	aqueous
Ar	aryl
BHT	3,5-di-*tert*-butyl-4-hydroxytoluene
Boc	*N*-*tert*-butoxycarbonyl
Bpin	pinacolboryl
BTMSA	bis(trimethylsilyl)acetylene
cat.	catalytic
Cbz	*N*-carboxybenzoyl
dan	naphthalene-1,8-diamine
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dil.	dilute
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
eq.	equivalents
EWG	electron withdrawing group
GC	gas chromatography
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol
KHMDS	potassium hexamethyldisilazane
LCMS	liquid chromatography mass spectrometry

lit.	literature
MeCN	acetonitrile
mp	melting point
Nf	nonafluorobutanesulfonyl
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
non	*n*-nonyl
Ph	phenyl
ppm	parts per million
pyr	pyridine
rt	room temperature
sat.	saturated
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TEBAC	triethylbenzylammonium chloride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	toluene
Triflate	trifluoromethanesulfonate
Ts; tosyl	4-toluenesulfonyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Appendix 2: crystallographic data

Table A1 Crystal data and structure refinement for **283**.

Empirical formula	$C_{248}H_{215}O_{24.50}$
Formula weight	3587.20
Temperature	150.05(16) K
Wavelength	0.7107 Å
Crystal system, space group	Triclinic
Space group	P -1
Unit cell parameters	a = 10.9330(3) Å α = 81.206(4)°
	b = 26.5055(12) Å β = 80.853(3)°
	c = 34.0449(14) Å γ = 85.145(3)°
Volume	9607.3(6) $Å^3$
Z	2
Density (calculated)	1.240 g/cm^3
Absorption coefficient μ	0.079 mm^{-1}
F(000)	3798
Crystal size	0.40 × 0.20 × 0.03 mm^3
θ range for data collection	3.05 to 29.04°
Index ranges	h -13 to 14, k -35 to 34, l -42 to 44
Completeness to θ = 25.00°	99.8 %
Reflections collected	83884
Independent reflections	43489 (R_{int} = 0.0510)
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.79201
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	43489 / 2 / 2462
Goodness-of-fit on F^2	1.054
Final R indices [$F^2>2\sigma$]	R1 = 0.1193, wR2 = 0.3035
R indices (all data)	R1 = 0.1782, wR2 = 0.3443
Largest diff. peak and hole	2.666 and -0.790 e $Å^{-3}$

Table A2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å^2 $\times 10^3$) for **283**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	2176(4)	219(2)	2975(1)	21(1)
C(2)	874(4)	389(2)	2937(1)	19(1)
C(3)	382(4)	428(2)	2570(1)	21(1)
C(4)	-894(4)	398(2)	2587(1)	25(1)
C(5)	-1671(4)	348(2)	2950(1)	24(1)
C(6)	-1219(4)	396(2)	3298(1)	22(1)
C(7)	52(4)	455(2)	3291(1)	20(1)
C(8)	567(4)	618(2)	3625(1)	17(1)
C(9)	1859(4)	526(2)	3633(1)	19(1)
C(10)	2616(4)	225(2)	3342(1)	19(1)
C(11)	3763(4)	-42(2)	3414(1)	22(1)
C(12)	4492(4)	-261(2)	3107(1)	26(1)
C(13)	4086(4)	-253(2)	2738(1)	28(1)
C(14)	2943(4)	-28(2)	2676(1)	25(1)
C(15)	4184(4)	-150(2)	3812(1)	20(1)
C(16)	3424(4)	-397(2)	4144(1)	25(1)
C(17)	3852(4)	-542(2)	4506(1)	27(1)
C(18)	5057(4)	-444(2)	4547(1)	25(1)
C(19)	5814(4)	-202(2)	4226(1)	26(1)
C(20)	5372(4)	-55(2)	3863(1)	24(1)
C(22)	6618(5)	-528(2)	4977(2)	41(1)
C(23)	2420(4)	761(2)	3899(1)	24(1)
C(24)	1734(5)	1069(2)	4149(1)	27(1)
C(25)	467(4)	1144(2)	4152(1)	26(1)
C(26)	-140(4)	930(2)	3892(1)	21(1)
C(27)	-1489(4)	1084(2)	3907(1)	19(1)
C(28)	-1932(4)	1441(2)	3610(1)	23(1)
C(29)	-3173(4)	1610(2)	3642(1)	24(1)
C(30)	-4000(4)	1419(2)	3971(1)	22(1)
C(31)	-3582(4)	1066(2)	4272(1)	28(1)
C(32)	-2341(4)	905(2)	4241(1)	26(1)
C(34)	-5664(5)	2004(2)	3788(2)	37(1)
C(35)	1159(4)	549(2)	2171(1)	22(1)
C(36)	1965(4)	945(2)	2107(1)	25(1)
C(37)	2692(5)	1074(2)	1737(2)	31(1)
C(38)	2633(5)	799(2)	1426(2)	34(1)
C(39)	1823(5)	409(2)	1481(2)	32(1)
C(40)	1099(4)	284(2)	1848(1)	26(1)
C(42)	4293(8)	1240(3)	1004(2)	76(2)

Continued on following page

Table A2 *continued*

C(43)	2970(4)	4842(2)	5204(1)	20(1)
C(44)	3762(4)	4380(2)	5133(1)	22(1)
C(45)	4946(4)	4283(2)	5255(1)	25(1)
C(46)	5601(4)	3823(2)	5221(2)	28(1)
C(47)	5033(4)	3430(2)	5110(2)	29(1)
C(48)	3887(4)	3509(2)	4982(1)	22(1)
C(49)	3318(4)	4011(2)	4936(1)	21(1)
C(50)	2433(4)	4202(2)	4655(1)	22(1)
C(51)	1973(4)	4718(2)	4619(1)	21(1)
C(52)	2067(4)	5010(2)	4950(1)	23(1)
C(53)	1233(4)	5424(2)	5030(1)	25(1)
C(54)	1327(5)	5690(2)	5339(1)	29(1)
C(55)	2227(5)	5530(2)	5589(2)	30(1)
C(56)	3021(4)	5106(2)	5533(1)	25(1)
C(57)	3823(4)	4932(2)	5853(1)	27(1)
C(58)	3665(5)	4476(2)	6110(2)	32(1)
C(59)	4381(5)	4325(2)	6417(2)	32(1)
C(60)	5275(4)	4645(2)	6470(2)	32(1)
C(61)	5424(5)	5110(2)	6218(2)	32(1)
C(62)	4716(4)	5246(2)	5916(2)	29(1)
C(64)	5938(6)	4059(3)	7014(2)	53(2)
C(65)	2219(4)	3902(2)	4365(1)	24(1)
C(66)	1580(4)	4112(2)	4052(1)	26(1)
C(67)	1209(4)	4629(2)	4002(1)	26(1)
C(68)	1409(4)	4938(2)	4276(1)	23(1)
C(69)	1100(4)	5499(2)	4174(1)	23(1)
C(70)	2017(4)	5848(2)	4115(1)	29(1)
C(71)	1745(5)	6369(2)	4012(2)	34(1)
C(72)	540(5)	6550(2)	3966(2)	33(1)
C(73)	-382(5)	6209(2)	4021(2)	35(1)
C(74)	-94(4)	5684(2)	4121(2)	28(1)
C(76)	-741(7)	7286(3)	3774(2)	60(2)
C(77)	3246(4)	3044(2)	4950(1)	23(1)
C(78)	3873(4)	2627(2)	4781(1)	28(1)
C(79)	3307(5)	2169(2)	4800(2)	32(1)
C(80)	2102(4)	2123(2)	4995(1)	25(1)
C(81)	1454(4)	2529(2)	5168(1)	26(1)
C(82)	2037(4)	2984(2)	5139(1)	22(1)
C(84)	363(5)	1607(2)	5187(2)	38(1)
C(85)	2803(4)	3757(2)	9893(1)	20(1)
C(86)	1986(4)	3964(2)	10223(1)	20(1)
C(87)	2501(4)	4121(2)	10536(1)	22(1)
C(88)	1756(4)	4336(2)	10839(1)	24(1)

Continued on following page

Table A2 *continued*

C(89)	477(4)	4392(2)	10841(1)	22(1)
C(90)	-69(4)	4260(2)	10531(1)	20(1)
C(91)	695(4)	4052(2)	10209(1)	19(1)
C(92)	258(4)	3991(2)	9832(1)	21(1)
C(93)	1117(4)	4014(2)	9472(1)	21(1)
C(94)	2427(4)	3850(2)	9504(1)	22(1)
C(95)	3275(4)	3705(2)	9180(1)	28(1)
C(96)	4449(4)	3495(2)	9228(1)	28(1)
C(97)	4774(4)	3381(2)	9611(2)	29(1)
C(98)	3958(4)	3488(2)	9946(1)	22(1)
C(99)	4256(4)	3250(2)	10348(1)	24(1)
C(100)	3422(4)	2936(2)	10602(2)	30(1)
C(101)	3705(5)	2675(2)	10959(2)	32(1)
C(102)	4831(4)	2730(2)	11079(1)	28(1)
C(103)	5685(4)	3045(2)	10835(1)	27(1)
C(104)	5390(4)	3299(2)	10470(1)	28(1)
C(106)	6179(5)	2508(3)	11579(2)	43(1)
C(107)	640(4)	4130(2)	9099(1)	22(1)
C(108)	-636(4)	4112(2)	9098(1)	26(1)
C(109)	-1430(4)	3988(2)	9452(1)	25(1)
C(110)	-1009(4)	3938(2)	9815(1)	24(1)
C(111)	1414(4)	4287(2)	8706(1)	22(1)
C(112)	2217(4)	4686(2)	8653(1)	25(1)
C(113)	2920(4)	4834(2)	8282(1)	26(1)
C(114)	2835(4)	4588(2)	7960(1)	27(1)
C(115)	2027(4)	4198(2)	8005(2)	29(1)
C(116)	1323(4)	4049(2)	8375(1)	26(1)
C(118)	4380(6)	5076(3)	7523(2)	50(2)
C(119)	-1432(4)	4384(2)	10566(1)	20(1)
C(120)	-2239(4)	4112(2)	10868(1)	24(1)
C(121)	-3492(4)	4247(2)	10927(1)	24(1)
C(122)	-3979(4)	4664(2)	10686(1)	22(1)
C(123)	-3203(4)	4941(2)	10387(1)	23(1)
C(124)	-1936(4)	4799(2)	10326(1)	23(1)
C(126)	-5740(5)	5234(2)	10578(2)	36(1)
C(127)	9710(4)	2708(2)	3329(1)	19(1)
C(128)	9195(4)	2552(2)	2994(1)	18(1)
C(129)	9899(4)	2246(2)	2716(1)	20(1)
C(130)	9294(4)	2035(2)	2456(1)	24(1)
C(131)	8027(4)	2115(2)	2459(1)	25(1)
C(132)	7342(4)	2412(2)	2718(1)	22(1)
C(133)	7910(4)	2644(2)	2985(1)	20(1)
C(134)	7154(4)	2939(2)	3282(1)	20(1)

Continued on following page

Table A2 *continued*

C(135)	7599(4)	2937(2)	3653(1)	22(1)
C(136)	8894(4)	2765(2)	3688(1)	20(1)
C(137)	9408(4)	2728(2)	4049(1)	22(1)
C(138)	10678(4)	2761(2)	4031(1)	25(1)
C(139)	11443(4)	2821(2)	3664(2)	27(1)
C(140)	10991(4)	2772(2)	3316(1)	23(1)
C(141)	8651(4)	2608(2)	4452(1)	22(1)
C(142)	7849(4)	2209(2)	4526(1)	22(1)
C(143)	7163(4)	2083(2)	4903(1)	26(1)
C(144)	7277(4)	2352(2)	5215(1)	28(1)
C(145)	8104(4)	2745(2)	5145(1)	28(1)
C(146)	8768(4)	2867(2)	4769(1)	25(1)
C(148)	5779(6)	1872(3)	5678(2)	56(2)
C(149)	6010(4)	3209(2)	3214(1)	21(1)
C(150)	5274(4)	3426(2)	3527(1)	26(1)
C(151)	5670(4)	3403(2)	3894(1)	26(1)
C(152)	6830(4)	3174(2)	3954(1)	24(1)
C(153)	5584(4)	3320(2)	2815(1)	20(1)
C(154)	6355(4)	3544(2)	2478(2)	27(1)
C(155)	5947(5)	3664(2)	2111(2)	30(1)
C(156)	4739(4)	3568(2)	2070(1)	27(1)
C(157)	3959(4)	3348(2)	2400(1)	27(1)
C(158)	4388(4)	3227(2)	2766(1)	26(1)
C(160)	3226(5)	3586(2)	1633(2)	38(1)
C(161)	11247(4)	2087(2)	2702(1)	22(1)
C(162)	11694(4)	1743(2)	3006(1)	22(1)
C(163)	12943(4)	1574(2)	2974(1)	23(1)
C(164)	13762(4)	1752(2)	2638(1)	24(1)
C(165)	13322(4)	2089(2)	2329(1)	26(1)
C(166)	12077(4)	2251(2)	2366(1)	26(1)
C(168)	15427(5)	1181(2)	2844(2)	40(1)
C(169)	3499(4)	887(2)	8190(1)	25(1)
C(170)	2600(4)	1070(2)	7908(1)	24(1)
C(171)	2355(4)	749(2)	7638(1)	28(1)
C(172)	1719(5)	944(2)	7326(2)	33(1)
C(173)	1352(5)	1466(2)	7260(2)	32(1)
C(174)	1592(4)	1793(2)	7518(2)	26(1)
C(175)	2171(4)	1590(2)	7856(1)	25(1)
C(176)	2334(4)	1896(2)	8168(2)	27(1)
C(177)	3262(4)	1737(2)	8414(1)	25(1)
C(178)	4018(4)	1266(2)	8356(1)	26(1)
C(179)	4049(4)	378(2)	8251(1)	24(1)
C(180)	5204(4)	300(2)	8376(2)	28(1)

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Table A2 *continued*

C(181)	5836(5)	697(2)	8454(2)	31(1)
C(182)	5217(4)	1173(2)	8465(2)	30(1)
C(183)	3387(4)	-89(2)	8249(1)	24(1)
C(184)	3991(5)	-513(2)	8090(2)	32(1)
C(185)	3431(5)	-975(2)	8140(2)	33(1)
C(186)	2243(4)	-1016(2)	8352(2)	26(1)
C(187)	1621(4)	-600(2)	8510(1)	24(1)
C(188)	2194(4)	-141(2)	8456(1)	24(1)
C(190)	528(5)	-1544(2)	8570(2)	39(1)
C(191)	3371(5)	2020(2)	8729(2)	33(1)
C(192)	2610(6)	2460(2)	8773(2)	41(1)
C(193)	1693(5)	2612(2)	8535(2)	39(1)
C(194)	1525(5)	2328(2)	8246(2)	32(1)
C(195)	4170(5)	1855(2)	9051(2)	37(1)
C(196)	5016(5)	2182(2)	9124(2)	40(1)
C(197)	5655(5)	2062(3)	9451(2)	48(2)
C(198)	5471(6)	1617(3)	9705(2)	49(2)
C(199)	4654(6)	1271(3)	9634(2)	48(2)
C(200)	4021(6)	1398(2)	9306(2)	44(1)
C(202)	6804(12)	1804(5)	10152(3)	145(6)
C(203)	1283(4)	2352(2)	7399(2)	28(1)
C(204)	88(5)	2536(2)	7341(2)	34(1)
C(205)	-189(5)	3060(2)	7230(2)	38(1)
C(206)	734(5)	3398(2)	7166(2)	36(1)
C(207)	1939(5)	3219(2)	7213(2)	33(1)
C(208)	2207(5)	2704(2)	7329(2)	29(1)
C(210)	-556(7)	4132(3)	6966(2)	62(2)
C(211)	1105(7)	7373(5)	9402(3)	101(3)
C(212)	144(6)	7220(3)	9190(2)	64(2)
C(214)	-163(7)	6950(3)	8592(3)	74(2)
C(215)	544(8)	6734(3)	8226(3)	76(2)
C(216)	3173(4)	7072(2)	1775(1)	25(1)
C(217)	2275(4)	7264(2)	1497(1)	25(1)
C(218)	2016(5)	6962(2)	1216(2)	31(1)
C(219)	1377(5)	7166(2)	907(2)	35(1)
C(220)	1008(5)	7683(2)	860(2)	35(1)
C(221)	1245(4)	7998(2)	1126(2)	28(1)
C(222)	1829(4)	7784(2)	1461(2)	28(1)
C(223)	1986(4)	8086(2)	1778(2)	27(1)
C(224)	2891(4)	7909(2)	2036(2)	26(1)
C(225)	3640(4)	7438(2)	1968(1)	26(1)
C(226)	4834(4)	7336(2)	2085(1)	28(1)
C(227)	5467(4)	6873(2)	2057(2)	32(1)

Continued on following page

Table A2 *continued*

C(228)	4873(4)	6478(2)	1954(2)	28(1)
C(229)	3728(4)	6562(2)	1821(1)	24(1)
C(230)	3105(4)	6096(2)	1784(1)	22(1)
C(231)	1894(4)	6026(2)	1975(1)	26(1)
C(232)	1334(4)	5570(2)	1996(1)	24(1)
C(233)	1985(4)	5170(2)	1818(1)	25(1)
C(234)	3197(4)	5232(2)	1622(2)	29(1)
C(235)	3741(4)	5688(2)	1605(1)	27(1)
C(237)	249(5)	4650(2)	1988(2)	34(1)
C(238)	2980(5)	8180(2)	2359(2)	30(1)
C(239)	2240(5)	8628(2)	2400(2)	35(1)
C(240)	1353(5)	8799(2)	2148(2)	35(1)
C(241)	1215(5)	8517(2)	1852(2)	30(1)
C(242)	3755(5)	8003(2)	2678(2)	30(1)
C(243)	4660(5)	8313(2)	2746(2)	33(1)
C(244)	5351(5)	8161(2)	3059(2)	36(1)
C(245)	5179(5)	7700(2)	3303(2)	35(1)
C(246)	4294(5)	7389(2)	3243(2)	38(1)
C(247)	3585(5)	7543(2)	2933(2)	37(1)
C(249)	5809(7)	7099(3)	3849(2)	62(2)
C(250)	948(5)	8556(2)	1003(2)	35(1)
C(251)	-257(6)	8740(2)	943(2)	42(1)
C(252)	-522(8)	9247(3)	795(2)	62(2)
C(253)	437(10)	9579(3)	701(2)	73(3)
C(254)	1624(9)	9405(3)	753(2)	65(2)
C(255)	1869(6)	8902(2)	906(2)	45(1)
C(256)	-875(14)	10273(6)	443(5)	170(6)
C(257)	2513(6)	4523(2)	2852(2)	44(1)
C(258)	1450(5)	4179(2)	2929(2)	39(1)
C(259)	-720(6)	4167(2)	3145(2)	48(2)
C(260)	-1875(7)	4498(3)	3210(2)	71(2)
C(262)	2604(6)	1416(3)	6059(2)	51(2)
C(263)	1570(5)	1057(2)	6178(2)	43(1)
C(264)	-601(6)	1046(3)	6392(2)	59(2)
C(265)	-1766(7)	1384(4)	6421(3)	78(2)
O(1)	5377(3)	-602(2)	4921(1)	37(1)
O(2)	-5252(3)	1552(1)	4026(1)	32(1)
O(3)	3344(4)	883(2)	1058(1)	53(1)
O(4)	6042(3)	4534(2)	6756(1)	43(1)
O(5)	383(5)	7073(2)	3869(1)	61(1)
O(6)	1623(3)	1660(1)	5004(1)	36(1)
O(7)	5023(3)	2464(2)	11445(1)	39(1)
O(8)	3510(3)	4688(2)	7585(1)	37(1)

Continued on following page

Table A2 *continued*

O(9)	-5238(3)	4768(1)	10769(1)	33(1)
O(10)	6638(4)	2268(2)	5595(1)	40(1)
O(11)	4428(3)	3696(2)	1692(1)	38(1)
O(12)	15006(3)	1616(1)	2586(1)	34(1)
O(13)	1771(3)	-1490(1)	8383(1)	36(1)
O(14)	6039(4)	1454(2)	10041(1)	72(2)
O(15)	576(5)	3922(2)	7058(2)	65(1)
O(16)	290(8)	10086(2)	551(2)	106(2)
O(17)	1527(3)	4705(1)	1820(1)	34(1)
O(18)	5940(4)	7579(2)	3592(1)	47(1)
O(19)	725(4)	7066(2)	8812(2)	62(1)
O(20)	325(4)	4471(2)	3033(1)	40(1)
O(21)	434(4)	1350(2)	6263(1)	46(1)
O(22)	4816(9)	9983(4)	-15(3)	41(2)
C(266)	4773(13)	10057(6)	387(4)	60(4)
C(267)	5688(16)	10067(8)	573(5)	68(5)
C(268)	3852(13)	9921(6)	-183(4)	66(4)
C(269)	3864(17)	9849(7)	-565(5)	66(5)
O(23)	8593(4)	7348(2)	199(1)	56(1)
O(24)	8141(9)	8292(4)	9690(3)	163(4)
O(25)	10138(4)	229(2)	5457(1)	12(1)
O(25S)	9587(6)	157(3)	5252(2)	15(2)

Table A3 Bond lengths [Å] and angles [°] for **283**.

C(1)-C(10)	1.412(6)	C(1)-C(14)	1.417(6)
C(1)-C(2)	1.476(6)	C(2)-C(7)	1.409(6)
C(2)-C(3)	1.423(6)	C(3)-C(4)	1.394(6)
C(3)-C(35)	1.489(6)	C(4)-C(5)	1.379(7)
C(4)-H(4)	0.9300	C(5)-C(6)	1.380(6)
C(5)-H(5)	0.9300	C(6)-C(7)	1.407(6)
C(6)-H(6)	0.9300	C(7)-C(8)	1.480(6)
C(8)-C(26)	1.417(6)	C(8)-C(9)	1.418(6)
C(9)-C(23)	1.412(6)	C(9)-C(10)	1.473(6)
C(10)-C(11)	1.424(6)	C(11)-C(12)	1.379(6)
C(11)-C(15)	1.479(6)	C(12)-C(13)	1.396(6)
C(12)-H(12)	0.9300	C(13)-C(14)	1.370(6)
C(13)-H(13)	0.9300	C(14)-H(14)	0.9300
C(15)-C(20)	1.387(6)	C(15)-C(16)	1.400(6)
C(16)-C(17)	1.379(6)	C(16)-H(16)	0.9300
C(17)-C(18)	1.395(7)	C(17)-H(17)	0.9300
C(18)-O(1)	1.366(5)	C(18)-C(19)	1.373(7)
C(19)-C(20)	1.385(6)	C(19)-H(19)	0.9300
C(20)-H(20)	0.9300	C(22)-O(1)	1.434(6)
C(22)-H(22A)	0.9600	C(22)-H(22B)	0.9600
C(22)-H(22C)	0.9600	C(23)-C(24)	1.364(6)
C(23)-H(23)	0.9300	C(24)-C(25)	1.382(6)
C(24)-H(24)	0.9300	C(25)-C(26)	1.396(6)
C(25)-H(25)	0.9300	C(26)-C(27)	1.492(6)
C(27)-C(28)	1.393(6)	C(27)-C(32)	1.398(6)
C(28)-C(29)	1.385(6)	C(28)-H(28)	0.9300
C(29)-C(30)	1.381(6)	C(29)-H(29)	0.9300
C(30)-O(2)	1.374(5)	C(30)-C(31)	1.386(6)
C(31)-C(32)	1.380(6)	C(31)-H(31)	0.9300
C(32)-H(32)	0.9300	C(34)-O(2)	1.422(6)
C(34)-H(34A)	0.9600	C(34)-H(34B)	0.9600
C(34)-H(34C)	0.9600	C(35)-C(36)	1.397(6)
C(35)-C(40)	1.402(6)	C(36)-C(37)	1.390(7)
C(36)-H(36)	0.9300	C(37)-C(38)	1.385(7)
C(37)-H(37)	0.9300	C(38)-O(3)	1.363(6)
C(38)-C(39)	1.389(7)	C(39)-C(40)	1.380(7)
C(39)-H(39)	0.9300	C(40)-H(40)	0.9300
C(42)-O(3)	1.434(8)	C(42)-H(42A)	0.9600
C(42)-H(42B)	0.9600	C(42)-H(42C)	0.9600
C(43)-C(52)	1.415(6)	C(43)-C(56)	1.419(6)
C(43)-C(44)	1.467(6)	C(44)-C(45)	1.414(6)
C(44)-C(49)	1.422(6)	C(45)-C(46)	1.373(7)

Continued on following page

Table A3 *continued*

C(45)-H(45)	0.9300	C(46)-C(47)	1.384(7)
C(46)-H(46)	0.9300	C(47)-C(48)	1.380(6)
C(47)-H(47)	0.9300	C(48)-C(49)	1.418(6)
C(48)-C(77)	1.495(6)	C(49)-C(50)	1.473(6)
C(50)-C(51)	1.412(6)	C(50)-C(65)	1.415(6)
C(51)-C(68)	1.430(6)	C(51)-C(52)	1.481(6)
C(52)-C(53)	1.399(6)	C(53)-C(54)	1.371(7)
C(53)-H(53)	0.9300	C(54)-C(55)	1.399(7)
C(54)-H(54)	0.9300	C(55)-C(56)	1.378(7)
C(55)-H(55)	0.9300	C(56)-C(57)	1.502(6)
C(57)-C(58)	1.385(7)	C(57)-C(62)	1.396(6)
C(58)-C(59)	1.394(7)	C(58)-H(58)	0.9300
C(59)-C(60)	1.395(7)	C(59)-H(59)	0.9300
C(60)-O(4)	1.367(6)	C(60)-C(61)	1.396(8)
C(61)-C(62)	1.370(7)	C(61)-H(61)	0.9300
C(62)-H(62)	0.9300	C(64)-O(4)	1.423(7)
C(64)-H(64A)	0.9600	C(64)-H(64B)	0.9600
C(64)-H(64C)	0.9600	C(65)-C(66)	1.388(6)
C(65)-H(65)	0.9300	C(66)-C(67)	1.389(7)
C(66)-H(66)	0.9300	C(67)-C(68)	1.382(6)
C(67)-H(67)	0.9300	C(68)-C(69)	1.498(6)
C(69)-C(74)	1.385(6)	C(69)-C(70)	1.392(7)
C(70)-C(71)	1.391(7)	C(70)-H(70)	0.9300
C(71)-C(72)	1.387(7)	C(71)-H(71)	0.9300
C(72)-O(5)	1.379(6)	C(72)-C(73)	1.383(8)
C(73)-C(74)	1.400(7)	C(73)-H(73)	0.9300
C(74)-H(74)	0.9300	C(76)-O(5)	1.373(8)
C(76)-H(76A)	0.9600	C(76)-H(76B)	0.9600
C(76)-H(76C)	0.9600	C(77)-C(82)	1.386(6)
C(77)-C(78)	1.401(6)	C(78)-C(79)	1.396(7)
C(78)-H(78)	0.9300	C(79)-C(80)	1.384(7)
C(79)-H(79)	0.9300	C(80)-O(6)	1.370(6)
C(80)-C(81)	1.392(7)	C(81)-C(82)	1.394(6)
C(81)-H(81)	0.9300	C(82)-H(82)	0.9300
C(84)-O(6)	1.427(6)	C(84)-H(84A)	0.9600
C(84)-H(84B)	0.9600	C(84)-H(84C)	0.9600
C(85)-C(98)	1.420(6)	C(85)-C(94)	1.428(6)
C(85)-C(86)	1.465(6)	C(86)-C(87)	1.411(6)
C(86)-C(91)	1.418(6)	C(87)-C(88)	1.374(6)
C(87)-H(87)	0.9300	C(88)-C(89)	1.392(6)
C(88)-H(88)	0.9300	C(89)-C(90)	1.394(6)
C(89)-H(89)	0.9300	C(90)-C(91)	1.420(6)
C(90)-C(119)	1.488(6)	C(91)-C(92)	1.477(6)

Continued on following page

Table A3 *continued*

C(92)-C(110)	1.415(6)	C(92)-C(93)	1.415(6)
C(93)-C(107)	1.432(6)	C(93)-C(94)	1.477(6)
C(94)-C(95)	1.403(6)	C(95)-C(96)	1.379(6)
C(95)-H(95)	0.9300	C(96)-C(97)	1.386(7)
C(96)-H(96)	0.9300	C(97)-C(98)	1.383(6)
C(97)-H(97)	0.9300	C(98)-C(99)	1.490(6)
C(99)-C(100)	1.388(7)	C(99)-C(104)	1.391(6)
C(100)-C(101)	1.371(7)	C(100)-H(100)	0.9300
C(101)-C(102)	1.383(7)	C(101)-H(101)	0.9300
C(102)-O(7)	1.373(6)	C(102)-C(103)	1.390(7)
C(103)-C(104)	1.394(6)	C(103)-H(103)	0.9300
C(104)-H(104)	0.9300	C(106)-O(7)	1.429(6)
C(106)-H(10A)	0.9600	C(106)-H(10B)	0.9600
C(106)-H(10C)	0.9600	C(107)-C(108)	1.399(6)
C(107)-C(111)	1.486(6)	C(108)-C(109)	1.380(7)
C(108)-H(108)	0.9300	C(109)-C(110)	1.371(6)
C(109)-H(109)	0.9300	C(110)-H(110)	0.9300
C(111)-C(116)	1.394(6)	C(111)-C(112)	1.403(6)
C(112)-C(113)	1.389(7)	C(112)-H(112)	0.9300
C(113)-C(114)	1.376(6)	C(113)-H(113)	0.9300
C(114)-O(8)	1.369(6)	C(114)-C(115)	1.392(7)
C(115)-C(116)	1.388(7)	C(115)-H(115)	0.9300
C(116)-H(116)	0.9300	C(118)-O(8)	1.428(7)
C(118)-H(11A)	0.9600	C(118)-H(11B)	0.9600
C(118)-H(11C)	0.9600	C(119)-C(124)	1.394(6)
C(119)-C(120)	1.397(6)	C(120)-C(121)	1.378(6)
C(120)-H(120)	0.9300	C(121)-C(122)	1.391(6)
C(121)-H(121)	0.9300	C(122)-O(9)	1.373(5)
C(122)-C(123)	1.379(6)	C(123)-C(124)	1.396(6)
C(123)-H(123)	0.9300	C(124)-H(124)	0.9300
C(126)-O(9)	1.416(6)	C(126)-H(12A)	0.9600
C(126)-H(12B)	0.9600	C(126)-H(12C)	0.9600
C(127)-C(136)	1.413(6)	C(127)-C(140)	1.418(6)
C(127)-C(128)	1.477(6)	C(128)-C(133)	1.410(6)
C(128)-C(129)	1.428(6)	C(129)-C(130)	1.392(6)
C(129)-C(161)	1.492(6)	C(130)-C(131)	1.382(6)
C(130)-H(130)	0.9300	C(131)-C(132)	1.365(6)
C(131)-H(131)	0.9300	C(132)-C(133)	1.414(6)
C(132)-H(132)	0.9300	C(133)-C(134)	1.477(6)
C(134)-C(149)	1.421(6)	C(134)-C(135)	1.424(6)
C(135)-C(152)	1.408(6)	C(135)-C(136)	1.467(6)
C(136)-C(137)	1.417(6)	C(137)-C(138)	1.391(6)
C(137)-C(141)	1.490(6)	C(138)-C(139)	1.385(7)

Continued on following page

Table A3 *continued*

C(138)-H(138)	0.9300	C(139)-C(140)	1.381(6)
C(139)-H(139)	0.9300	C(140)-H(140)	0.9300
C(141)-C(146)	1.393(6)	C(141)-C(142)	1.397(6)
C(142)-C(143)	1.388(6)	C(142)-H(142)	0.9300
C(143)-C(144)	1.390(6)	C(143)-H(143)	0.9300
C(144)-O(10)	1.365(6)	C(144)-C(145)	1.405(7)
C(145)-C(146)	1.376(7)	C(145)-H(145)	0.9300
C(146)-H(146)	0.9300	C(148)-O(10)	1.433(7)
C(148)-H(14A)	0.9600	C(148)-H(14B)	0.9600
C(148)-H(14C)	0.9600	C(149)-C(150)	1.398(6)
C(149)-C(153)	1.484(6)	C(150)-C(151)	1.378(6)
C(150)-H(150)	0.9300	C(151)-C(152)	1.390(6)
C(151)-H(151)	0.9300	C(152)-H(152)	0.9300
C(153)-C(158)	1.392(6)	C(153)-C(154)	1.396(7)
C(154)-C(155)	1.375(6)	C(154)-H(154)	0.9300
C(155)-C(156)	1.398(7)	C(155)-H(155)	0.9300
C(156)-O(11)	1.368(5)	C(156)-C(157)	1.383(7)
C(157)-C(158)	1.383(6)	C(157)-H(157)	0.9300
C(158)-H(158)	0.9300	C(160)-O(11)	1.421(6)
C(160)-H(16D)	0.9600	C(160)-H(16E)	0.9600
C(160)-H(16F)	0.9600	C(161)-C(166)	1.381(6)
C(161)-C(162)	1.391(6)	C(162)-C(163)	1.392(6)
C(162)-H(162)	0.9300	C(163)-C(164)	1.385(6)
C(163)-H(163)	0.9300	C(164)-O(12)	1.369(5)
C(164)-C(165)	1.391(6)	C(165)-C(166)	1.385(6)
C(165)-H(165)	0.9300	C(166)-H(166)	0.9300
C(168)-O(12)	1.428(6)	C(168)-H(16A)	0.9600
C(168)-H(16B)	0.9600	C(168)-H(16C)	0.9600
C(169)-C(178)	1.422(6)	C(169)-C(179)	1.430(6)
C(169)-C(170)	1.484(6)	C(170)-C(175)	1.412(6)
C(170)-C(171)	1.413(6)	C(171)-C(172)	1.372(7)
C(171)-H(171)	0.9300	C(172)-C(173)	1.402(7)
C(172)-H(172)	0.9300	C(173)-C(174)	1.391(7)
C(173)-H(173)	0.9300	C(174)-C(175)	1.413(7)
C(174)-C(203)	1.499(6)	C(175)-C(176)	1.474(7)
C(176)-C(177)	1.414(7)	C(176)-C(194)	1.416(7)
C(177)-C(191)	1.421(7)	C(177)-C(178)	1.460(6)
C(178)-C(182)	1.410(7)	C(179)-C(180)	1.385(6)
C(179)-C(183)	1.485(6)	C(180)-C(181)	1.387(7)
C(180)-H(180)	0.9300	C(181)-C(182)	1.383(7)
C(181)-H(181)	0.9300	C(182)-H(182)	0.9300
C(183)-C(188)	1.388(6)	C(183)-C(184)	1.392(7)
C(184)-C(185)	1.392(7)	C(184)-H(184)	0.9300

Continued on following page

Table A3 *continued*

C(185)-C(186)	1.385(7)	C(185)-H(185)	0.9300
C(186)-O(13)	1.381(6)	C(186)-C(187)	1.382(7)
C(187)-C(188)	1.389(6)	C(187)-H(187)	0.9300
C(188)-H(188)	0.9300	C(190)-O(13)	1.415(6)
C(190)-H(19A)	0.9600	C(190)-H(19B)	0.9600
C(190)-H(19C)	0.9600	C(191)-C(192)	1.387(7)
C(191)-C(195)	1.501(8)	C(192)-C(193)	1.383(8)
C(192)-H(192)	0.9300	C(193)-C(194)	1.372(7)
C(193)-H(193)	0.9300	C(194)-H(194)	0.9300
C(195)-C(200)	1.384(8)	C(195)-C(196)	1.395(7)
C(196)-C(197)	1.387(8)	C(196)-H(196)	0.9300
C(197)-C(198)	1.363(9)	C(197)-H(197)	0.9300
C(198)-O(14)	1.381(7)	C(198)-C(199)	1.403(8)
C(199)-C(200)	1.392(8)	C(199)-H(199)	0.9300
C(200)-H(200)	0.9300	C(202)-O(14)	1.429(9)
C(202)-H(20A)	0.9600	C(202)-H(20B)	0.9600
C(202)-H(20C)	0.9600	C(203)-C(204)	1.389(7)
C(203)-C(208)	1.400(7)	C(204)-C(205)	1.403(7)
C(204)-H(204)	0.9300	C(205)-C(206)	1.376(8)
C(205)-H(205)	0.9300	C(206)-O(15)	1.384(7)
C(206)-C(207)	1.387(8)	C(207)-C(208)	1.382(7)
C(207)-H(207)	0.9300	C(208)-H(208)	0.9300
C(210)-O(15)	1.377(8)	C(210)-H(21A)	0.9600
C(210)-H(21B)	0.9600	C(210)-H(21C)	0.9600
C(211)-C(212)	1.480(12)	C(211)-H(21I)	0.9600
C(211)-H(21J)	0.9600	C(211)-H(21K)	0.9600
C(212)-O(19)	1.442(9)	C(212)-H(21G)	0.9700
C(212)-H(21H)	0.9700	C(214)-O(19)	1.398(9)
C(214)-C(215)	1.523(12)	C(214)-H(21L)	0.9700
C(214)-H(21M)	0.9700	C(215)-H(21D)	0.9600
C(215)-H(21E)	0.9600	C(215)-H(21F)	0.9600
C(216)-C(225)	1.421(6)	C(216)-C(229)	1.430(6)
C(216)-C(217)	1.479(6)	C(217)-C(218)	1.410(7)
C(217)-C(222)	1.416(7)	C(218)-C(219)	1.373(7)
C(218)-H(218)	0.9300	C(219)-C(220)	1.389(7)
C(219)-H(219)	0.9300	C(220)-C(221)	1.387(7)
C(220)-H(220)	0.9300	C(221)-C(222)	1.414(7)
C(221)-C(250)	1.498(7)	C(222)-C(223)	1.478(7)
C(223)-C(241)	1.392(7)	C(223)-C(224)	1.428(7)
C(224)-C(238)	1.424(6)	C(224)-C(225)	1.460(7)
C(225)-C(226)	1.418(6)	C(226)-C(227)	1.366(7)
C(226)-H(226)	0.9300	C(227)-C(228)	1.393(7)
C(227)-H(227)	0.9300	C(228)-C(229)	1.388(6)

Continued on following page

Table A3 *continued*

C(228)-H(228)	0.9300	C(229)-C(230)	1.491(6)
C(230)-C(231)	1.394(6)	C(230)-C(235)	1.400(6)
C(231)-C(232)	1.389(6)	C(231)-H(231)	0.9300
C(232)-C(233)	1.389(6)	C(232)-H(232)	0.9300
C(233)-O(17)	1.366(6)	C(233)-C(234)	1.396(7)
C(234)-C(235)	1.381(7)	C(234)-H(234)	0.9300
C(235)-H(235)	0.9300	C(237)-O(17)	1.434(6)
C(237)-H(23A)	0.9600	C(237)-H(23B)	0.9600
C(237)-H(23C)	0.9600	C(238)-C(239)	1.391(7)
C(238)-C(242)	1.480(7)	C(239)-C(240)	1.397(8)
C(239)-H(239)	0.9300	C(240)-C(241)	1.379(7)
C(240)-H(240)	0.9300	C(241)-H(241)	0.9300
C(242)-C(247)	1.391(7)	C(242)-C(243)	1.405(7)
C(243)-C(244)	1.393(8)	C(243)-H(243)	0.9300
C(244)-C(245)	1.376(8)	C(244)-H(244)	0.9300
C(245)-O(18)	1.371(6)	C(245)-C(246)	1.380(7)
C(246)-C(247)	1.400(8)	C(246)-H(246)	0.9300
C(247)-H(247)	0.9300	C(249)-O(18)	1.435(8)
C(249)-H(24A)	0.9600	C(249)-H(24B)	0.9600
C(249)-H(24C)	0.9600	C(250)-C(255)	1.384(8)
C(250)-C(251)	1.401(8)	C(251)-C(252)	1.384(8)
C(251)-H(251)	0.9300	C(252)-C(253)	1.391(12)
C(252)-H(252)	0.9300	C(253)-O(16)	1.369(8)
C(253)-C(254)	1.370(12)	C(254)-C(255)	1.376(9)
C(254)-H(254)	0.9300	C(255)-H(255)	0.9300
C(256)-O(16)	1.410(15)	C(256)-H(25A)	0.9600
C(256)-H(25B)	0.9600	C(256)-H(25C)	0.9600
C(257)-C(258)	1.503(8)	C(257)-H(25D)	0.9600
C(257)-H(25E)	0.9600	C(257)-H(25F)	0.9600
C(258)-O(20)	1.422(6)	C(258)-H(25G)	0.9700
C(258)-H(25H)	0.9700	C(259)-O(20)	1.422(7)
C(259)-C(260)	1.482(9)	C(259)-H(25I)	0.9700
C(259)-H(25J)	0.9700	C(260)-H(26A)	0.9600
C(260)-H(26B)	0.9600	C(260)-H(26C)	0.9600
C(262)-C(263)	1.507(8)	C(262)-H(26F)	0.9600
C(262)-H(26G)	0.9600	C(262)-H(26H)	0.9600
C(263)-O(21)	1.421(7)	C(263)-H(26I)	0.9700
C(263)-H(26J)	0.9700	C(264)-O(21)	1.417(8)
C(264)-C(265)	1.493(10)	C(264)-H(26K)	0.9700
C(264)-H(26L)	0.9700	C(265)-H(26M)	0.9600
C(265)-H(26N)	0.9600	C(265)-H(26O)	0.9600
O(22)-C(268)	1.308(14)	O(22)-C(266)	1.407(15)
C(266)-C(267)	1.269(16)	C(266)-H(26P)	0.9700

Continued on following page

Table A3 *continued*

C(266)-H(26Q)	0.9700	C(267)-H(26R)	0.9600
C(267)-H(26S)	0.9600	C(267)-H(26T)	0.9600
C(268)-C(269)	1.342(16)	C(268)-H(26V)	0.9700
C(268)-H(26U)	0.9700	C(269)-H(26Y)	0.9600
C(269)-H(26W)	0.9600	C(269)-H(26X)	0.9600
C(10)-C(1)-C(14)	118.1(4)	C(10)-C(1)-C(2)	119.6(4)
C(14)-C(1)-C(2)	121.4(4)	C(7)-C(2)-C(3)	118.5(4)
C(7)-C(2)-C(1)	117.9(4)	C(3)-C(2)-C(1)	123.1(4)
C(4)-C(3)-C(2)	118.5(4)	C(4)-C(3)-C(35)	119.0(4)
C(2)-C(3)-C(35)	122.2(4)	C(5)-C(4)-C(3)	121.1(4)
C(5)-C(4)-H(4)	119.5	C(3)-C(4)-H(4)	119.5
C(4)-C(5)-C(6)	119.9(4)	C(4)-C(5)-H(5)	120.1
C(6)-C(5)-H(5)	120.1	C(5)-C(6)-C(7)	120.5(4)
C(5)-C(6)-H(6)	119.7	C(7)-C(6)-H(6)	119.7
C(6)-C(7)-C(2)	118.5(4)	C(6)-C(7)-C(8)	123.7(4)
C(2)-C(7)-C(8)	117.7(4)	C(26)-C(8)-C(9)	119.3(4)
C(26)-C(8)-C(7)	122.1(4)	C(9)-C(8)-C(7)	117.9(4)
C(23)-C(9)-C(8)	119.2(4)	C(23)-C(9)-C(10)	120.8(4)
C(8)-C(9)-C(10)	119.8(4)	C(1)-C(10)-C(11)	119.9(4)
C(1)-C(10)-C(9)	117.2(4)	C(11)-C(10)-C(9)	122.9(4)
C(12)-C(11)-C(10)	119.3(4)	C(12)-C(11)-C(15)	116.2(4)
C(10)-C(11)-C(15)	124.1(4)	C(11)-C(12)-C(13)	121.0(4)
C(11)-C(12)-H(12)	119.5	C(13)-C(12)-H(12)	119.5
C(14)-C(13)-C(12)	119.9(4)	C(14)-C(13)-H(13)	120.0
C(12)-C(13)-H(13)	120.0	C(13)-C(14)-C(1)	121.4(4)
C(13)-C(14)-H(14)	119.3	C(1)-C(14)-H(14)	119.3
C(20)-C(15)-C(16)	117.6(4)	C(20)-C(15)-C(11)	121.8(4)
C(16)-C(15)-C(11)	120.4(4)	C(17)-C(16)-C(15)	120.9(4)
C(17)-C(16)-H(16)	119.6	C(15)-C(16)-H(16)	119.6
C(16)-C(17)-C(18)	120.2(4)	C(16)-C(17)-H(17)	119.9
C(18)-C(17)-H(17)	119.9	O(1)-C(18)-C(19)	125.2(4)
O(1)-C(18)-C(17)	115.0(4)	C(19)-C(18)-C(17)	119.8(4)
C(18)-C(19)-C(20)	119.5(4)	C(18)-C(19)-H(19)	120.2
C(20)-C(19)-H(19)	120.2	C(19)-C(20)-C(15)	122.0(4)
C(19)-C(20)-H(20)	119.0	C(15)-C(20)-H(20)	119.0
O(1)-C(22)-H(22A)	109.5	O(1)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5	O(1)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5	H(22B)-C(22)-H(22C)	109.5
C(24)-C(23)-C(9)	121.0(4)	C(24)-C(23)-H(23)	119.5
C(9)-C(23)-H(23)	119.5	C(23)-C(24)-C(25)	119.9(4)
C(23)-C(24)-H(24)	120.1	C(25)-C(24)-H(24)	120.1
C(24)-C(25)-C(26)	121.9(4)	C(24)-C(25)-H(25)	119.0

Continued on following page

Table A3 *continued*

C(26)-C(25)-H(25)	119.0	C(25)-C(26)-C(8)	118.7(4)
C(25)-C(26)-C(27)	115.4(4)	C(8)-C(26)-C(27)	125.8(4)
C(28)-C(27)-C(32)	117.6(4)	C(28)-C(27)-C(26)	121.6(4)
C(32)-C(27)-C(26)	120.5(4)	C(29)-C(28)-C(27)	121.1(4)
C(29)-C(28)-H(28)	119.4	C(27)-C(28)-H(28)	119.4
C(30)-C(29)-C(28)	120.1(4)	C(30)-C(29)-H(29)	119.9
C(28)-C(29)-H(29)	119.9	O(2)-C(30)-C(29)	124.5(4)
O(2)-C(30)-C(31)	115.6(4)	C(29)-C(30)-C(31)	119.9(4)
C(32)-C(31)-C(30)	119.7(4)	C(32)-C(31)-H(31)	120.2
C(30)-C(31)-H(31)	120.2	C(31)-C(32)-C(27)	121.6(4)
C(31)-C(32)-H(32)	119.2	C(27)-C(32)-H(32)	119.2
O(2)-C(34)-H(34A)	109.5	O(2)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	109.5	O(2)-C(34)-H(34C)	109.5
H(34A)-C(34)-H(34C)	109.5	H(34B)-C(34)-H(34C)	109.5
C(36)-C(35)-C(40)	117.9(4)	C(36)-C(35)-C(3)	119.7(4)
C(40)-C(35)-C(3)	122.4(4)	C(37)-C(36)-C(35)	121.5(4)
C(37)-C(36)-H(36)	119.3	C(35)-C(36)-H(36)	119.3
C(38)-C(37)-C(36)	119.3(5)	C(38)-C(37)-H(37)	120.4
C(36)-C(37)-H(37)	120.4	O(3)-C(38)-C(37)	123.7(5)
O(3)-C(38)-C(39)	116.0(5)	C(37)-C(38)-C(39)	120.2(5)
C(40)-C(39)-C(38)	120.1(4)	C(40)-C(39)-H(39)	119.9
C(38)-C(39)-H(39)	119.9	C(39)-C(40)-C(35)	120.9(5)
C(39)-C(40)-H(40)	119.5	C(35)-C(40)-H(40)	119.5
O(3)-C(42)-H(42A)	109.5	O(3)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5	O(3)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5	H(42B)-C(42)-H(42C)	109.5
C(52)-C(43)-C(56)	118.8(4)	C(52)-C(43)-C(44)	118.5(4)
C(56)-C(43)-C(44)	122.5(4)	C(45)-C(44)-C(49)	118.6(4)
C(45)-C(44)-C(43)	122.6(4)	C(49)-C(44)-C(43)	118.8(4)
C(46)-C(45)-C(44)	120.7(4)	C(46)-C(45)-H(45)	119.7
C(44)-C(45)-H(45)	119.7	C(45)-C(46)-C(47)	119.3(4)
C(45)-C(46)-H(46)	120.4	C(47)-C(46)-H(46)	120.4
C(48)-C(47)-C(46)	121.6(5)	C(48)-C(47)-H(47)	119.2
C(46)-C(47)-H(47)	119.2	C(47)-C(48)-C(49)	119.2(4)
C(47)-C(48)-C(77)	117.0(4)	C(49)-C(48)-C(77)	123.4(4)
C(48)-C(49)-C(44)	117.6(4)	C(48)-C(49)-C(50)	125.0(4)
C(44)-C(49)-C(50)	116.8(4)	C(51)-C(50)-C(65)	118.4(4)
C(51)-C(50)-C(49)	120.2(4)	C(65)-C(50)-C(49)	120.3(4)
C(50)-C(51)-C(68)	119.8(4)	C(50)-C(51)-C(52)	117.9(4)
C(68)-C(51)-C(52)	122.3(4)	C(53)-C(52)-C(43)	119.8(4)
C(53)-C(52)-C(51)	121.3(4)	C(43)-C(52)-C(51)	118.8(4)
C(54)-C(53)-C(52)	120.7(4)	C(54)-C(53)-H(53)	119.6
C(52)-C(53)-H(53)	119.6	C(53)-C(54)-C(55)	119.8(4)

Continued on following page

Table A3 *continued*

C(53)-C(54)-H(54)	120.1	C(55)-C(54)-H(54)	120.1
C(56)-C(55)-C(54)	121.2(4)	C(56)-C(55)-H(55)	119.4
C(54)-C(55)-H(55)	119.4	C(55)-C(56)-C(43)	119.6(4)
C(55)-C(56)-C(57)	116.0(4)	C(43)-C(56)-C(57)	124.3(4)
C(58)-C(57)-C(62)	117.8(4)	C(58)-C(57)-C(56)	122.1(4)
C(62)-C(57)-C(56)	120.1(4)	C(57)-C(58)-C(59)	121.8(5)
C(57)-C(58)-H(58)	119.1	C(59)-C(58)-H(58)	119.1
C(58)-C(59)-C(60)	119.2(5)	C(58)-C(59)-H(59)	120.4
C(60)-C(59)-H(59)	120.4	O(4)-C(60)-C(59)	124.4(5)
O(4)-C(60)-C(61)	116.2(5)	C(59)-C(60)-C(61)	119.4(4)
C(62)-C(61)-C(60)	120.2(5)	C(62)-C(61)-H(61)	119.9
C(60)-C(61)-H(61)	119.9	C(61)-C(62)-C(57)	121.6(5)
C(61)-C(62)-H(62)	119.2	C(57)-C(62)-H(62)	119.2
O(4)-C(64)-H(64A)	109.5	O(4)-C(64)-H(64B)	109.5
H(64A)-C(64)-H(64B)	109.5	O(4)-C(64)-H(64C)	109.5
H(64A)-C(64)-H(64C)	109.5	H(64B)-C(64)-H(64C)	109.5
C(66)-C(65)-C(50)	120.8(4)	C(66)-C(65)-H(65)	119.6
C(50)-C(65)-H(65)	119.6	C(65)-C(66)-C(67)	120.3(4)
C(65)-C(66)-H(66)	119.8	C(67)-C(66)-H(66)	119.8
C(68)-C(67)-C(66)	120.7(4)	C(68)-C(67)-H(67)	119.6
C(66)-C(67)-H(67)	119.6	C(67)-C(68)-C(51)	119.5(4)
C(67)-C(68)-C(69)	116.7(4)	C(51)-C(68)-C(69)	123.6(4)
C(74)-C(69)-C(70)	118.1(4)	C(74)-C(69)-C(68)	121.1(4)
C(70)-C(69)-C(68)	120.8(4)	C(71)-C(70)-C(69)	121.3(5)
C(71)-C(70)-H(70)	119.4	C(69)-C(70)-H(70)	119.4
C(72)-C(71)-C(70)	119.9(5)	C(72)-C(71)-H(71)	120.0
C(70)-C(71)-H(71)	120.0	O(5)-C(72)-C(73)	125.8(5)
O(5)-C(72)-C(71)	114.6(5)	C(73)-C(72)-C(71)	119.6(5)
C(72)-C(73)-C(74)	119.9(5)	C(72)-C(73)-H(73)	120.0
C(74)-C(73)-H(73)	120.0	C(69)-C(74)-C(73)	121.2(5)
C(69)-C(74)-H(74)	119.4	C(73)-C(74)-H(74)	119.4
O(5)-C(76)-H(76A)	109.5	O(5)-C(76)-H(76B)	109.5
H(76A)-C(76)-H(76B)	109.5	O(5)-C(76)-H(76C)	109.5
H(76A)-C(76)-H(76C)	109.5	H(76B)-C(76)-H(76C)	109.5
C(82)-C(77)-C(78)	117.3(4)	C(82)-C(77)-C(48)	119.9(4)
C(78)-C(77)-C(48)	122.2(4)	C(79)-C(78)-C(77)	121.6(4)
C(79)-C(78)-H(78)	119.2	C(77)-C(78)-H(78)	119.2
C(80)-C(79)-C(78)	119.2(5)	C(80)-C(79)-H(79)	120.4
C(78)-C(79)-H(79)	120.4	O(6)-C(80)-C(79)	115.4(4)
O(6)-C(80)-C(81)	123.9(4)	C(79)-C(80)-C(81)	120.6(4)
C(80)-C(81)-C(82)	118.8(4)	C(80)-C(81)-H(81)	120.6
C(82)-C(81)-H(81)	120.6	C(77)-C(82)-C(81)	122.4(4)
C(77)-C(82)-H(82)	118.8	C(81)-C(82)-H(82)	118.8

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Table A3 *continued*

O(6)-C(84)-H(84A)	109.5	O(6)-C(84)-H(84B)	109.5
H(84A)-C(84)-H(84B)	109.5	O(6)-C(84)-H(84C)	109.5
H(84A)-C(84)-H(84C)	109.5	H(84B)-C(84)-H(84C)	109.5
C(98)-C(85)-C(94)	119.9(4)	C(98)-C(85)-C(86)	122.3(4)
C(94)-C(85)-C(86)	117.8(4)	C(87)-C(86)-C(91)	119.8(4)
C(87)-C(86)-C(85)	119.7(4)	C(91)-C(86)-C(85)	120.2(4)
C(88)-C(87)-C(86)	120.7(4)	C(88)-C(87)-H(87)	119.7
C(86)-C(87)-H(87)	119.7	C(87)-C(88)-C(89)	119.7(4)
C(87)-C(88)-H(88)	120.2	C(89)-C(88)-H(88)	120.2
C(88)-C(89)-C(90)	121.7(4)	C(88)-C(89)-H(89)	119.2
C(90)-C(89)-H(89)	119.2	C(89)-C(90)-C(91)	119.1(4)
C(89)-C(90)-C(119)	114.3(4)	C(91)-C(90)-C(119)	126.4(4)
C(86)-C(91)-C(90)	118.9(4)	C(86)-C(91)-C(92)	117.1(4)
C(90)-C(91)-C(92)	123.5(4)	C(110)-C(92)-C(93)	119.0(4)
C(110)-C(92)-C(91)	121.8(4)	C(93)-C(92)-C(91)	119.1(4)
C(92)-C(93)-C(107)	117.9(4)	C(92)-C(93)-C(94)	118.0(4)
C(107)-C(93)-C(94)	123.6(4)	C(95)-C(94)-C(85)	117.7(4)
C(95)-C(94)-C(93)	123.0(4)	C(85)-C(94)-C(93)	118.6(4)
C(96)-C(95)-C(94)	121.9(4)	C(96)-C(95)-H(95)	119.1
C(94)-C(95)-H(95)	119.1	C(95)-C(96)-C(97)	119.6(4)
C(95)-C(96)-H(96)	120.2	C(97)-C(96)-H(96)	120.2
C(98)-C(97)-C(96)	121.4(4)	C(98)-C(97)-H(97)	119.3
C(96)-C(97)-H(97)	119.3	C(97)-C(98)-C(85)	119.0(4)
C(97)-C(98)-C(99)	117.8(4)	C(85)-C(98)-C(99)	122.6(4)
C(100)-C(99)-C(104)	117.9(4)	C(100)-C(99)-C(98)	119.7(4)
C(104)-C(99)-C(98)	122.1(4)	C(101)-C(100)-C(99)	121.5(4)
C(101)-C(100)-H(100)	119.2	C(99)-C(100)-H(100)	119.2
C(100)-C(101)-C(102)	120.1(5)	C(100)-C(101)-H(101)	119.9
C(102)-C(101)-H(101)	119.9	O(7)-C(102)-C(101)	116.1(4)
O(7)-C(102)-C(103)	123.9(4)	C(101)-C(102)-C(103)	120.0(4)
C(102)-C(103)-C(104)	119.0(4)	C(102)-C(103)-H(103)	120.5
C(104)-C(103)-H(103)	120.5	C(99)-C(104)-C(103)	121.4(4)
C(99)-C(104)-H(104)	119.3	C(103)-C(104)-H(104)	119.3
O(7)-C(106)-H(10A)	109.5	O(7)-C(106)-H(10B)	109.5
H(10A)-C(106)-H(10B)	109.5	O(7)-C(106)-H(10C)	109.5
H(10A)-C(106)-H(10C)	109.5	H(10B)-C(106)-H(10C)	109.5
C(108)-C(107)-C(93)	119.0(4)	C(108)-C(107)-C(111)	117.0(4)
C(93)-C(107)-C(111)	123.9(4)	C(109)-C(108)-C(107)	120.9(4)
C(109)-C(108)-H(108)	119.5	C(107)-C(108)-H(108)	119.5
C(110)-C(109)-C(108)	120.4(4)	C(110)-C(109)-H(109)	119.8
C(108)-C(109)-H(109)	119.8	C(109)-C(110)-C(92)	120.4(4)
C(109)-C(110)-H(110)	119.8	C(92)-C(110)-H(110)	119.8
C(116)-C(111)-C(112)	118.2(4)	C(116)-C(111)-C(107)	120.1(4)

Continued on following page

Table A3 *continued*

C(112)-C(111)-C(107)	121.6(4)	C(113)-C(112)-C(111)	120.9(4)
C(113)-C(112)-H(112)	119.5	C(111)-C(112)-H(112)	119.5
C(114)-C(113)-C(112)	120.0(4)	C(114)-C(113)-H(113)	120.0
C(112)-C(113)-H(113)	120.0	O(8)-C(114)-C(113)	125.2(5)
O(8)-C(114)-C(115)	114.8(4)	C(113)-C(114)-C(115)	119.9(5)
C(116)-C(115)-C(114)	120.2(4)	C(116)-C(115)-H(115)	119.9
C(114)-C(115)-H(115)	119.9	C(115)-C(116)-C(111)	120.6(4)
C(115)-C(116)-H(116)	119.7	C(111)-C(116)-H(116)	119.7
O(8)-C(118)-H(11A)	109.5	O(8)-C(118)-H(11B)	109.5
H(11A)-C(118)-H(11B)	109.5	O(8)-C(118)-H(11C)	109.5
H(11A)-C(118)-H(11C)	109.5	H(11B)-C(118)-H(11C)	109.5
C(124)-C(119)-C(120)	117.8(4)	C(124)-C(119)-C(90)	121.8(4)
C(120)-C(119)-C(90)	120.2(4)	C(121)-C(120)-C(119)	121.1(4)
C(121)-C(120)-H(120)	119.5	C(119)-C(120)-H(120)	119.5
C(120)-C(121)-C(122)	120.4(4)	C(120)-C(121)-H(121)	119.8
C(122)-C(121)-H(121)	119.8	O(9)-C(122)-C(123)	124.3(4)
O(9)-C(122)-C(121)	115.9(4)	C(123)-C(122)-C(121)	119.8(4)
C(122)-C(123)-C(124)	119.6(4)	C(122)-C(123)-H(123)	120.2
C(124)-C(123)-H(123)	120.2	C(119)-C(124)-C(123)	121.3(4)
C(119)-C(124)-H(124)	119.3	C(123)-C(124)-H(124)	119.3
O(9)-C(126)-H(12A)	109.5	O(9)-C(126)-H(12B)	109.5
H(12A)-C(126)-H(12B)	109.5	O(9)-C(126)-H(12C)	109.5
H(12A)-C(126)-H(12C)	109.5	H(12B)-C(126)-H(12C)	109.5
C(136)-C(127)-C(140)	118.8(4)	C(136)-C(127)-C(128)	118.1(4)
C(140)-C(127)-C(128)	123.0(4)	C(133)-C(128)-C(129)	118.7(4)
C(133)-C(128)-C(127)	118.0(4)	C(129)-C(128)-C(127)	122.6(4)
C(130)-C(129)-C(128)	119.2(4)	C(130)-C(129)-C(161)	115.2(4)
C(128)-C(129)-C(161)	125.3(4)	C(131)-C(130)-C(129)	121.5(4)
C(131)-C(130)-H(130)	119.2	C(129)-C(130)-H(130)	119.2
C(132)-C(131)-C(130)	120.0(4)	C(132)-C(131)-H(131)	120.0
C(130)-C(131)-H(131)	120.0	C(131)-C(132)-C(133)	121.0(4)
C(131)-C(132)-H(132)	119.5	C(133)-C(132)-H(132)	119.5
C(128)-C(133)-C(132)	119.5(4)	C(128)-C(133)-C(134)	119.5(4)
C(132)-C(133)-C(134)	120.7(4)	C(149)-C(134)-C(135)	119.8(4)
C(149)-C(134)-C(133)	122.8(4)	C(135)-C(134)-C(133)	117.4(4)
C(152)-C(135)-C(134)	117.9(4)	C(152)-C(135)-C(136)	122.0(4)
C(134)-C(135)-C(136)	119.4(4)	C(127)-C(136)-C(137)	118.1(4)
C(127)-C(136)-C(135)	117.6(4)	C(137)-C(136)-C(135)	123.6(4)
C(138)-C(137)-C(136)	119.6(4)	C(138)-C(137)-C(141)	118.0(4)
C(136)-C(137)-C(141)	122.2(4)	C(139)-C(138)-C(137)	120.4(4)
C(139)-C(138)-H(138)	119.8	C(137)-C(138)-H(138)	119.8
C(140)-C(139)-C(138)	120.4(4)	C(140)-C(139)-H(139)	119.8
C(138)-C(139)-H(139)	119.8	C(139)-C(140)-C(127)	119.8(4)

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Table A3 *continued*

C(139)-C(140)-H(140)	120.1	C(127)-C(140)-H(140)	120.1
C(146)-C(141)-C(142)	118.3(4)	C(146)-C(141)-C(137)	121.4(4)
C(142)-C(141)-C(137)	120.2(4)	C(143)-C(142)-C(141)	121.0(4)
C(143)-C(142)-H(142)	119.5	C(141)-C(142)-H(142)	119.5
C(142)-C(143)-C(144)	120.0(4)	C(142)-C(143)-H(143)	120.0
C(144)-C(143)-H(143)	120.0	O(10)-C(144)-C(143)	125.2(5)
O(10)-C(144)-C(145)	115.4(4)	C(143)-C(144)-C(145)	119.5(4)
C(146)-C(145)-C(144)	119.7(4)	C(146)-C(145)-H(145)	120.1
C(144)-C(145)-H(145)	120.1	C(145)-C(146)-C(141)	121.6(4)
C(145)-C(146)-H(146)	119.2	C(141)-C(146)-H(146)	119.2
O(10)-C(148)-H(14A)	109.5	O(10)-C(148)-H(14B)	109.5
H(14A)-C(148)-H(14B)	109.5	O(10)-C(148)-H(14C)	109.5
H(14A)-C(148)-H(14C)	109.5	H(14B)-C(148)-H(14C)	109.5
C(150)-C(149)-C(134)	119.4(4)	C(150)-C(149)-C(153)	116.4(4)
C(134)-C(149)-C(153)	123.9(4)	C(151)-C(150)-C(149)	120.9(4)
C(151)-C(150)-H(150)	119.6	C(149)-C(150)-H(150)	119.6
C(150)-C(151)-C(152)	120.1(4)	C(150)-C(151)-H(151)	119.9
C(152)-C(151)-H(151)	119.9	C(151)-C(152)-C(135)	121.6(4)
C(151)-C(152)-H(152)	119.2	C(135)-C(152)-H(152)	119.2
C(158)-C(153)-C(154)	117.5(4)	C(158)-C(153)-C(149)	121.5(4)
C(154)-C(153)-C(149)	121.0(4)	C(155)-C(154)-C(153)	121.1(4)
C(155)-C(154)-H(154)	119.4	C(153)-C(154)-H(154)	119.4
C(154)-C(155)-C(156)	120.3(4)	C(154)-C(155)-H(155)	119.8
C(156)-C(155)-H(155)	119.8	O(11)-C(156)-C(157)	124.7(4)
O(11)-C(156)-C(155)	115.8(4)	C(157)-C(156)-C(155)	119.5(4)
C(156)-C(157)-C(158)	119.3(4)	C(156)-C(157)-H(157)	120.3
C(158)-C(157)-H(157)	120.3	C(157)-C(158)-C(153)	122.2(4)
C(157)-C(158)-H(158)	118.9	C(153)-C(158)-H(158)	118.9
O(11)-C(160)-H(16D)	109.5	O(11)-C(160)-H(16E)	109.5
H(16D)-C(160)-H(16E)	109.5	O(11)-C(160)-H(16F)	109.5
H(16D)-C(160)-H(16F)	109.5	H(16E)-C(160)-H(16F)	109.5
C(166)-C(161)-C(162)	117.9(4)	C(166)-C(161)-C(129)	119.9(4)
C(162)-C(161)-C(129)	122.1(4)	C(161)-C(162)-C(163)	121.1(4)
C(161)-C(162)-H(162)	119.4	C(163)-C(162)-H(162)	119.4
C(164)-C(163)-C(162)	120.0(4)	C(164)-C(163)-H(163)	120.0
C(162)-C(163)-H(163)	120.0	O(12)-C(164)-C(163)	123.8(4)
O(12)-C(164)-C(165)	116.7(4)	C(163)-C(164)-C(165)	119.5(4)
C(166)-C(165)-C(164)	119.6(4)	C(166)-C(165)-H(165)	120.2
C(164)-C(165)-H(165)	120.2	C(161)-C(166)-C(165)	121.9(4)
C(161)-C(166)-H(166)	119.0	C(165)-C(166)-H(166)	119.0
O(12)-C(168)-H(16A)	109.5	O(12)-C(168)-H(16B)	109.5
H(16A)-C(168)-H(16B)	109.5	O(12)-C(168)-H(16C)	109.5
H(16A)-C(168)-H(16C)	109.5	H(16B)-C(168)-H(16C)	109.5

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Table A3 *continued*

C(178)-C(169)-C(179)	117.0(4)	C(178)-C(169)-C(170)	117.0(4)
C(179)-C(169)-C(170)	125.0(4)	C(175)-C(170)-C(171)	119.3(4)
C(175)-C(170)-C(169)	120.0(4)	C(171)-C(170)-C(169)	119.6(4)
C(172)-C(171)-C(170)	120.1(5)	C(172)-C(171)-H(171)	119.9
C(170)-C(171)-H(171)	119.9	C(171)-C(172)-C(173)	120.7(5)
C(171)-C(172)-H(172)	119.6	C(173)-C(172)-H(172)	119.6
C(174)-C(173)-C(172)	120.5(5)	C(174)-C(173)-H(173)	119.7
C(172)-C(173)-H(173)	119.7	C(173)-C(174)-C(175)	119.2(4)
C(173)-C(174)-C(203)	116.4(4)	C(175)-C(174)-C(203)	124.3(4)
C(170)-C(175)-C(174)	119.9(4)	C(170)-C(175)-C(176)	117.3(4)
C(174)-C(175)-C(176)	122.7(4)	C(177)-C(176)-C(194)	119.1(4)
C(177)-C(176)-C(175)	119.4(4)	C(194)-C(176)-C(175)	121.3(4)
C(176)-C(177)-C(191)	119.1(4)	C(176)-C(177)-C(178)	118.7(4)
C(191)-C(177)-C(178)	122.0(4)	C(182)-C(178)-C(169)	119.7(4)
C(182)-C(178)-C(177)	122.5(4)	C(169)-C(178)-C(177)	117.9(4)
C(180)-C(179)-C(169)	118.9(4)	C(180)-C(179)-C(183)	116.3(4)
C(169)-C(179)-C(183)	124.1(4)	C(179)-C(180)-C(181)	122.4(5)
C(179)-C(180)-H(180)	118.8	C(181)-C(180)-H(180)	118.8
C(182)-C(181)-C(180)	118.5(4)	C(182)-C(181)-H(181)	120.7
C(180)-C(181)-H(181)	120.7	C(181)-C(182)-C(178)	120.6(4)
C(181)-C(182)-H(182)	119.7	C(178)-C(182)-H(182)	119.7
C(188)-C(183)-C(184)	117.5(4)	C(188)-C(183)-C(179)	120.4(4)
C(184)-C(183)-C(179)	121.5(4)	C(183)-C(184)-C(185)	121.5(5)
C(183)-C(184)-H(184)	119.2	C(185)-C(184)-H(184)	119.2
C(186)-C(185)-C(184)	119.5(5)	C(186)-C(185)-H(185)	120.3
C(184)-C(185)-H(185)	120.3	O(13)-C(186)-C(187)	124.9(4)
O(13)-C(186)-C(185)	114.9(4)	C(187)-C(186)-C(185)	120.2(4)
C(186)-C(187)-C(188)	119.5(4)	C(186)-C(187)-H(187)	120.3
C(188)-C(187)-H(187)	120.3	C(183)-C(188)-C(187)	121.8(4)
C(183)-C(188)-H(188)	119.1	C(187)-C(188)-H(188)	119.1
O(13)-C(190)-H(19A)	109.5	O(13)-C(190)-H(19B)	109.5
H(19A)-C(190)-H(19B)	109.5	O(13)-C(190)-H(19C)	109.5
H(19A)-C(190)-H(19C)	109.5	H(19B)-C(190)-H(19C)	109.5
C(192)-C(191)-C(177)	119.3(5)	C(192)-C(191)-C(195)	115.4(5)
C(177)-C(191)-C(195)	125.0(5)	C(193)-C(192)-C(191)	121.5(5)
C(193)-C(192)-H(192)	119.2	C(191)-C(192)-H(192)	119.2
C(194)-C(193)-C(192)	120.1(5)	C(194)-C(193)-H(193)	120.0
C(192)-C(193)-H(193)	120.0	C(193)-C(194)-C(176)	120.7(5)
C(193)-C(194)-H(194)	119.7	C(176)-C(194)-H(194)	119.7
C(200)-C(195)-C(196)	117.9(5)	C(200)-C(195)-C(191)	121.5(5)
C(196)-C(195)-C(191)	120.4(5)	C(197)-C(196)-C(195)	121.1(6)
C(197)-C(196)-H(196)	119.4	C(195)-C(196)-H(196)	119.4
C(198)-C(197)-C(196)	120.2(5)	C(198)-C(197)-H(197)	119.9

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Table A3 *continued*

C(196)-C(197)-H(197)	119.9	C(197)-C(198)-O(14)	125.9(6)
C(197)-C(198)-C(199)	120.3(6)	O(14)-C(198)-C(199)	113.8(6)
C(200)-C(199)-C(198)	118.7(6)	C(200)-C(199)-H(199)	120.6
C(198)-C(199)-H(199)	120.6	C(195)-C(200)-C(199)	121.7(5)
C(195)-C(200)-H(200)	119.1	C(199)-C(200)-H(200)	119.1
O(14)-C(202)-H(20A)	109.5	O(14)-C(202)-H(20B)	109.5
H(20A)-C(202)-H(20B)	109.5	O(14)-C(202)-H(20C)	109.5
H(20A)-C(202)-H(20C)	109.5	H(20B)-C(202)-H(20C)	109.5
C(204)-C(203)-C(208)	117.8(5)	C(204)-C(203)-C(174)	121.4(4)
C(208)-C(203)-C(174)	120.7(4)	C(203)-C(204)-C(205)	120.9(5)
C(203)-C(204)-H(204)	119.6	C(205)-C(204)-H(204)	119.6
C(206)-C(205)-C(204)	120.1(5)	C(206)-C(205)-H(205)	120.0
C(204)-C(205)-H(205)	120.0	C(205)-C(206)-O(15)	125.5(5)
C(205)-C(206)-C(207)	119.8(5)	O(15)-C(206)-C(207)	114.7(5)
C(208)-C(207)-C(206)	120.1(5)	C(208)-C(207)-H(207)	119.9
C(206)-C(207)-H(207)	119.9	C(207)-C(208)-C(203)	121.3(5)
C(207)-C(208)-H(208)	119.3	C(203)-C(208)-H(208)	119.3
O(15)-C(210)-H(21A)	109.5	O(15)-C(210)-H(21B)	109.5
H(21A)-C(210)-H(21B)	109.5	O(15)-C(210)-H(21C)	109.5
H(21A)-C(210)-H(21C)	109.5	H(21B)-C(210)-H(21C)	109.5
C(212)-C(211)-H(21I)	109.5	C(212)-C(211)-H(21J)	109.5
H(21I)-C(211)-H(21J)	109.5	C(212)-C(211)-H(21K)	109.5
H(21I)-C(211)-H(21K)	109.5	H(21J)-C(211)-H(21K)	109.5
O(19)-C(212)-C(211)	109.4(6)	O(19)-C(212)-H(21G)	109.8
C(211)-C(212)-H(21G)	109.8	O(19)-C(212)-H(21H)	109.8
C(211)-C(212)-H(21H)	109.8	H(21G)-C(212)-H(21H)	108.2
O(19)-C(214)-C(215)	106.7(6)	O(19)-C(214)-H(21L)	110.4
C(215)-C(214)-H(21L)	110.4	O(19)-C(214)-H(21M)	110.4
C(215)-C(214)-H(21M)	110.4	H(21L)-C(214)-H(21M)	108.6
C(214)-C(215)-H(21D)	109.5	C(214)-C(215)-H(21E)	109.5
H(21D)-C(215)-H(21E)	109.5	C(214)-C(215)-H(21F)	109.5
H(21D)-C(215)-H(21F)	109.5	H(21E)-C(215)-H(21F)	109.5
C(225)-C(216)-C(229)	117.8(4)	C(225)-C(216)-C(217)	117.1(4)
C(229)-C(216)-C(217)	124.5(4)	C(218)-C(217)-C(222)	118.5(4)
C(218)-C(217)-C(216)	120.6(4)	C(222)-C(217)-C(216)	119.9(4)
C(219)-C(218)-C(217)	121.4(5)	C(219)-C(218)-H(218)	119.3
C(217)-C(218)-H(218)	119.3	C(218)-C(219)-C(220)	119.6(5)
C(218)-C(219)-H(219)	120.2	C(220)-C(219)-H(219)	120.2
C(221)-C(220)-C(219)	121.3(5)	C(221)-C(220)-H(220)	119.3
C(219)-C(220)-H(220)	119.3	C(220)-C(221)-C(222)	119.4(5)
C(220)-C(221)-C(250)	114.8(4)	C(222)-C(221)-C(250)	125.6(4)
C(221)-C(222)-C(217)	119.4(4)	C(221)-C(222)-C(223)	122.1(4)
C(217)-C(222)-C(223)	118.5(4)	C(241)-C(223)-C(224)	119.0(4)

Continued on following page

Table A3 *continued*

C(241)-C(223)-C(222)	121.7(4)	C(224)-C(223)-C(222)	119.1(4)
C(238)-C(224)-C(223)	119.0(4)	C(238)-C(224)-C(225)	122.8(4)
C(223)-C(224)-C(225)	118.1(4)	C(226)-C(225)-C(216)	118.5(4)
C(226)-C(225)-C(224)	122.0(4)	C(216)-C(225)-C(224)	119.6(4)
C(227)-C(226)-C(225)	121.1(4)	C(227)-C(226)-H(226)	119.5
C(225)-C(226)-H(226)	119.5	C(226)-C(227)-C(228)	119.1(4)
C(226)-C(227)-H(227)	120.4	C(228)-C(227)-H(227)	120.4
C(229)-C(228)-C(227)	121.7(5)	C(229)-C(228)-H(228)	119.1
C(227)-C(228)-H(228)	119.1	C(228)-C(229)-C(216)	118.6(4)
C(228)-C(229)-C(230)	116.0(4)	C(216)-C(229)-C(230)	125.0(4)
C(231)-C(230)-C(235)	117.4(4)	C(231)-C(230)-C(229)	119.9(4)
C(235)-C(230)-C(229)	122.3(4)	C(232)-C(231)-C(230)	122.0(4)
C(232)-C(231)-H(231)	119.0	C(230)-C(231)-H(231)	119.0
C(231)-C(232)-C(233)	119.6(4)	C(231)-C(232)-H(232)	120.2
C(233)-C(232)-H(232)	120.2	O(17)-C(233)-C(232)	124.6(4)
O(17)-C(233)-C(234)	116.0(4)	C(232)-C(233)-C(234)	119.4(4)
C(235)-C(234)-C(233)	120.2(4)	C(235)-C(234)-H(234)	119.9
C(233)-C(234)-H(234)	119.9	C(234)-C(235)-C(230)	121.4(4)
C(234)-C(235)-H(235)	119.3	C(230)-C(235)-H(235)	119.3
O(17)-C(237)-H(23A)	109.5	O(17)-C(237)-H(23B)	109.5
H(23A)-C(237)-H(23B)	109.5	O(17)-C(237)-H(23C)	109.5
H(23A)-C(237)-H(23C)	109.5	H(23B)-C(237)-H(23C)	109.5
C(239)-C(238)-C(224)	119.1(5)	C(239)-C(238)-C(242)	116.2(4)
C(224)-C(238)-C(242)	124.6(5)	C(238)-C(239)-C(240)	121.7(5)
C(238)-C(239)-H(239)	119.2	C(240)-C(239)-H(239)	119.2
C(241)-C(240)-C(239)	118.9(5)	C(241)-C(240)-H(240)	120.5
C(239)-C(240)-H(240)	120.5	C(240)-C(241)-C(223)	122.0(5)
C(240)-C(241)-H(241)	119.0	C(223)-C(241)-H(241)	119.0
C(247)-C(242)-C(243)	117.5(5)	C(247)-C(242)-C(238)	122.2(4)
C(243)-C(242)-C(238)	120.2(5)	C(244)-C(243)-C(242)	120.7(5)
C(244)-C(243)-H(243)	119.7	C(242)-C(243)-H(243)	119.7
C(245)-C(244)-C(243)	120.7(5)	C(245)-C(244)-H(244)	119.7
C(243)-C(244)-H(244)	119.7	O(18)-C(245)-C(244)	115.9(5)
O(18)-C(245)-C(246)	124.2(5)	C(244)-C(245)-C(246)	119.9(5)
C(245)-C(246)-C(247)	119.6(5)	C(245)-C(246)-H(246)	120.2
C(247)-C(246)-H(246)	120.2	C(242)-C(247)-C(246)	121.6(5)
C(242)-C(247)-H(247)	119.2	C(246)-C(247)-H(247)	119.2
O(18)-C(249)-H(24A)	109.5	O(18)-C(249)-H(24B)	109.5
H(24A)-C(249)-H(24B)	109.5	O(18)-C(249)-H(24C)	109.5
H(24A)-C(249)-H(24C)	109.5	H(24B)-C(249)-H(24C)	109.5
C(255)-C(250)-C(251)	117.3(5)	C(255)-C(250)-C(221)	121.5(5)
C(251)-C(250)-C(221)	120.9(5)	C(252)-C(251)-C(250)	121.5(6)
C(252)-C(251)-H(251)	119.2	C(250)-C(251)-H(251)	119.2

Continued on following page

Table A3 *continued*

C(251)-C(252)-C(253)	118.9(7)	C(251)-C(252)-H(252)	120.5
C(253)-C(252)-H(252)	120.5	O(16)-C(253)-C(254)	115.3(9)
O(16)-C(253)-C(252)	124.3(9)	C(254)-C(253)-C(252)	120.4(6)
C(253)-C(254)-C(255)	119.9(7)	C(253)-C(254)-H(254)	120.0
C(255)-C(254)-H(254)	120.0	C(254)-C(255)-C(250)	121.9(7)
C(254)-C(255)-H(255)	119.1	C(250)-C(255)-H(255)	119.1
O(16)-C(256)-H(25A)	109.5	O(16)-C(256)-H(25B)	109.5
H(25A)-C(256)-H(25B)	109.5	O(16)-C(256)-H(25C)	109.5
H(25A)-C(256)-H(25C)	109.5	H(25B)-C(256)-H(25C)	109.5
C(258)-C(257)-H(25D)	109.5	C(258)-C(257)-H(25E)	109.5
H(25D)-C(257)-H(25E)	109.5	C(258)-C(257)-H(25F)	109.5
H(25D)-C(257)-H(25F)	109.5	H(25E)-C(257)-H(25F)	109.5
O(20)-C(258)-C(257)	109.2(5)	O(20)-C(258)-H(25G)	109.8
C(257)-C(258)-H(25G)	109.8	O(20)-C(258)-H(25H)	109.8
C(257)-C(258)-H(25H)	109.8	H(25G)-C(258)-H(25H)	108.3
O(20)-C(259)-C(260)	110.3(6)	O(20)-C(259)-H(25I)	109.6
C(260)-C(259)-H(25I)	109.6	O(20)-C(259)-H(25J)	109.6
C(260)-C(259)-H(25J)	109.6	H(25I)-C(259)-H(25J)	108.1
C(259)-C(260)-H(26A)	109.5	C(259)-C(260)-H(26B)	109.5
H(26A)-C(260)-H(26B)	109.5	C(259)-C(260)-H(26C)	109.5
H(26A)-C(260)-H(26C)	109.5	H(26B)-C(260)-H(26C)	109.5
C(263)-C(262)-H(26F)	109.5	C(263)-C(262)-H(26G)	109.5
H(26F)-C(262)-H(26G)	109.5	C(263)-C(262)-H(26H)	109.5
H(26F)-C(262)-H(26H)	109.5	H(26G)-C(262)-H(26H)	109.5
O(21)-C(263)-C(262)	108.5(5)	O(21)-C(263)-H(26I)	110.0
C(262)-C(263)-H(26I)	110.0	O(21)-C(263)-H(26J)	110.0
C(262)-C(263)-H(26J)	110.0	H(26I)-C(263)-H(26J)	108.4
O(21)-C(264)-C(265)	109.5(6)	O(21)-C(264)-H(26K)	109.8
C(265)-C(264)-H(26K)	109.8	O(21)-C(264)-H(26L)	109.8
C(265)-C(264)-H(26L)	109.8	H(26K)-C(264)-H(26L)	108.2
C(264)-C(265)-H(26M)	109.5	C(264)-C(265)-H(26N)	109.5
H(26M)-C(265)-H(26N)	109.5	C(264)-C(265)-H(26O)	109.5
H(26M)-C(265)-H(26O)	109.5	H(26N)-C(265)-H(26O)	109.5
C(18)-O(1)-C(22)	117.5(4)	C(30)-O(2)-C(34)	117.1(4)
C(38)-O(3)-C(42)	117.8(5)	C(60)-O(4)-C(64)	118.1(5)
C(76)-O(5)-C(72)	119.3(6)	C(80)-O(6)-C(84)	116.9(4)
C(102)-O(7)-C(106)	117.8(4)	C(114)-O(8)-C(118)	117.5(4)
C(122)-O(9)-C(126)	117.6(4)	C(144)-O(10)-C(148)	117.3(4)
C(156)-O(11)-C(160)	117.6(4)	C(164)-O(12)-C(168)	117.4(4)
C(186)-O(13)-C(190)	117.5(4)	C(198)-O(14)-C(202)	117.1(7)
C(210)-O(15)-C(206)	119.3(6)	C(253)-O(16)-C(256)	118.0(10)
C(233)-O(17)-C(237)	116.7(4)	C(245)-O(18)-C(249)	118.0(5)
C(214)-O(19)-C(212)	111.0(6)	C(258)-O(20)-C(259)	113.0(4)

Continued on following page

Table A3 *continued*

C(264)-O(21)-C(263)	113.3(5)	C(268)-O(22)-C(266)	125.1(12)
C(267)-C(266)-O(22)	127.1(15)	C(267)-C(266)-H(26P)	105.5
O(22)-C(266)-H(26P)	105.5	C(267)-C(266)-H(26Q)	105.5
O(22)-C(266)-H(26Q)	105.5	H(26P)-C(266)-H(26Q)	106.1
O(22)-C(268)-C(269)	126.5(16)	O(22)-C(268)-H(26V)	105.7
C(269)-C(268)-H(26V)	105.7	O(22)-C(268)-H(26U)	105.7
C(269)-C(268)-H(26U)	105.7	H(26V)-C(268)-H(26U)	106.1

Table A4 Anisotropic displacement parameters (Å^2 $\times 10^3$) for **283**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}\mathrm{U}^{11} + ... + 2hka^*b^*\mathrm{U}^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(2)	24(2)	17(2)	-4(2)	-2(2)	-1(2)
C(2)	24(2)	15(2)	18(2)	-2(2)	-6(2)	-1(2)
C(3)	29(2)	18(2)	18(2)	-5(2)	-6(2)	0(2)
C(4)	30(2)	26(2)	23(2)	-7(2)	-10(2)	-3(2)
C(5)	24(2)	19(2)	31(3)	-3(2)	-9(2)	-4(2)
C(6)	24(2)	19(2)	22(2)	-3(2)	-1(2)	0(2)
C(7)	26(2)	17(2)	18(2)	-4(2)	-7(2)	2(2)
C(8)	23(2)	13(2)	15(2)	0(2)	-4(2)	2(2)
C(9)	23(2)	17(2)	16(2)	-1(2)	-5(2)	2(2)
C(10)	19(2)	19(2)	17(2)	1(2)	0(2)	-1(2)
C(11)	20(2)	30(2)	17(2)	-2(2)	-6(2)	-1(2)
C(12)	24(2)	31(3)	23(2)	-6(2)	-5(2)	5(2)
C(13)	32(3)	30(3)	21(2)	-9(2)	-2(2)	8(2)
C(14)	31(2)	28(2)	17(2)	-8(2)	-7(2)	5(2)
C(15)	21(2)	21(2)	20(2)	-2(2)	-6(2)	3(2)
C(16)	26(2)	21(2)	26(2)	-2(2)	-5(2)	0(2)
C(17)	35(3)	27(2)	19(2)	0(2)	-4(2)	-4(2)
C(18)	31(3)	25(2)	17(2)	-1(2)	-7(2)	6(2)
C(19)	20(2)	34(3)	23(2)	-1(2)	-4(2)	2(2)
C(20)	24(2)	27(2)	19(2)	0(2)	0(2)	0(2)
C(22)	43(3)	54(4)	26(3)	-4(2)	-16(2)	7(3)
C(23)	26(2)	29(2)	20(2)	-5(2)	-10(2)	2(2)
C(24)	39(3)	26(2)	21(2)	-10(2)	-13(2)	2(2)
C(25)	31(3)	31(3)	20(2)	-9(2)	-7(2)	5(2)
C(26)	23(2)	21(2)	17(2)	2(2)	-4(2)	1(2)
C(27)	25(2)	16(2)	16(2)	-5(2)	0(2)	0(2)
C(28)	25(2)	26(2)	16(2)	-2(2)	0(2)	-5(2)
C(29)	29(2)	19(2)	23(2)	1(2)	-9(2)	0(2)
C(30)	23(2)	17(2)	26(2)	-1(2)	-4(2)	-3(2)
C(31)	27(2)	30(3)	23(2)	3(2)	4(2)	-2(2)
C(32)	28(2)	30(3)	15(2)	4(2)	0(2)	2(2)
C(34)	31(3)	37(3)	44(3)	-4(2)	-10(2)	8(2)
C(35)	28(2)	22(2)	18(2)	-2(2)	-9(2)	6(2)
C(36)	32(3)	21(2)	22(2)	-4(2)	-6(2)	4(2)
C(37)	33(3)	26(3)	29(3)	-2(2)	3(2)	1(2)
C(38)	44(3)	33(3)	20(2)	-4(2)	3(2)	7(2)
C(39)	39(3)	34(3)	25(3)	-12(2)	-7(2)	9(2)
C(40)	33(3)	23(2)	24(2)	-5(2)	-12(2)	2(2)
C(42)	99(6)	53(5)	65(5)	-10(4)	35(4)	-25(4)

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Table A4 *continued*

C(43)	20(2)	22(2)	19(2)	-3(2)	0(2)	-5(2)
C(44)	23(2)	24(2)	17(2)	-1(2)	0(2)	-6(2)
C(45)	26(2)	29(3)	20(2)	-1(2)	-2(2)	-7(2)
C(46)	20(2)	35(3)	30(3)	-3(2)	-7(2)	0(2)
C(47)	24(2)	31(3)	32(3)	-5(2)	-4(2)	4(2)
C(48)	21(2)	26(2)	17(2)	-3(2)	2(2)	0(2)
C(49)	20(2)	21(2)	20(2)	-3(2)	-2(2)	-2(2)
C(50)	20(2)	26(2)	19(2)	-3(2)	-1(2)	-3(2)
C(51)	21(2)	23(2)	18(2)	-3(2)	1(2)	-4(2)
C(52)	22(2)	22(2)	22(2)	-6(2)	4(2)	-3(2)
C(53)	26(2)	23(2)	22(2)	-2(2)	4(2)	-1(2)
C(54)	37(3)	21(2)	27(3)	-5(2)	2(2)	3(2)
C(55)	41(3)	25(2)	24(2)	-9(2)	2(2)	-7(2)
C(56)	26(2)	25(2)	23(2)	-6(2)	1(2)	-4(2)
C(57)	30(3)	33(3)	19(2)	-10(2)	0(2)	-6(2)
C(58)	37(3)	34(3)	27(3)	-4(2)	-6(2)	-13(2)
C(59)	41(3)	31(3)	25(3)	-3(2)	-6(2)	-6(2)
C(60)	27(3)	47(3)	23(2)	-14(2)	-4(2)	1(2)
C(61)	30(3)	40(3)	33(3)	-20(2)	-2(2)	-8(2)
C(62)	33(3)	27(3)	28(3)	-10(2)	2(2)	-7(2)
C(64)	68(4)	49(4)	44(4)	-3(3)	-25(3)	6(3)
C(65)	27(2)	21(2)	24(2)	-4(2)	-4(2)	-2(2)
C(66)	33(3)	29(3)	18(2)	-7(2)	-6(2)	-3(2)
C(67)	27(2)	27(2)	23(2)	0(2)	-6(2)	-2(2)
C(68)	21(2)	24(2)	22(2)	0(2)	-3(2)	1(2)
C(69)	27(2)	25(2)	15(2)	-4(2)	0(2)	2(2)
C(70)	27(2)	32(3)	26(2)	-5(2)	2(2)	-2(2)
C(71)	46(3)	27(3)	26(3)	-8(2)	8(2)	-6(2)
C(72)	55(3)	22(3)	22(3)	-4(2)	-6(2)	3(2)
C(73)	38(3)	35(3)	34(3)	-9(2)	-12(2)	10(2)
C(74)	27(2)	31(3)	29(3)	-4(2)	-8(2)	-1(2)
C(76)	86(5)	48(4)	45(4)	-11(3)	-11(3)	15(4)
C(77)	28(2)	27(2)	14(2)	-4(2)	-7(2)	3(2)
C(78)	29(3)	28(3)	24(2)	-6(2)	0(2)	3(2)
C(79)	39(3)	28(3)	30(3)	-13(2)	-4(2)	7(2)
C(80)	33(3)	24(2)	20(2)	-4(2)	-10(2)	0(2)
C(81)	27(2)	29(3)	21(2)	-7(2)	-4(2)	1(2)
C(82)	25(2)	21(2)	21(2)	-6(2)	-6(2)	5(2)
C(84)	37(3)	34(3)	46(3)	-2(2)	-14(2)	-8(2)
C(85)	22(2)	21(2)	18(2)	-2(2)	-3(2)	0(2)
C(86)	25(2)	18(2)	16(2)	0(2)	-3(2)	2(2)
C(87)	21(2)	30(2)	16(2)	-2(2)	-7(2)	-1(2)
C(88)	31(2)	26(2)	20(2)	-7(2)	-10(2)	1(2)

Continued on following page

Table A4 *continued*

C(89)	30(2)	22(2)	15(2)	-4(2)	-2(2)	3(2)
C(90)	28(2)	20(2)	13(2)	3(2)	-4(2)	-2(2)
C(91)	23(2)	19(2)	15(2)	-3(2)	-5(2)	2(2)
C(92)	24(2)	15(2)	24(2)	-5(2)	-6(2)	3(2)
C(93)	26(2)	20(2)	19(2)	-6(2)	-6(2)	-3(2)
C(94)	23(2)	24(2)	20(2)	-3(2)	-3(2)	-1(2)
C(95)	29(3)	34(3)	20(2)	-3(2)	-4(2)	0(2)
C(96)	29(3)	30(3)	23(2)	-6(2)	2(2)	2(2)
C(97)	21(2)	32(3)	33(3)	-5(2)	-3(2)	3(2)
C(98)	23(2)	22(2)	22(2)	-2(2)	-4(2)	0(2)
C(99)	24(2)	23(2)	26(2)	-5(2)	-4(2)	3(2)
C(100)	25(2)	31(3)	33(3)	0(2)	-9(2)	-1(2)
C(101)	28(3)	30(3)	35(3)	5(2)	-3(2)	-4(2)
C(102)	30(3)	32(3)	21(2)	1(2)	-7(2)	4(2)
C(103)	23(2)	32(3)	27(2)	-1(2)	-10(2)	2(2)
C(104)	26(2)	33(3)	25(2)	2(2)	-4(2)	-3(2)
C(106)	36(3)	64(4)	24(3)	4(3)	-9(2)	14(3)
C(107)	26(2)	21(2)	20(2)	-8(2)	-6(2)	0(2)
C(108)	34(3)	25(2)	22(2)	-4(2)	-12(2)	0(2)
C(109)	25(2)	24(2)	29(3)	-10(2)	-8(2)	0(2)
C(110)	24(2)	22(2)	28(2)	-5(2)	-6(2)	1(2)
C(111)	30(2)	16(2)	23(2)	-4(2)	-9(2)	3(2)
C(112)	33(3)	24(2)	20(2)	-8(2)	-8(2)	3(2)
C(113)	30(2)	23(2)	26(2)	-6(2)	-6(2)	1(2)
C(114)	31(3)	28(3)	22(2)	-5(2)	-6(2)	9(2)
C(115)	33(3)	30(3)	27(3)	-16(2)	-8(2)	10(2)
C(116)	32(3)	23(2)	26(2)	-7(2)	-11(2)	1(2)
C(118)	61(4)	51(4)	35(3)	-9(3)	10(3)	-16(3)
C(119)	28(2)	15(2)	17(2)	-5(2)	-3(2)	-2(2)
C(120)	29(2)	21(2)	20(2)	1(2)	-7(2)	0(2)
C(121)	26(2)	25(2)	22(2)	0(2)	-2(2)	-5(2)
C(122)	21(2)	20(2)	28(2)	-8(2)	-3(2)	-2(2)
C(123)	28(2)	20(2)	22(2)	-2(2)	-7(2)	2(2)
C(124)	26(2)	24(2)	19(2)	0(2)	-3(2)	-4(2)
C(126)	27(3)	35(3)	46(3)	-10(2)	-12(2)	9(2)
C(127)	24(2)	15(2)	18(2)	-3(2)	-2(2)	0(2)
C(128)	23(2)	16(2)	16(2)	0(2)	-3(2)	-2(2)
C(129)	21(2)	21(2)	17(2)	0(2)	-3(2)	-3(2)
C(130)	31(2)	24(2)	18(2)	-9(2)	-2(2)	4(2)
C(131)	27(2)	29(2)	23(2)	-8(2)	-10(2)	-1(2)
C(132)	21(2)	24(2)	21(2)	-3(2)	-5(2)	0(2)
C(133)	26(2)	17(2)	17(2)	0(2)	-5(2)	3(2)
C(134)	21(2)	20(2)	19(2)	-3(2)	-2(2)	-3(2)

Continued on following page

Table A4 *continued*

C(135)	29(2)	19(2)	17(2)	-2(2)	-5(2)	1(2)
C(136)	24(2)	17(2)	19(2)	-2(2)	-6(2)	-4(2)
C(137)	30(2)	18(2)	19(2)	-5(2)	-7(2)	-2(2)
C(138)	30(3)	23(2)	25(2)	-4(2)	-13(2)	0(2)
C(139)	25(2)	23(2)	34(3)	-7(2)	-10(2)	-1(2)
C(140)	27(2)	18(2)	23(2)	-1(2)	-5(2)	-1(2)
C(141)	25(2)	26(2)	19(2)	-7(2)	-8(2)	0(2)
C(142)	27(2)	24(2)	18(2)	-8(2)	-7(2)	1(2)
C(143)	28(2)	24(2)	24(2)	-4(2)	-2(2)	-1(2)
C(144)	30(3)	30(3)	22(2)	-5(2)	-2(2)	7(2)
C(145)	36(3)	28(3)	23(2)	-12(2)	-11(2)	7(2)
C(146)	31(3)	22(2)	26(2)	-9(2)	-10(2)	1(2)
C(148)	70(4)	51(4)	41(4)	-12(3)	20(3)	-15(3)
C(149)	24(2)	20(2)	19(2)	-2(2)	-4(2)	0(2)
C(150)	23(2)	28(3)	27(2)	-3(2)	-2(2)	5(2)
C(151)	28(2)	25(2)	24(2)	-7(2)	-3(2)	4(2)
C(152)	26(2)	27(2)	19(2)	-3(2)	-4(2)	2(2)
C(153)	22(2)	17(2)	22(2)	-4(2)	-4(2)	7(2)
C(154)	25(2)	26(2)	31(3)	0(2)	-6(2)	-2(2)
C(155)	33(3)	30(3)	24(2)	6(2)	-4(2)	-7(2)
C(156)	32(3)	30(3)	17(2)	0(2)	-9(2)	3(2)
C(157)	22(2)	33(3)	24(2)	-2(2)	-4(2)	0(2)
C(158)	25(2)	32(3)	18(2)	1(2)	0(2)	2(2)
C(160)	37(3)	51(3)	30(3)	-6(2)	-17(2)	8(2)
C(161)	20(2)	24(2)	22(2)	-4(2)	-2(2)	-2(2)
C(162)	24(2)	21(2)	19(2)	0(2)	0(2)	-3(2)
C(163)	26(2)	22(2)	21(2)	0(2)	-6(2)	0(2)
C(164)	22(2)	20(2)	29(2)	-7(2)	-5(2)	6(2)
C(165)	25(2)	25(2)	25(2)	-3(2)	2(2)	2(2)
C(166)	30(3)	23(2)	21(2)	3(2)	-2(2)	2(2)
C(168)	33(3)	39(3)	45(3)	-1(3)	-13(2)	13(2)
C(169)	26(2)	25(2)	23(2)	-5(2)	1(2)	-2(2)
C(170)	23(2)	21(2)	26(2)	-3(2)	-1(2)	-2(2)
C(171)	33(3)	22(2)	29(3)	-6(2)	-6(2)	-2(2)
C(172)	31(3)	33(3)	36(3)	-6(2)	-10(2)	-2(2)
C(173)	29(3)	31(3)	35(3)	-2(2)	-8(2)	-1(2)
C(174)	21(2)	22(2)	31(3)	0(2)	0(2)	0(2)
C(175)	22(2)	20(2)	29(2)	-3(2)	4(2)	-5(2)
C(176)	31(3)	18(2)	29(3)	-2(2)	2(2)	-4(2)
C(177)	29(2)	19(2)	26(2)	-4(2)	3(2)	-5(2)
C(178)	28(2)	25(2)	26(2)	-3(2)	0(2)	-3(2)
C(179)	25(2)	22(2)	24(2)	-6(2)	-2(2)	0(2)
C(180)	26(2)	27(3)	32(3)	-6(2)	-1(2)	1(2)

Continued on following page

Table A4 *continued*

C(181)	26(2)	33(3)	34(3)	-5(2)	-6(2)	-2(2)
C(182)	29(3)	29(3)	34(3)	-6(2)	-5(2)	-8(2)
C(183)	24(2)	22(2)	25(2)	-5(2)	-3(2)	0(2)
C(184)	29(3)	28(3)	37(3)	-10(2)	2(2)	0(2)
C(185)	37(3)	24(3)	36(3)	-14(2)	1(2)	6(2)
C(186)	28(2)	21(2)	31(3)	-3(2)	-10(2)	0(2)
C(187)	24(2)	24(2)	25(2)	-2(2)	-4(2)	2(2)
C(188)	24(2)	22(2)	26(2)	-8(2)	-2(2)	5(2)
C(190)	40(3)	26(3)	50(3)	-3(2)	-6(2)	-9(2)
C(191)	43(3)	24(3)	33(3)	-3(2)	-2(2)	-11(2)
C(192)	57(4)	25(3)	41(3)	-13(2)	-1(3)	-2(2)
C(193)	55(4)	23(3)	33(3)	-6(2)	8(2)	3(2)
C(194)	36(3)	24(3)	32(3)	-3(2)	3(2)	3(2)
C(195)	46(3)	30(3)	38(3)	-17(2)	-5(2)	-4(2)
C(196)	47(3)	39(3)	35(3)	-22(2)	6(2)	-11(2)
C(197)	44(3)	70(4)	35(3)	-26(3)	4(2)	-22(3)
C(198)	44(3)	78(5)	28(3)	-17(3)	0(2)	-13(3)
C(199)	58(4)	48(4)	41(3)	-8(3)	-15(3)	-8(3)
C(200)	52(4)	36(3)	48(4)	-9(3)	-15(3)	-12(3)
C(202)	173(11)	217(14)	70(7)	17(7)	-63(7)	-136(11)
C(203)	31(3)	22(2)	27(3)	-2(2)	2(2)	-2(2)
C(204)	35(3)	33(3)	35(3)	-2(2)	-6(2)	-3(2)
C(205)	37(3)	38(3)	37(3)	-6(2)	-7(2)	9(2)
C(206)	56(4)	29(3)	23(3)	-8(2)	-5(2)	2(2)
C(207)	46(3)	22(2)	29(3)	-7(2)	3(2)	-6(2)
C(208)	30(3)	25(2)	30(3)	-6(2)	1(2)	0(2)
C(210)	92(6)	47(4)	47(4)	-9(3)	-13(4)	15(4)
C(211)	50(5)	157(10)	86(7)	-19(7)	1(4)	29(6)
C(212)	41(4)	50(4)	84(5)	22(4)	14(3)	5(3)
C(214)	50(4)	43(4)	121(8)	18(4)	-21(5)	-3(3)
C(215)	83(6)	49(4)	96(7)	10(4)	-32(5)	-8(4)
C(216)	18(2)	28(2)	30(3)	-8(2)	2(2)	-2(2)
C(217)	24(2)	24(2)	29(3)	-6(2)	-2(2)	-4(2)
C(218)	32(3)	27(3)	33(3)	-4(2)	-8(2)	0(2)
C(219)	43(3)	29(3)	37(3)	-6(2)	-13(2)	-4(2)
C(220)	34(3)	37(3)	38(3)	-7(2)	-11(2)	-5(2)
C(221)	28(2)	23(2)	33(3)	-3(2)	-3(2)	-3(2)
C(222)	25(2)	28(3)	31(3)	-5(2)	2(2)	-6(2)
C(223)	28(2)	22(2)	29(3)	-6(2)	4(2)	-5(2)
C(224)	27(2)	22(2)	30(3)	-7(2)	3(2)	-6(2)
C(225)	25(2)	28(2)	25(2)	-5(2)	-1(2)	-3(2)
C(226)	23(2)	33(3)	29(3)	-10(2)	-1(2)	-8(2)
C(227)	21(2)	39(3)	37(3)	-12(2)	-5(2)	-3(2)

Continued on following page

Table A4 *continued*

C(228)	25(2)	32(3)	30(3)	-8(2)	-4(2)	1(2)
C(229)	18(2)	27(2)	23(2)	-8(2)	4(2)	0(2)
C(230)	22(2)	24(2)	21(2)	-6(2)	-2(2)	4(2)
C(231)	27(2)	23(2)	27(2)	-8(2)	-1(2)	2(2)
C(232)	26(2)	26(2)	21(2)	-3(2)	-4(2)	0(2)
C(233)	36(3)	20(2)	20(2)	-3(2)	-9(2)	1(2)
C(234)	32(3)	27(3)	28(3)	-13(2)	-1(2)	3(2)
C(235)	26(2)	29(3)	26(2)	-8(2)	-1(2)	5(2)
C(237)	38(3)	27(3)	39(3)	-6(2)	-8(2)	-7(2)
C(238)	33(3)	26(3)	30(3)	-7(2)	1(2)	-10(2)
C(239)	48(3)	30(3)	28(3)	-8(2)	1(2)	-8(2)
C(240)	43(3)	25(3)	34(3)	-8(2)	5(2)	-1(2)
C(241)	33(3)	27(3)	29(3)	-5(2)	4(2)	-4(2)
C(242)	31(3)	33(3)	27(3)	-13(2)	3(2)	-7(2)
C(243)	39(3)	29(3)	33(3)	-12(2)	3(2)	-5(2)
C(244)	34(3)	38(3)	41(3)	-20(2)	1(2)	-6(2)
C(245)	33(3)	44(3)	30(3)	-16(2)	-1(2)	0(2)
C(246)	46(3)	37(3)	31(3)	-9(2)	0(2)	-9(2)
C(247)	42(3)	41(3)	30(3)	-11(2)	0(2)	-17(2)
C(249)	78(5)	65(5)	45(4)	-8(3)	-23(3)	8(4)
C(250)	51(3)	28(3)	25(3)	-2(2)	-5(2)	0(2)
C(251)	53(4)	37(3)	34(3)	-4(2)	-4(2)	13(3)
C(252)	97(6)	43(4)	44(4)	-10(3)	-17(4)	23(4)
C(253)	159(9)	26(3)	34(4)	-2(3)	-18(4)	4(4)
C(254)	124(7)	38(4)	32(3)	-3(3)	1(4)	-30(4)
C(255)	64(4)	37(3)	33(3)	-10(2)	7(3)	-18(3)
C(257)	50(4)	43(3)	40(3)	-4(3)	-10(3)	-4(3)
C(258)	53(3)	29(3)	36(3)	-6(2)	-9(2)	4(2)
C(259)	52(4)	46(4)	45(4)	-2(3)	-5(3)	-7(3)
C(260)	54(4)	82(6)	68(5)	0(4)	1(3)	4(4)
C(262)	50(4)	48(4)	58(4)	-13(3)	-13(3)	1(3)
C(263)	46(3)	42(3)	43(3)	-9(3)	-10(3)	4(3)
C(264)	54(4)	66(5)	57(4)	-14(4)	1(3)	-16(3)
C(265)	49(4)	110(7)	69(5)	-16(5)	3(4)	8(4)
O(1)	38(2)	48(2)	21(2)	7(2)	-11(1)	1(2)
O(2)	21(2)	30(2)	43(2)	1(2)	-1(1)	0(1)
O(3)	65(3)	61(3)	29(2)	-11(2)	15(2)	-4(2)
O(4)	40(2)	61(3)	33(2)	-16(2)	-12(2)	-2(2)
O(5)	99(4)	31(2)	54(3)	-5(2)	-24(3)	19(2)
O(6)	41(2)	25(2)	45(2)	-12(2)	-11(2)	-2(2)
O(7)	36(2)	48(2)	30(2)	9(2)	-11(2)	1(2)
O(8)	41(2)	45(2)	24(2)	-11(2)	4(2)	-3(2)
O(9)	21(2)	33(2)	42(2)	0(2)	-4(1)	0(1)

Continued on following page

Table A4 *continued*

O(10)	50(2)	45(2)	22(2)	-9(2)	5(2)	-1(2)
O(11)	37(2)	52(2)	23(2)	5(2)	-12(2)	-2(2)
O(12)	19(2)	34(2)	46(2)	-3(2)	-2(1)	7(1)
O(13)	37(2)	19(2)	51(2)	-7(2)	-7(2)	-3(1)
O(14)	63(3)	128(5)	34(3)	-14(3)	-17(2)	-26(3)
O(15)	105(4)	28(2)	63(3)	-6(2)	-27(3)	19(2)
O(16)	203(8)	42(3)	75(4)	-3(3)	-48(5)	18(4)
O(17)	37(2)	27(2)	39(2)	-8(2)	-3(2)	-4(2)
O(18)	46(2)	59(3)	40(2)	-17(2)	-13(2)	1(2)
O(19)	37(2)	56(3)	82(4)	17(3)	-2(2)	0(2)
O(20)	47(2)	34(2)	36(2)	-5(2)	-1(2)	1(2)
O(21)	46(2)	47(2)	47(2)	-13(2)	-5(2)	4(2)

Table A5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters (Å^2 $\times 10^3$) for **283**.

	x	y	z	U
H(4)	-1225	413	2350	30
H(5)	-2498	281	2961	29
H(6)	-1759	389	3539	26
H(12)	5265	-417	3148	31
H(13)	4591	-399	2533	33
H(14)	2664	-39	2434	30
H(16)	2621	-464	4119	29
H(17)	3338	-705	4724	32
H(19)	6618	-136	4251	32
H(20)	5888	112	3648	29
H(22A)	7197	-717	4802	61
H(22B)	6722	-648	5251	61
H(22C)	6768	-171	4915	61
H(23)	3269	705	3903	29
H(24)	2120	1229	4317	33
H(25)	5	1342	4333	32
H(28)	-1384	1569	3386	27
H(29)	-3450	1852	3443	29
H(31)	-4136	937	4494	34
H(32)	-2064	673	4446	31
H(34A)	-5522	1956	3510	56
H(34B)	-5214	2286	3822	56
H(34C)	-6535	2075	3870	56
H(36)	2015	1126	2316	30
H(37)	3213	1343	1698	37
H(39)	1768	232	1269	39
H(40)	563	22	1883	31
H(42A)	4748	1252	738	114
H(42B)	4847	1134	1198	114
H(42C)	3918	1574	1041	114
H(45)	5285	4534	5360	30
H(46)	6417	3775	5271	34
H(47)	5433	3105	5122	35
H(53)	607	5521	4873	30
H(54)	795	5976	5381	35
H(55)	2290	5712	5796	36
H(58)	3065	4264	6076	38
H(59)	4265	4016	6584	39
H(61)	6006	5328	6255	39
H(62)	4833	5555	5749	35

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Table A5 *continued*

H(64A)	6164	3784	6858	79
H(64B)	5098	4032	7146	79
H(64C)	6483	4042	7211	79
H(65)	2510	3561	4385	29
H(66)	1400	3905	3874	31
H(67)	821	4769	3783	31
H(70)	2828	5730	4145	34
H(71)	2370	6597	3974	40
H(73)	-1192	6327	3991	42
H(74)	-717	5457	4153	34
H(76A)	-958	7131	3559	90
H(76B)	-683	7647	3690	90
H(76C)	-1366	7230	4005	90
H(78)	4686	2656	4652	33
H(79)	3735	1898	4683	38
H(81)	646	2497	5301	31
H(82)	1599	3257	5250	27
H(84A)	-162	1862	5051	57
H(84B)	281	1652	5465	57
H(84C)	123	1273	5168	57
H(87)	3354	4078	10537	27
H(88)	2104	4444	11041	29
H(89)	-25	4520	11055	27
H(95)	3039	3752	8926	34
H(96)	5019	3429	9006	34
H(97)	5558	3229	9643	35
H(100)	2654	2901	10527	36
H(101)	3138	2461	11121	39
H(103)	6441	3086	10915	32
H(104)	5963	3507	10304	34
H(10A)	6840	2356	11406	64
H(10B)	6160	2335	11849	64
H(10C)	6313	2863	11572	64
H(108)	-952	4185	8857	31
H(109)	-2257	3938	9443	30
H(110)	-1560	3869	10051	29
H(112)	2280	4854	8869	30
H(113)	3447	5099	8251	31
H(115)	1958	4036	7786	35
H(116)	785	3788	8402	31
H(11A)	4788	5110	7250	75
H(11B)	4985	4982	7701	75
H(11C)	3951	5395	7576	75

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Table A5 *continued*

H(120)	-1925	3834	11032	29
H(121)	-4014	4060	11129	29
H(123)	-3522	5221	10226	28
H(124)	-1417	4985	10122	28
H(12A)	-5613	5234	10293	53
H(12B)	-5335	5514	10639	53
H(12C)	-6613	5272	10674	53
H(130)	9753	1835	2276	29
H(131)	7642	1967	2285	30
H(132)	6489	2464	2720	26
H(138)	11016	2744	4267	30
H(139)	12267	2894	3651	32
H(140)	11525	2780	3073	27
H(142)	7774	2026	4320	27
H(143)	6627	1819	4948	31
H(145)	8201	2921	5353	33
H(146)	9309	3129	4725	30
H(14A)	5126	1961	5517	84
H(14B)	5432	1833	5957	84
H(14C)	6204	1556	5615	84
H(150)	4506	3588	3487	32
H(151)	5159	3540	4102	31
H(152)	7105	3178	4198	29
H(154)	7158	3612	2501	33
H(155)	6476	3811	1889	36
H(157)	3153	3282	2376	32
H(158)	3858	3078	2987	31
H(16D)	3168	3644	1351	58
H(16E)	2613	3804	1771	58
H(16F)	3085	3235	1738	58
H(162)	11150	1624	3234	26
H(163)	13226	1343	3179	27
H(165)	13861	2205	2099	31
H(166)	11791	2477	2159	31
H(16A)	16309	1123	2777	59
H(16B)	15024	886	2811	59
H(16C)	15230	1243	3119	59
H(171)	2626	405	7671	33
H(172)	1528	727	7156	39
H(173)	946	1595	7042	38
H(180)	5570	-30	8408	34
H(181)	6658	645	8498	37
H(182)	5595	1434	8545	36

Continued on following page

Table A5 *continued*

H(184)	4787	-486	7947	38
H(185)	3850	-1254	8032	39
H(187)	823	-627	8653	29
H(188)	1768	138	8561	29
H(19A)	-14	-1308	8425	58
H(19B)	446	-1474	8842	58
H(19C)	308	-1887	8571	58
H(192)	2720	2657	8967	49
H(193)	1190	2907	8572	47
H(194)	873	2419	8098	38
H(196)	5154	2486	8952	47
H(197)	6211	2286	9496	57
H(199)	4538	963	9804	57
H(200)	3483	1169	9256	53
H(20A)	7460	1891	9935	218
H(20B)	7153	1648	10386	218
H(20C)	6311	2109	10211	218
H(204)	-537	2309	7376	41
H(205)	-998	3178	7199	45
H(207)	2567	3445	7165	39
H(208)	3016	2589	7363	35
H(21A)	-741	3998	6737	94
H(21B)	-527	4497	6905	94
H(21C)	-1189	4047	7191	94
H(21I)	1612	7615	9224	151
H(21J)	1613	7076	9489	151
H(21K)	712	7527	9632	151
H(21G)	-289	6939	9354	77
H(21H)	-457	7505	9143	77
H(21L)	-665	7256	8509	89
H(21M)	-705	6701	8753	89
H(21D)	-29	6677	8053	114
H(21E)	980	6416	8311	114
H(21F)	1128	6973	8082	114
H(218)	2284	6618	1242	37
H(219)	1193	6958	730	42
H(220)	594	7821	646	42
H(226)	5191	7588	2183	33
H(227)	6285	6822	2106	38
H(228)	5254	6150	1975	34
H(231)	1446	6293	2092	31
H(232)	528	5532	2129	29
H(234)	3640	4966	1504	35

Continued on following page

Table A5 *continued*

H(235)	4546	5726	1472	33
H(23A)	-266	4884	1831	51
H(23B)	116	4723	2259	51
H(23C)	41	4306	1985	51
H(239)	2338	8818	2600	42
H(240)	864	9099	2181	42
H(241)	587	8618	1696	36
H(243)	4799	8622	2581	40
H(244)	5935	8373	3104	44
H(246)	4170	7078	3408	45
H(247)	2984	7334	2896	44
H(24A)	5941	6826	3689	92
H(24B)	4989	7092	4000	92
H(24C)	6410	7058	4031	92
H(251)	-893	8517	1005	51
H(252)	-1328	9364	758	74
H(254)	2264	9626	685	78
H(255)	2676	8790	946	54
H(25A)	-1100	10071	258	255
H(25B)	-829	10623	320	255
H(25C)	-1488	10252	680	255
H(25D)	2409	4781	2628	66
H(25E)	3279	4325	2794	66
H(25F)	2531	4682	3086	66
H(25G)	1409	4026	2691	47
H(25H)	1573	3906	3147	47
H(25I)	-627	3936	3390	58
H(25J)	-770	3963	2935	58
H(26A)	-1984	4717	2965	106
H(26B)	-1819	4703	3415	106
H(26C)	-2571	4288	3293	106
H(26F)	2434	1659	5831	77
H(26G)	3373	1225	5990	77
H(26H)	2663	1595	6280	77
H(26I)	1528	864	5960	52
H(26J)	1720	818	6413	52
H(26K)	-525	849	6652	71
H(26L)	-627	810	6203	71
H(26M)	-1808	1597	6168	117
H(26N)	-1771	1596	6626	117
H(26O)	-2470	1177	6487	117
H(26P)	4297	10380	412	72
H(26Q)	4264	9794	545	72

Continued on following page

Table A5 *continued*

H(26R)	5704	9773	775	102
H(26S)	5608	10372	697	102
H(26T)	6445	10063	386	102
H(26V)	3291	10219	-145	80
H(26U)	3449	9633	-18	80
H(26Y)	3265	10085	-684	99
H(26W)	3659	9505	-571	99
H(26X)	4675	9904	-714	99

Table A6 Torsion angles [°] for **283**.

C(10)-C(1)-C(2)-C(7)	-12.3(6)	C(14)-C(1)-C(2)-C(7)	157.1(4)
C(10)-C(1)-C(2)-C(3)	175.6(4)	C(14)-C(1)-C(2)-C(3)	-14.9(7)
C(7)-C(2)-C(3)-C(4)	-16.2(6)	C(1)-C(2)-C(3)-C(4)	155.8(4)
C(7)-C(2)-C(3)-C(35)	157.8(4)	C(1)-C(2)-C(3)-C(35)	-30.2(6)
C(2)-C(3)-C(4)-C(5)	1.9(7)	C(35)-C(3)-C(4)-C(5)	-172.3(4)
C(3)-C(4)-C(5)-C(6)	8.8(7)	C(4)-C(5)-C(6)-C(7)	-5.1(7)
C(5)-C(6)-C(7)-C(2)	-9.2(6)	C(5)-C(6)-C(7)-C(8)	166.5(4)
C(3)-C(2)-C(7)-C(6)	19.7(6)	C(1)-C(2)-C(7)-C(6)	-152.7(4)
C(3)-C(2)-C(7)-C(8)	-156.2(4)	C(1)-C(2)-C(7)-C(8)	31.3(6)
C(6)-C(7)-C(8)-C(26)	-27.9(6)	C(2)-C(7)-C(8)-C(26)	147.8(4)
C(6)-C(7)-C(8)-C(9)	162.4(4)	C(2)-C(7)-C(8)-C(9)	-21.9(6)
C(26)-C(8)-C(9)-C(23)	-2.1(6)	C(7)-C(8)-C(9)-C(23)	167.8(4)
C(26)-C(8)-C(9)-C(10)	-176.7(4)	C(7)-C(8)-C(9)-C(10)	-6.7(6)
C(14)-C(1)-C(10)-C(11)	-4.0(6)	C(2)-C(1)-C(10)-C(11)	165.7(4)
C(14)-C(1)-C(10)-C(9)	174.3(4)	C(2)-C(1)-C(10)-C(9)	-15.9(6)
C(23)-C(9)-C(10)-C(1)	-149.0(4)	C(8)-C(9)-C(10)-C(1)	25.5(6)
C(23)-C(9)-C(10)-C(11)	29.3(6)	C(8)-C(9)-C(10)-C(11)	-156.2(4)
C(1)-C(10)-C(11)-C(12)	6.4(7)	C(9)-C(10)-C(11)-C(12)	-171.9(4)
C(1)-C(10)-C(11)-C(15)	-167.0(4)	C(9)-C(10)-C(11)-C(15)	14.7(7)
C(10)-C(11)-C(12)-C(13)	-4.1(7)	C(15)-C(11)-C(12)-C(13)	169.9(4)
C(11)-C(12)-C(13)-C(14)	-0.6(8)	C(12)-C(13)-C(14)-C(1)	3.0(8)
C(10)-C(1)-C(14)-C(13)	-0.7(7)	C(2)-C(1)-C(14)-C(13)	-170.3(4)
C(12)-C(11)-C(15)-C(20)	54.1(6)	C(10)-C(11)-C(15)-C(20)	-132.3(5)
C(12)-C(11)-C(15)-C(16)	-120.0(5)	C(10)-C(11)-C(15)-C(16)	53.6(7)
C(20)-C(15)-C(16)-C(17)	-0.4(7)	C(11)-C(15)-C(16)-C(17)	173.9(4)
C(15)-C(16)-C(17)-C(18)	-0.1(7)	C(16)-C(17)-C(18)-O(1)	179.6(4)
C(16)-C(17)-C(18)-C(19)	0.2(7)	O(1)-C(18)-C(19)-C(20)	-179.2(4)
C(17)-C(18)-C(19)-C(20)	0.1(7)	C(18)-C(19)-C(20)-C(15)	-0.6(7)
C(16)-C(15)-C(20)-C(19)	0.8(7)	C(11)-C(15)-C(20)-C(19)	-173.4(4)
C(8)-C(9)-C(23)-C(24)	0.8(7)	C(10)-C(9)-C(23)-C(24)	175.3(4)
C(9)-C(23)-C(24)-C(25)	1.7(7)	C(23)-C(24)-C(25)-C(26)	-2.9(7)
C(24)-C(25)-C(26)-C(8)	1.6(7)	C(24)-C(25)-C(26)-C(27)	-174.8(4)
C(9)-C(8)-C(26)-C(25)	1.0(6)	C(7)-C(8)-C(26)-C(25)	-168.6(4)
C(9)-C(8)-C(26)-C(27)	176.9(4)	C(7)-C(8)-C(26)-C(27)	7.3(7)
C(25)-C(26)-C(27)-C(28)	103.5(5)	C(8)-C(26)-C(27)-C(28)	-72.6(6)
C(25)-C(26)-C(27)-C(32)	-70.9(6)	C(8)-C(26)-C(27)-C(32)	113.0(5)
C(32)-C(27)-C(28)-C(29)	-0.5(7)	C(26)-C(27)-C(28)-C(29)	-175.1(4)
C(27)-C(28)-C(29)-C(30)	-0.8(7)	C(28)-C(29)-C(30)-O(2)	-178.3(4)
C(28)-C(29)-C(30)-C(31)	1.2(7)	O(2)-C(30)-C(31)-C(32)	179.3(4)
C(29)-C(30)-C(31)-C(32)	-0.2(7)	C(30)-C(31)-C(32)-C(27)	-1.2(7)
C(28)-C(27)-C(32)-C(31)	1.5(7)	C(26)-C(27)-C(32)-C(31)	176.1(4)
C(4)-C(3)-C(35)-C(36)	128.3(5)	C(2)-C(3)-C(35)-C(36)	-45.7(6)

Continued on following page

Table A6 *continued*

C(4)-C(3)-C(35)-C(40)	-50.4(6)	C(2)-C(3)-C(35)-C(40)	135.7(5)
C(40)-C(35)-C(36)-C(37)	-0.4(7)	C(3)-C(35)-C(36)-C(37)	-179.0(4)
C(35)-C(36)-C(37)-C(38)	-1.1(7)	C(36)-C(37)-C(38)-O(3)	-177.4(5)
C(36)-C(37)-C(38)-C(39)	2.2(8)	O(3)-C(38)-C(39)-C(40)	177.7(5)
C(37)-C(38)-C(39)-C(40)	-1.9(8)	C(38)-C(39)-C(40)-C(35)	0.5(7)
C(36)-C(35)-C(40)-C(39)	0.7(7)	C(3)-C(35)-C(40)-C(39)	179.3(4)
C(52)-C(43)-C(44)-C(45)	155.7(4)	C(56)-C(43)-C(44)-C(45)	-28.5(7)
C(52)-C(43)-C(44)-C(49)	-24.9(6)	C(56)-C(43)-C(44)-C(49)	150.9(4)
C(49)-C(44)-C(45)-C(46)	-6.2(7)	C(43)-C(44)-C(45)-C(46)	173.1(4)
C(44)-C(45)-C(46)-C(47)	-7.7(7)	C(45)-C(46)-C(47)-C(48)	8.7(8)
C(46)-C(47)-C(48)-C(49)	4.4(7)	C(46)-C(47)-C(48)-C(77)	-167.9(4)
C(47)-C(48)-C(49)-C(44)	-18.1(6)	C(77)-C(48)-C(49)-C(44)	153.7(4)
C(47)-C(48)-C(49)-C(50)	152.4(4)	C(77)-C(48)-C(49)-C(50)	-35.8(7)
C(45)-C(44)-C(49)-C(48)	18.9(6)	C(43)-C(44)-C(49)-C(48)	-160.5(4)
C(45)-C(44)-C(49)-C(50)	-152.4(4)	C(43)-C(44)-C(49)-C(50)	28.2(6)
C(48)-C(49)-C(50)-C(51)	-176.5(4)	C(44)-C(49)-C(50)-C(51)	-6.0(6)
C(48)-C(49)-C(50)-C(65)	-8.7(7)	C(44)-C(49)-C(50)-C(65)	161.9(4)
C(65)-C(50)-C(51)-C(68)	-5.7(6)	C(49)-C(50)-C(51)-C(68)	162.4(4)
C(65)-C(50)-C(51)-C(52)	172.7(4)	C(49)-C(50)-C(51)-C(52)	-19.2(6)
C(56)-C(43)-C(52)-C(53)	-1.1(6)	C(44)-C(43)-C(52)-C(53)	174.8(4)
C(56)-C(43)-C(52)-C(51)	-176.9(4)	C(44)-C(43)-C(52)-C(51)	-1.0(6)
C(50)-C(51)-C(52)-C(53)	-153.0(4)	C(68)-C(51)-C(52)-C(53)	25.3(6)
C(50)-C(51)-C(52)-C(43)	22.8(6)	C(68)-C(51)-C(52)-C(43)	-158.9(4)
C(43)-C(52)-C(53)-C(54)	4.0(7)	C(51)-C(52)-C(53)-C(54)	179.7(4)
C(52)-C(53)-C(54)-C(55)	-3.3(7)	C(53)-C(54)-C(55)-C(56)	-0.4(7)
C(54)-C(55)-C(56)-C(43)	3.2(7)	C(54)-C(55)-C(56)-C(57)	-171.9(4)
C(52)-C(43)-C(56)-C(55)	-2.5(7)	C(44)-C(43)-C(56)-C(55)	-178.2(4)
C(52)-C(43)-C(56)-C(57)	172.3(4)	C(44)-C(43)-C(56)-C(57)	-3.4(7)
C(55)-C(56)-C(57)-C(58)	111.6(5)	C(43)-C(56)-C(57)-C(58)	-63.3(7)
C(55)-C(56)-C(57)-C(62)	-64.6(6)	C(43)-C(56)-C(57)-C(62)	120.5(5)
C(62)-C(57)-C(58)-C(59)	-1.2(8)	C(56)-C(57)-C(58)-C(59)	-177.5(5)
C(57)-C(58)-C(59)-C(60)	0.6(8)	C(58)-C(59)-C(60)-O(4)	-179.0(5)
C(58)-C(59)-C(60)-C(61)	0.7(8)	O(4)-C(60)-C(61)-C(62)	178.4(4)
C(59)-C(60)-C(61)-C(62)	-1.3(7)	C(60)-C(61)-C(62)-C(57)	0.7(8)
C(58)-C(57)-C(62)-C(61)	0.5(7)	C(56)-C(57)-C(62)-C(61)	176.9(4)
C(51)-C(50)-C(65)-C(66)	0.5(7)	C(49)-C(50)-C(65)-C(66)	-167.6(4)
C(50)-C(65)-C(66)-C(67)	4.1(7)	C(65)-C(66)-C(67)-C(68)	-3.4(7)
C(66)-C(67)-C(68)-C(51)	-1.8(7)	C(66)-C(67)-C(68)-C(69)	173.7(4)
C(50)-C(51)-C(68)-C(67)	6.4(6)	C(52)-C(51)-C(68)-C(67)	-171.9(4)
C(50)-C(51)-C(68)-C(69)	-168.8(4)	C(52)-C(51)-C(68)-C(69)	12.9(7)
C(67)-C(68)-C(69)-C(74)	60.2(6)	C(51)-C(68)-C(69)-C(74)	-124.5(5)
C(67)-C(68)-C(69)-C(70)	-117.5(5)	C(51)-C(68)-C(69)-C(70)	57.8(6)
C(74)-C(69)-C(70)-C(71)	0.9(7)	C(68)-C(69)-C(70)-C(71)	178.7(4)

Continued on following page

Table A6 *continued*

C(69)-C(70)-C(71)-C(72)	0.0(7)	C(70)-C(71)-C(72)-O(5)	179.2(5)
C(70)-C(71)-C(72)-C(73)	-0.4(7)	O(5)-C(72)-C(73)-C(74)	-179.7(5)
C(71)-C(72)-C(73)-C(74)	-0.1(8)	C(70)-C(69)-C(74)-C(73)	-1.4(7)
C(68)-C(69)-C(74)-C(73)	-179.2(4)	C(72)-C(73)-C(74)-C(69)	1.1(8)
C(47)-C(48)-C(77)-C(82)	127.4(5)	C(49)-C(48)-C(77)-C(82)	-44.6(6)
C(47)-C(48)-C(77)-C(78)	-43.6(6)	C(49)-C(48)-C(77)-C(78)	144.4(5)
C(82)-C(77)-C(78)-C(79)	0.2(7)	C(48)-C(77)-C(78)-C(79)	171.4(4)
C(77)-C(78)-C(79)-C(80)	-0.8(7)	C(78)-C(79)-C(80)-O(6)	-179.2(4)
C(78)-C(79)-C(80)-C(81)	0.4(7)	O(6)-C(80)-C(81)-C(82)	-179.9(4)
C(79)-C(80)-C(81)-C(82)	0.5(7)	C(78)-C(77)-C(82)-C(81)	0.8(6)
C(48)-C(77)-C(82)-C(81)	-170.7(4)	C(80)-C(81)-C(82)-C(77)	-1.1(7)
C(98)-C(85)-C(86)-C(87)	30.0(6)	C(94)-C(85)-C(86)-C(87)	-147.7(4)
C(98)-C(85)-C(86)-C(91)	-156.1(4)	C(94)-C(85)-C(86)-C(91)	26.3(6)
C(91)-C(86)-C(87)-C(88)	3.2(7)	C(85)-C(86)-C(87)-C(88)	177.2(4)
C(86)-C(87)-C(88)-C(89)	1.1(7)	C(87)-C(88)-C(89)-C(90)	-3.6(7)
C(88)-C(89)-C(90)-C(91)	1.7(7)	C(88)-C(89)-C(90)-C(119)	-175.2(4)
C(87)-C(86)-C(91)-C(90)	-5.1(6)	C(85)-C(86)-C(91)-C(90)	-179.0(4)
C(87)-C(86)-C(91)-C(92)	166.2(4)	C(85)-C(86)-C(91)-C(92)	-7.7(6)
C(89)-C(90)-C(91)-C(86)	2.7(6)	C(119)-C(90)-C(91)-C(86)	179.2(4)
C(89)-C(90)-C(91)-C(92)	-168.0(4)	C(119)-C(90)-C(91)-C(92)	8.5(7)
C(86)-C(91)-C(92)-C(110)	163.4(4)	C(90)-C(91)-C(92)-C(110)	-25.7(7)
C(86)-C(91)-C(92)-C(93)	-20.2(6)	C(90)-C(91)-C(92)-C(93)	150.7(4)
C(110)-C(92)-C(93)-C(107)	17.5(6)	C(91)-C(92)-C(93)-C(107)	-159.0(4)
C(110)-C(92)-C(93)-C(94)	-154.4(4)	C(91)-C(92)-C(93)-C(94)	29.1(6)
C(98)-C(85)-C(94)-C(95)	-5.0(6)	C(86)-C(85)-C(94)-C(95)	172.7(4)
C(98)-C(85)-C(94)-C(93)	165.3(4)	C(86)-C(85)-C(94)-C(93)	-17.0(6)
C(92)-C(93)-C(94)-C(95)	159.6(4)	C(107)-C(93)-C(94)-C(95)	-11.8(7)
C(92)-C(93)-C(94)-C(85)	-10.1(6)	C(107)-C(93)-C(94)-C(85)	178.5(4)
C(85)-C(94)-C(95)-C(96)	-2.1(7)	C(93)-C(94)-C(95)-C(96)	-172.0(5)
C(94)-C(95)-C(96)-C(97)	5.7(8)	C(95)-C(96)-C(97)-C(98)	-2.0(8)
C(96)-C(97)-C(98)-C(85)	-5.0(7)	C(96)-C(97)-C(98)-C(99)	166.1(4)
C(94)-C(85)-C(98)-C(97)	8.5(7)	C(86)-C(85)-C(98)-C(97)	-169.0(4)
C(94)-C(85)-C(98)-C(99)	-162.2(4)	C(86)-C(85)-C(98)-C(99)	20.2(7)
C(97)-C(98)-C(99)-C(100)	-121.1(5)	C(85)-C(98)-C(99)-C(100)	49.7(6)
C(97)-C(98)-C(99)-C(104)	54.1(6)	C(85)-C(98)-C(99)-C(104)	-135.1(5)
C(104)-C(99)-C(100)-C(101)	-0.9(8)	C(98)-C(99)-C(100)-C(101)	174.6(5)
C(99)-C(100)-C(101)-C(102)	1.4(8)	C(100)-C(101)-C(102)-O(7)	178.6(5)
C(100)-C(101)-C(102)-C(103)	-0.7(8)	O(7)-C(102)-C(103)-C(104)	-179.8(5)
C(101)-C(102)-C(103)-C(104)	-0.4(8)	C(100)-C(99)-C(104)-C(103)	-0.3(7)
C(98)-C(99)-C(104)-C(103)	-175.6(5)	C(102)-C(103)-C(104)-C(99)	1.0(8)
C(92)-C(93)-C(107)-C(108)	-12.9(6)	C(94)-C(93)-C(107)-C(108)	158.5(4)
C(92)-C(93)-C(107)-C(111)	165.1(4)	C(94)-C(93)-C(107)-C(111)	-23.5(7)
C(93)-C(107)-C(108)-C(109)	0.4(7)	C(111)-C(107)-C(108)-C(109)	-177.7(4)

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Table A6 *continued*

C(107)-C(108)-C(109)-C(110)	7.7(7)	C(108)-C(109)-C(110)-C(92)	-2.8(7)
C(93)-C(92)-C(110)-C(109)	-10.0(6)	C(91)-C(92)-C(110)-C(109)	166.5(4)
C(108)-C(107)-C(111)-C(116)	-50.9(6)	C(93)-C(107)-C(111)-C(116)	131.1(5)
C(108)-C(107)-C(111)-C(112)	126.9(5)	C(93)-C(107)-C(111)-C(112)	-51.1(6)
C(116)-C(111)-C(112)-C(113)	-1.1(7)	C(107)-C(111)-C(112)-C(113)	-178.9(4)
C(111)-C(112)-C(113)-C(114)	-0.1(7)	C(112)-C(113)-C(114)-O(8)	-177.6(4)
C(112)-C(113)-C(114)-C(115)	1.3(7)	O(8)-C(114)-C(115)-C(116)	177.8(4)
C(113)-C(114)-C(115)-C(116)	-1.3(7)	C(114)-C(115)-C(116)-C(111)	0.0(7)
C(112)-C(111)-C(116)-C(115)	1.1(7)	C(107)-C(111)-C(116)-C(115)	179.0(4)
C(89)-C(90)-C(119)-C(124)	104.7(5)	C(91)-C(90)-C(119)-C(124)	-71.9(6)
C(89)-C(90)-C(119)-C(120)	-69.6(5)	C(91)-C(90)-C(119)-C(120)	113.8(5)
C(124)-C(119)-C(120)-C(121)	0.1(7)	C(90)-C(119)-C(120)-C(121)	174.6(4)
C(119)-C(120)-C(121)-C(122)	-0.3(7)	C(120)-C(121)-C(122)-O(9)	180.0(4)
C(120)-C(121)-C(122)-C(123)	0.1(7)	O(9)-C(122)-C(123)-C(124)	-179.5(4)
C(121)-C(122)-C(123)-C(124)	0.4(7)	C(120)-C(119)-C(124)-C(123)	0.5(6)
C(90)-C(119)-C(124)-C(123)	-173.9(4)	C(122)-C(123)-C(124)-C(119)	-0.7(7)
C(136)-C(127)-C(128)-C(133)	22.4(6)	C(140)-C(127)-C(128)-C(133)	-161.6(4)
C(136)-C(127)-C(128)-C(129)	-147.8(4)	C(140)-C(127)-C(128)-C(129)	28.2(6)
C(133)-C(128)-C(129)-C(130)	-2.0(6)	C(127)-C(128)-C(129)-C(130)	168.1(4)
C(133)-C(128)-C(129)-C(161)	-176.2(4)	C(127)-C(128)-C(129)-C(161)	-6.1(7)
C(128)-C(129)-C(130)-C(131)	0.1(7)	C(161)-C(129)-C(130)-C(131)	174.8(4)
C(129)-C(130)-C(131)-C(132)	0.8(7)	C(130)-C(131)-C(132)-C(133)	0.3(7)
C(129)-C(128)-C(133)-C(132)	3.1(6)	C(127)-C(128)-C(133)-C(132)	-167.5(4)
C(129)-C(128)-C(133)-C(134)	177.1(4)	C(127)-C(128)-C(133)-C(134)	6.5(6)
C(131)-C(132)-C(133)-C(128)	-2.3(7)	C(131)-C(132)-C(133)-C(134)	-176.2(4)
C(128)-C(133)-C(134)-C(149)	156.0(4)	C(132)-C(133)-C(134)-C(149)	-30.1(6)
C(128)-C(133)-C(134)-C(135)	-25.4(6)	C(132)-C(133)-C(134)-C(135)	148.5(4)
C(149)-C(134)-C(135)-C(152)	4.8(6)	C(133)-C(134)-C(135)-C(152)	-173.9(4)
C(149)-C(134)-C(135)-C(136)	-165.7(4)	C(133)-C(134)-C(135)-C(136)	15.6(6)
C(140)-C(127)-C(136)-C(137)	-18.9(6)	C(128)-C(127)-C(136)-C(137)	157.3(4)
C(140)-C(127)-C(136)-C(135)	151.9(4)	C(128)-C(127)-C(136)-C(135)	-32.0(6)
C(152)-C(135)-C(136)-C(127)	-157.4(4)	C(134)-C(135)-C(136)-C(127)	12.7(6)
C(152)-C(135)-C(136)-C(137)	12.8(7)	C(134)-C(135)-C(136)-C(137)	-177.1(4)
C(127)-C(136)-C(137)-C(138)	15.4(6)	C(135)-C(136)-C(137)-C(138)	-154.7(4)
C(127)-C(136)-C(137)-C(141)	-159.1(4)	C(135)-C(136)-C(137)-C(141)	30.8(7)
C(136)-C(137)-C(138)-C(139)	-1.3(7)	C(141)-C(137)-C(138)-C(139)	173.5(4)
C(137)-C(138)-C(139)-C(140)	-9.7(7)	C(138)-C(139)-C(140)-C(127)	6.0(7)
C(136)-C(127)-C(140)-C(139)	8.4(6)	C(128)-C(127)-C(140)-C(139)	-167.6(4)
C(138)-C(137)-C(141)-C(146)	48.1(6)	C(136)-C(137)-C(141)-C(146)	-137.3(5)
C(138)-C(137)-C(141)-C(142)	-128.4(5)	C(136)-C(137)-C(141)-C(142)	46.2(6)
C(146)-C(141)-C(142)-C(143)	1.6(7)	C(137)-C(141)-C(142)-C(143)	178.2(4)
C(141)-C(142)-C(143)-C(144)	-0.6(7)	C(142)-C(143)-C(144)-O(10)	178.9(4)
C(142)-C(143)-C(144)-C(145)	-0.9(7)	O(10)-C(144)-C(145)-C(146)	-178.4(4)

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Table A6 *continued*

C(143)-C(144)-C(145)-C(146)	1.5(7)	C(144)-C(145)-C(146)-C(141)	-0.5(7)
C(142)-C(141)-C(146)-C(145)	-1.0(7)	C(137)-C(141)-C(146)-C(145)	-177.6(4)
C(135)-C(134)-C(149)-C(150)	-6.4(6)	C(133)-C(134)-C(149)-C(150)	172.2(4)
C(135)-C(134)-C(149)-C(153)	167.6(4)	C(133)-C(134)-C(149)-C(153)	-13.8(7)
C(134)-C(149)-C(150)-C(151)	3.1(7)	C(153)-C(149)-C(150)-C(151)	-171.4(4)
C(149)-C(150)-C(151)-C(152)	1.9(7)	C(150)-C(151)-C(152)-C(135)	-3.6(7)
C(134)-C(135)-C(152)-C(151)	0.2(7)	C(136)-C(135)-C(152)-C(151)	170.4(4)
C(150)-C(149)-C(153)-C(158)	-53.5(6)	C(134)-C(149)-C(153)-C(158)	132.3(5)
C(150)-C(149)-C(153)-C(154)	123.5(5)	C(134)-C(149)-C(153)-C(154)	-50.6(6)
C(158)-C(153)-C(154)-C(155)	-0.4(7)	C(149)-C(153)-C(154)-C(155)	-177.6(4)
C(153)-C(154)-C(155)-C(156)	0.5(8)	C(154)-C(155)-C(156)-O(11)	-179.4(5)
C(154)-C(155)-C(156)-C(157)	-0.3(8)	O(11)-C(156)-C(157)-C(158)	179.0(5)
C(155)-C(156)-C(157)-C(158)	0.0(7)	C(156)-C(157)-C(158)-C(153)	0.1(8)
C(154)-C(153)-C(158)-C(157)	0.1(7)	C(149)-C(153)-C(158)-C(157)	177.2(4)
C(130)-C(129)-C(161)-C(166)	68.9(6)	C(128)-C(129)-C(161)-C(166)	-116.7(5)
C(130)-C(129)-C(161)-C(162)	-105.9(5)	C(128)-C(129)-C(161)-C(162)	68.5(6)
C(166)-C(161)-C(162)-C(163)	0.9(7)	C(129)-C(161)-C(162)-C(163)	175.7(4)
C(161)-C(162)-C(163)-C(164)	0.4(7)	C(162)-C(163)-C(164)-O(12)	178.5(4)
C(162)-C(163)-C(164)-C(165)	-1.5(7)	O(12)-C(164)-C(165)-C(166)	-178.6(4)
C(163)-C(164)-C(165)-C(166)	1.4(7)	C(162)-C(161)-C(166)-C(165)	-1.0(7)
C(129)-C(161)-C(166)-C(165)	-176.0(4)	C(164)-C(165)-C(166)-C(161)	-0.1(7)
C(178)-C(169)-C(170)-C(175)	-8.2(6)	C(179)-C(169)-C(170)-C(175)	-176.4(4)
C(178)-C(169)-C(170)-C(171)	159.9(4)	C(179)-C(169)-C(170)-C(171)	-8.3(7)
C(175)-C(170)-C(171)-C(172)	0.7(7)	C(169)-C(170)-C(171)-C(172)	-167.5(5)
C(170)-C(171)-C(172)-C(173)	2.9(8)	C(171)-C(172)-C(173)-C(174)	-2.1(8)
C(172)-C(173)-C(174)-C(175)	-2.2(7)	C(172)-C(173)-C(174)-C(203)	173.9(4)
C(171)-C(170)-C(175)-C(174)	-5.0(7)	C(169)-C(170)-C(175)-C(174)	163.1(4)
C(171)-C(170)-C(175)-C(176)	173.8(4)	C(169)-C(170)-C(175)-C(176)	-18.0(6)
C(173)-C(174)-C(175)-C(170)	5.7(7)	C(203)-C(174)-C(175)-C(170)	-170.0(4)
C(173)-C(174)-C(175)-C(176)	-173.0(4)	C(203)-C(174)-C(175)-C(176)	11.2(7)
C(170)-C(175)-C(176)-C(177)	22.9(6)	C(174)-C(175)-C(176)-C(177)	-158.3(4)
C(170)-C(175)-C(176)-C(194)	-152.6(4)	C(174)-C(175)-C(176)-C(194)	26.2(7)
C(194)-C(176)-C(177)-C(191)	-1.1(7)	C(175)-C(176)-C(177)-C(191)	-176.7(4)
C(194)-C(176)-C(177)-C(178)	174.5(4)	C(175)-C(176)-C(177)-C(178)	-1.1(7)
C(179)-C(169)-C(178)-C(182)	18.4(7)	C(170)-C(169)-C(178)-C(182)	-150.8(4)
C(179)-C(169)-C(178)-C(177)	-160.6(4)	C(170)-C(169)-C(178)-C(177)	30.3(6)
C(176)-C(177)-C(178)-C(182)	155.3(5)	C(191)-C(177)-C(178)-C(182)	-29.3(7)
C(176)-C(177)-C(178)-C(169)	-25.8(7)	C(191)-C(177)-C(178)-C(169)	149.7(5)
C(178)-C(169)-C(179)-C(180)	-15.6(7)	C(170)-C(169)-C(179)-C(180)	152.6(5)
C(178)-C(169)-C(179)-C(183)	154.9(4)	C(170)-C(169)-C(179)-C(183)	-36.9(7)
C(169)-C(179)-C(180)-C(181)	1.8(7)	C(183)-C(179)-C(180)-C(181)	-169.5(5)
C(179)-C(180)-C(181)-C(182)	9.7(8)	C(180)-C(181)-C(182)-C(178)	-6.7(8)
C(169)-C(178)-C(182)-C(181)	-7.4(7)	C(177)-C(178)-C(182)-C(181)	171.5(5)

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Table A6 *continued*

C(180)-C(179)-C(183)-C(188)	125.3(5)	C(169)-C(179)-C(183)-C(188)	-45.5(7)
C(180)-C(179)-C(183)-C(184)	-45.6(6)	C(169)-C(179)-C(183)-C(184)	143.7(5)
C(188)-C(183)-C(184)-C(185)	-0.8(7)	C(179)-C(183)-C(184)-C(185)	170.3(5)
C(183)-C(184)-C(185)-C(186)	0.2(8)	C(184)-C(185)-C(186)-O(13)	179.8(5)
C(184)-C(185)-C(186)-C(187)	0.2(7)	O(13)-C(186)-C(187)-C(188)	-179.5(4)
C(185)-C(186)-C(187)-C(188)	0.0(7)	C(184)-C(183)-C(188)-C(187)	1.0(7)
C(179)-C(183)-C(188)-C(187)	-170.2(4)	C(186)-C(187)-C(188)-C(183)	-0.6(7)
C(176)-C(177)-C(191)-C(192)	-3.4(7)	C(178)-C(177)-C(191)-C(192)	-178.8(5)
C(176)-C(177)-C(191)-C(195)	170.3(5)	C(178)-C(177)-C(191)-C(195)	-5.2(8)
C(177)-C(191)-C(192)-C(193)	4.3(8)	C(195)-C(191)-C(192)-C(193)	-169.9(5)
C(191)-C(192)-C(193)-C(194)	-0.5(9)	C(192)-C(193)-C(194)-C(176)	-4.2(8)
C(177)-C(176)-C(194)-C(193)	4.9(7)	C(175)-C(176)-C(194)-C(193)	-179.5(5)
C(192)-C(191)-C(195)-C(200)	115.6(6)	C(177)-C(191)-C(195)-C(200)	-58.2(8)
C(192)-C(191)-C(195)-C(196)	-58.7(7)	C(177)-C(191)-C(195)-C(196)	127.5(6)
C(200)-C(195)-C(196)-C(197)	-2.2(8)	C(191)-C(195)-C(196)-C(197)	172.3(5)
C(195)-C(196)-C(197)-C(198)	0.4(9)	C(196)-C(197)-C(198)-O(14)	-179.5(6)
C(196)-C(197)-C(198)-C(199)	1.4(9)	C(197)-C(198)-C(199)-C(200)	-1.4(10)
O(14)-C(198)-C(199)-C(200)	179.4(6)	C(196)-C(195)-C(200)-C(199)	2.2(9)
C(191)-C(195)-C(200)-C(199)	-172.2(6)	C(198)-C(199)-C(200)-C(195)	-0.5(10)
C(173)-C(174)-C(203)-C(204)	58.2(6)	C(175)-C(174)-C(203)-C(204)	-125.9(5)
C(173)-C(174)-C(203)-C(208)	-119.7(5)	C(175)-C(174)-C(203)-C(208)	56.2(7)
C(208)-C(203)-C(204)-C(205)	-2.1(8)	C(174)-C(203)-C(204)-C(205)	179.9(5)
C(203)-C(204)-C(205)-C(206)	1.7(8)	C(204)-C(205)-C(206)-O(15)	-179.7(5)
C(204)-C(205)-C(206)-C(207)	0.0(8)	C(205)-C(206)-C(207)-C(208)	-1.2(8)
O(15)-C(206)-C(207)-C(208)	178.5(5)	C(206)-C(207)-C(208)-C(203)	0.8(8)
C(204)-C(203)-C(208)-C(207)	0.9(7)	C(174)-C(203)-C(208)-C(207)	178.9(5)
C(225)-C(216)-C(217)-C(218)	163.2(4)	C(229)-C(216)-C(217)-C(218)	-7.7(7)
C(225)-C(216)-C(217)-C(222)	-5.9(7)	C(229)-C(216)-C(217)-C(222)	-176.8(4)
C(222)-C(217)-C(218)-C(219)	1.8(7)	C(216)-C(217)-C(218)-C(219)	-167.4(5)
C(217)-C(218)-C(219)-C(220)	2.0(8)	C(218)-C(219)-C(220)-C(221)	-1.6(8)
C(219)-C(220)-C(221)-C(222)	-2.6(8)	C(219)-C(220)-C(221)-C(250)	171.9(5)
C(220)-C(221)-C(222)-C(217)	6.4(7)	C(250)-C(221)-C(222)-C(217)	-167.5(5)
C(220)-C(221)-C(222)-C(223)	-173.3(5)	C(250)-C(221)-C(222)-C(223)	12.8(7)
C(218)-C(217)-C(222)-C(221)	-6.0(7)	C(216)-C(217)-C(222)-C(221)	163.4(4)
C(218)-C(217)-C(222)-C(223)	173.7(4)	C(216)-C(217)-C(222)-C(223)	-16.9(6)
C(221)-C(222)-C(223)-C(241)	23.9(7)	C(217)-C(222)-C(223)-C(241)	-155.8(5)
C(221)-C(222)-C(223)-C(224)	-160.9(4)	C(217)-C(222)-C(223)-C(224)	19.4(6)
C(241)-C(223)-C(224)-C(238)	-0.3(7)	C(222)-C(223)-C(224)-C(238)	-175.6(4)
C(241)-C(223)-C(224)-C(225)	176.3(4)	C(222)-C(223)-C(224)-C(225)	1.1(7)
C(229)-C(216)-C(225)-C(226)	19.2(7)	C(217)-C(216)-C(225)-C(226)	-152.3(4)
C(229)-C(216)-C(225)-C(224)	-161.5(4)	C(217)-C(216)-C(225)-C(224)	27.0(7)
C(238)-C(224)-C(225)-C(226)	-28.9(7)	C(223)-C(224)-C(225)-C(226)	154.6(5)
C(238)-C(224)-C(225)-C(216)	151.8(5)	C(223)-C(224)-C(225)-C(216)	-24.7(7)

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Table A6 *continued*

C(216)-C(225)-C(226)-C(227)	-7.4(7)	C(224)-C(225)-C(226)-C(227)	173.3(5)
C(225)-C(226)-C(227)-C(228)	-7.2(8)	C(226)-C(227)-C(228)-C(229)	9.9(8)
C(227)-C(228)-C(229)-C(216)	2.3(7)	C(227)-C(228)-C(229)-C(230)	-170.4(4)
C(225)-C(216)-C(229)-C(228)	-16.8(7)	C(217)-C(216)-C(229)-C(228)	154.1(5)
C(225)-C(216)-C(229)-C(230)	155.3(4)	C(217)-C(216)-C(229)-C(230)	-33.8(7)
C(228)-C(229)-C(230)-C(231)	126.6(5)	C(216)-C(229)-C(230)-C(231)	-45.7(7)
C(228)-C(229)-C(230)-C(235)	-45.5(6)	C(216)-C(229)-C(230)-C(235)	142.2(5)
C(235)-C(230)-C(231)-C(232)	1.2(7)	C(229)-C(230)-C(231)-C(232)	-171.2(4)
C(230)-C(231)-C(232)-C(233)	-0.9(7)	C(231)-C(232)-C(233)-O(17)	179.9(4)
C(231)-C(232)-C(233)-C(234)	0.5(7)	O(17)-C(233)-C(234)-C(235)	-179.8(4)
C(232)-C(233)-C(234)-C(235)	-0.3(7)	C(233)-C(234)-C(235)-C(230)	0.7(7)
C(231)-C(230)-C(235)-C(234)	-1.1(7)	C(229)-C(230)-C(235)-C(234)	171.1(4)
C(223)-C(224)-C(238)-C(239)	-4.1(7)	C(225)-C(224)-C(238)-C(239)	179.5(4)
C(223)-C(224)-C(238)-C(242)	171.7(4)	C(225)-C(224)-C(238)-C(242)	-4.8(7)
C(224)-C(238)-C(239)-C(240)	4.4(8)	C(242)-C(238)-C(239)-C(240)	-171.7(5)
C(238)-C(239)-C(240)-C(241)	-0.2(8)	C(239)-C(240)-C(241)-C(223)	-4.4(8)
C(224)-C(223)-C(241)-C(240)	4.6(7)	C(222)-C(223)-C(241)-C(240)	179.7(5)
C(239)-C(238)-C(242)-C(247)	115.8(6)	C(224)-C(238)-C(242)-C(247)	-60.1(7)
C(239)-C(238)-C(242)-C(243)	-61.0(6)	C(224)-C(238)-C(242)-C(243)	123.1(5)
C(247)-C(242)-C(243)-C(244)	-0.2(7)	C(238)-C(242)-C(243)-C(244)	176.8(5)
C(242)-C(243)-C(244)-C(245)	1.3(8)	C(243)-C(244)-C(245)-O(18)	177.7(5)
C(243)-C(244)-C(245)-C(246)	-1.5(8)	O(18)-C(245)-C(246)-C(247)	-178.6(5)
C(244)-C(245)-C(246)-C(247)	0.5(8)	C(243)-C(242)-C(247)-C(246)	-0.8(8)
C(238)-C(242)-C(247)-C(246)	-177.7(5)	C(245)-C(246)-C(247)-C(242)	0.6(8)
C(220)-C(221)-C(250)-C(255)	-114.3(6)	C(222)-C(221)-C(250)-C(255)	59.8(7)
C(220)-C(221)-C(250)-C(251)	59.2(7)	C(222)-C(221)-C(250)-C(251)	-126.7(6)
C(255)-C(250)-C(251)-C(252)	-0.2(8)	C(221)-C(250)-C(251)-C(252)	-174.0(5)
C(250)-C(251)-C(252)-C(253)	0.4(9)	C(251)-C(252)-C(253)-O(16)	179.7(6)
C(251)-C(252)-C(253)-C(254)	0.3(10)	O(16)-C(253)-C(254)-C(255)	179.3(6)
C(252)-C(253)-C(254)-C(255)	-1.2(10)	C(253)-C(254)-C(255)-C(250)	1.4(10)
C(251)-C(250)-C(255)-C(254)	-0.7(8)	C(221)-C(250)-C(255)-C(254)	173.0(5)
C(19)-C(18)-O(1)-C(22)	-2.8(7)	C(17)-C(18)-O(1)-C(22)	177.8(4)
C(29)-C(30)-O(2)-C(34)	-16.9(7)	C(31)-C(30)-O(2)-C(34)	163.6(4)
C(37)-C(38)-O(3)-C(42)	6.7(8)	C(39)-C(38)-O(3)-C(42)	-172.9(6)
C(59)-C(60)-O(4)-C(64)	0.9(8)	C(61)-C(60)-O(4)-C(64)	-178.8(5)
C(73)-C(72)-O(5)-C(76)	-7.5(8)	C(71)-C(72)-O(5)-C(76)	172.9(5)
C(79)-C(80)-O(6)-C(84)	-177.2(4)	C(81)-C(80)-O(6)-C(84)	3.2(7)
C(101)-C(102)-O(7)-C(106)	179.6(5)	C(103)-C(102)-O(7)-C(106)	-1.1(7)
C(113)-C(114)-O(8)-C(118)	0.5(7)	C(115)-C(114)-O(8)-C(118)	-178.4(5)
C(123)-C(122)-O(9)-C(126)	-10.4(7)	C(121)-C(122)-O(9)-C(126)	169.7(4)
C(143)-C(144)-O(10)-C(148)	-0.2(7)	C(145)-C(144)-O(10)-C(148)	179.7(5)
C(157)-C(156)-O(11)-C(160)	-1.5(7)	C(155)-C(156)-O(11)-C(160)	177.5(5)
C(163)-C(164)-O(12)-C(168)	15.2(7)	C(165)-C(164)-O(12)-C(168)	-164.8(4)

Continued on following page

Table A6 *continued*

C(187)-C(186)-O(13)-C(190)	4.1(7)	C(185)-C(186)-O(13)-C(190)	-175.5(4)
C(197)-C(198)-O(14)-C(202)	6.0(11)	C(199)-C(198)-O(14)-C(202)	-174.8(8)
C(205)-C(206)-O(15)-C(210)	-6.7(9)	C(207)-C(206)-O(15)-C(210)	173.6(5)
C(254)-C(253)-O(16)-C(256)	172.3(9)	C(252)-C(253)-O(16)-C(256)	-7.1(13)
C(232)-C(233)-O(17)-C(237)	5.9(6)	C(234)-C(233)-O(17)-C(237)	-174.6(4)
C(244)-C(245)-O(18)-C(249)	-179.1(5)	C(246)-C(245)-O(18)-C(249)	0.0(8)
C(215)-C(214)-O(19)-C(212)	-173.5(5)	C(211)-C(212)-O(19)-C(214)	-176.2(7)
C(257)-C(258)-O(20)-C(259)	-174.9(5)	C(260)-C(259)-O(20)-C(258)	-174.4(5)
C(265)-C(264)-O(21)-C(263)	-172.4(6)	C(262)-C(263)-O(21)-C(264)	-177.8(5)
C(268)-O(22)-C(266)-C(267)	172.3(19)	C(266)-O(22)-C(268)-C(269)	-179.8(16)

Table A7 Crystal data and structure refinement for **306**.

Chemical formula (moiety)	$C_{12}H_{11}NO_3$
Chemical formula (total)	$C_{12}H_{11}NO_3$
Formula weight	217.22
Temperature	150(2) K
Radiation, wavelength	CuKα, 1.54178 Å
Crystal system, space group	orthorhombic, Pbca
Unit cell parameters	a = 11.6473(6) Å $\alpha = 90°$
	b = 12.0060(7) Å $\beta = 90°$
	c = 15.0698(10) Å $\gamma = 90°$
Cell volume	2107.3(2) Å^3
Z	8
Calculated density	1.369 g/cm^3
Absorption coefficient μ	0.824 mm^{-1}
F(000)	912
Crystal colour and size	pale yellow, 0.16 × 0.10 × 0.08 mm^3
Reflections for cell refinement	5244 (θ range 2.9 to 73.9°)
Data collection method	Agilent Technologies SuperNova
	ω scans
θ range for data collection	5.9 to 74.0°
Index ranges	h -14 to 12, k -14 to 13, l -18 to 18
Completeness to θ = 74.0°	98.9 %
Reflections collected	14539
Independent reflections	2115 (R_{int} = 0.0567)
Reflections with $F^2>2\sigma$	1758
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.8794 and 0.9377
Structure solution	direct methods
Refinement method	full-matrix least-squares on F^2
Weighting parameters a, b	0.0574, 0.2269
Data / restraints / parameters	2115 / 0 / 189
Final R indices [$F^2>2\sigma$]	R1 = 0.0394, wR2 = 0.0963
R indices (all data)	R1 = 0.0496, wR2 = 0.1038
Goodness-of-fit on F^2	1.035
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.21 and -0.26 e Å^{-3}

Table A8 Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for **306**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.92600(12)	0.34204(11)	0.50626(9)	0.0263(3)
C(2)	0.98601(13)	0.27078(12)	0.44914(10)	0.0295(3)
C(3)	0.93819(13)	0.24025(13)	0.36894(10)	0.0316(3)
C(4)	0.83112(13)	0.27954(13)	0.34286(10)	0.0308(3)
C(5)	0.77014(12)	0.34917(12)	0.39961(9)	0.0271(3)
C(6)	0.73073(14)	0.56678(12)	0.52413(11)	0.0336(3)
N(7)	0.75145(10)	0.44853(10)	0.53927(8)	0.0259(3)
C(8)	0.71161(11)	0.41474(11)	0.61912(9)	0.0239(3)
O(9)	0.65367(9)	0.49974(8)	0.65806(7)	0.0302(3)
C(10)	0.64008(15)	0.58960(13)	0.59404(11)	0.0337(3)
O(11)	0.72120(9)	0.32475(8)	0.65409(7)	0.0310(3)
C(12)	0.81659(12)	0.37914(11)	0.48212(9)	0.0248(3)
O(13)	0.66485(9)	0.39274(9)	0.38133(7)	0.0341(3)
C(14)	0.62284(15)	0.37856(17)	0.29279(11)	0.0405(4)
C(15)	0.97948(12)	0.37975(12)	0.58678(10)	0.0292(3)
C(16)	1.03102(15)	0.41134(14)	0.64972(11)	0.0374(4)

Table A9 Bond lengths [Å] and angles [°] for **306**.

C(1)–C(2)	1.400(2)	C(1)–C(12)	1.398(2)
C(1)–C(15)	1.437(2)	C(2)–H(2)	0.97(2)
C(2)–C(3)	1.380(2)	C(3)–H(3)	0.96(2)
C(3)–C(4)	1.390(2)	C(4)–H(4)	0.95(2)
C(4)–C(5)	1.391(2)	C(5)–C(12)	1.403(2)
C(5)–O(13)	1.3614(18)	C(6)–H(6A)	0.97(2)
C(6)–H(6B)	1.01(2)	C(6)–N(7)	1.4581(18)
C(6)–C(10)	1.516(2)	N(7)–C(8)	1.3519(18)
N(7)–C(12)	1.4182(18)	C(8)–O(9)	1.3570(16)
C(8)–O(11)	1.2073(17)	O(9)–C(10)	1.4559(18)
C(10)–H(10A)	0.97(2)	C(10)–H(10B)	1.03(2)
O(13)–C(14)	1.431(2)	C(14)–H(14A)	0.96(2)
C(14)–H(14B)	0.98(2)	C(14)–H(14C)	0.97(2)
C(15)–C(16)	1.185(2)	C(16)–H(16)	0.93(2)
C(2)–C(1)–C(12)	119.31(13)	C(2)–C(1)–C(15)	119.67(13)
C(12)–C(1)–C(15)	120.96(13)	C(1)–C(2)–H(2)	117.1(11)
C(1)–C(2)–C(3)	119.94(14)	H(2)–C(2)–C(3)	123.0(11)
C(2)–C(3)–H(3)	119.7(11)	C(2)–C(3)–C(4)	121.29(14)
H(3)–C(3)–C(4)	119.1(11)	C(3)–C(4)–H(4)	120.8(13)
C(3)–C(4)–C(5)	119.23(14)	H(4)–C(4)–C(5)	119.9(13)
C(4)–C(5)–C(12)	120.14(13)	C(4)–C(5)–O(13)	124.50(13)
C(12)–C(5)–O(13)	115.36(13)	H(6A)–C(6)–H(6B)	108.3(17)
H(6A)–C(6)–N(7)	113.5(12)	H(6A)–C(6)–C(10)	113.0(12)
H(6B)–C(6)–N(7)	109.5(12)	H(6B)–C(6)–C(10)	111.9(13)
N(7)–C(6)–C(10)	100.51(11)	C(6)–N(7)–C(8)	112.00(12)
C(6)–N(7)–C(12)	124.43(11)	C(8)–N(7)–C(12)	123.22(11)
N(7)–C(8)–O(9)	109.26(11)	N(7)–C(8)–O(11)	128.70(13)
O(9)–C(8)–O(11)	122.03(13)	C(8)–O(9)–C(10)	108.95(11)
C(6)–C(10)–O(9)	104.52(11)	C(6)–C(10)–H(10A)	113.5(13)
C(6)–C(10)–H(10B)	110.5(12)	O(9)–C(10)–H(10A)	108.4(12)
O(9)–C(10)–H(10B)	108.5(11)	H(10A)–C(10)–H(10B)	111.1(16)
C(1)–C(12)–C(5)	120.02(13)	C(1)–C(12)–N(7)	121.11(13)
C(5)–C(12)–N(7)	118.85(13)	C(5)–O(13)–C(14)	116.80(12)
O(13)–C(14)–H(14A)	109.0(14)	O(13)–C(14)–H(14B)	110.8(13)
O(13)–C(14)–H(14C)	104.9(12)	H(14A)–C(14)–H(14B)	111.1(17)
H(14A)–C(14)–H(14C)	105.9(17)	H(14B)–C(14)–H(14C)	114.7(18)
C(1)–C(15)–C(16)	175.11(16)	C(15)–C(16)–H(16)	178.9(15)

Table A10 Anisotropic displacement parameters (Å^2) for **306**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}\mathrm{U}^{11} + ... + 2hka^*b^*\mathrm{U}^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	0.0277(7)	0.0273(7)	0.0240(7)	0.0028(5)	0.0021(5)	-0.0019(5)
C(2)	0.0277(7)	0.0302(7)	0.0306(8)	0.0014(5)	0.0024(6)	0.0022(6)
C(3)	0.0340(8)	0.0326(8)	0.0282(7)	-0.0029(6)	0.0069(6)	0.0005(6)
C(4)	0.0344(8)	0.0348(8)	0.0233(7)	-0.0014(5)	0.0019(6)	-0.0020(6)
C(5)	0.0267(7)	0.0300(7)	0.0245(7)	0.0035(5)	0.0007(5)	-0.0011(5)
C(6)	0.0383(8)	0.0242(7)	0.0383(9)	0.0053(6)	0.0083(7)	0.0024(6)
N(7)	0.0311(6)	0.0236(6)	0.0229(6)	0.0025(4)	0.0046(4)	0.0025(4)
C(8)	0.0223(6)	0.0263(7)	0.0230(6)	-0.0008(5)	-0.0014(5)	-0.0010(5)
O(9)	0.0343(6)	0.0292(5)	0.0271(5)	-0.0009(4)	0.0061(4)	0.0033(4)
C(10)	0.0409(9)	0.0259(7)	0.0342(8)	0.0009(6)	0.0053(7)	0.0049(6)
O(11)	0.0352(6)	0.0298(5)	0.0280(5)	0.0064(4)	0.0019(4)	0.0007(4)
C(12)	0.0278(7)	0.0239(6)	0.0226(7)	0.0016(5)	0.0041(5)	-0.0002(5)
O(13)	0.0287(5)	0.0467(7)	0.0269(6)	-0.0010(4)	-0.0029(4)	0.0056(4)
C(14)	0.0348(8)	0.0602(11)	0.0265(8)	0.0044(7)	-0.0047(6)	0.0041(8)
C(15)	0.0293(7)	0.0297(7)	0.0287(7)	0.0013(6)	0.0025(6)	-0.0006(6)
C(16)	0.0366(8)	0.0437(9)	0.0318(8)	-0.0024(7)	-0.0026(7)	-0.0048(7)

Table A11 Hydrogen coordinates and isotropic displacement parameters (Å^2) for **306**.

	x	y	z	U
H(2)	1.0606(18)	0.2443(15)	0.4691(13)	0.039(5)
H(3)	0.9795(17)	0.1906(16)	0.3301(13)	0.037(5)
H(4)	0.7981(19)	0.2569(16)	0.2884(15)	0.049(6)
H(6A)	0.7050(18)	0.5835(16)	0.4646(14)	0.043(5)
H(6B)	0.804(2)	0.6100(17)	0.5357(14)	0.049(6)
H(10A)	0.6507(18)	0.6597(17)	0.6245(14)	0.045(5)
H(10B)	0.5594(19)	0.5843(15)	0.5669(14)	0.041(5)
H(14A)	0.677(2)	0.4110(17)	0.2519(15)	0.052(6)
H(14B)	0.6101(19)	0.2998(19)	0.2796(14)	0.052(6)
H(14C)	0.555(2)	0.4245(17)	0.2897(14)	0.047(5)
H(16)	1.071(2)	0.4350(19)	0.6997(16)	0.060(7)

Table A12 Torsion angles [°] for **306**.

C(12)–C(1)–C(2)–C(3)	1.7(2)	C(15)–C(1)–C(2)–C(3)	-175.66(13)
C(1)–C(2)–C(3)–C(4)	0.5(2)	C(2)–C(3)–C(4)–C(5)	-1.3(2)
C(3)–C(4)–C(5)–C(12)	0.0(2)	C(3)–C(4)–C(5)–O(13)	179.96(13)
C(10)–C(6)–N(7)–C(8)	-17.07(16)	C(10)–C(6)–N(7)–C(12)	169.48(13)
C(6)–N(7)–C(8)–O(9)	5.93(16)	C(6)–N(7)–C(8)–O(11)	-174.97(14)
C(12)–N(7)–C(8)–O(9)	179.47(12)	C(12)–N(7)–C(8)–O(11)	-1.4(2)
N(7)–C(8)–O(9)–C(10)	8.94(15)	O(11)–C(8)–O(9)–C(10)	-170.23(14)
C(8)–O(9)–C(10)–C(6)	-19.31(16)	N(7)–C(6)–C(10)–O(9)	20.93(16)
C(2)–C(1)–C(12)–C(5)	-2.9(2)	C(2)–C(1)–C(12)–N(7)	178.01(12)
C(15)–C(1)–C(12)–C(5)	174.35(13)	C(15)–C(1)–C(12)–N(7)	-4.7(2)
C(4)–C(5)–C(12)–C(1)	2.1(2)	C(4)–C(5)–C(12)–N(7)	-178.81(13)
O(13)–C(5)–C(12)–C(1)	-177.83(12)	O(13)–C(5)–C(12)–N(7)	1.24(19)
C(6)–N(7)–C(12)–C(1)	107.27(16)	C(6)–N(7)–C(12)–C(5)	-71.80(19)
C(8)–N(7)–C(12)–C(1)	-65.47(18)	C(8)–N(7)–C(12)–C(5)	115.47(15)
C(4)–C(5)–O(13)–C(14)	-9.5(2)	C(12)–C(5)–O(13)–C(14)	170.46(13)
C(2)–C(1)–C(15)–C(16)	38(2)	C(12)–C(1)–C(15)–C(16)	-139.4(19)