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PERSPECTIVE

Recent advances and applications of iridium-catalysed asymmetric allylic substitution

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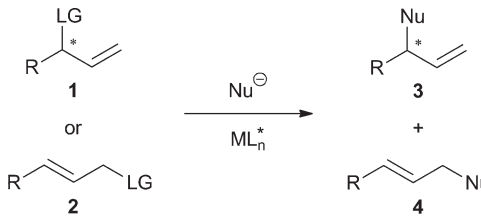
Since their discovery in 1997, iridium-catalysed asymmetric allylic substitutions have been developed into a broadly applicable tool for the synthesis of chiral building blocks *via* C–C and C–heteroatom bond formation. The remarkable generality of these reactions and the high levels of regio- and enantioselectivity that are usually obtained in favour of the branched products have been made possible by a thorough investigation of the catalyst system and its mode of action. Therefore, today the Ir-catalysed asymmetric allylic substitution is a powerful reaction in the organic chemist's repertoire and has been used extensively for several applications. This article aims to provide an overview of the development of iridium catalysts derived from an Ir salt and a chiral phosphoramidite and their application to the enantioselective synthesis of natural products and biologically relevant compounds.

1. Introduction

Metal-catalysed asymmetric allylic substitutions (AAS) are an important class of catalysed processes in organic chemistry, as they provide a valuable tool for the stereoselective formation of C–C and C–X bonds (X = N, O and S). Although palladium complexes have been used extensively for this chemistry over the last 40 years,[1] other metals including Mo, W,[2] Co, Fe, Ru, Rh, Ni, Pt,[3] Cu,[4] and Ir[5] have found interesting applications as competent catalysts for allylic substitutions. In particular, some iridium complexes display high levels of regioselectivity in favour of the branched isomer that are complementary to linear products usually observed with palladium when mono-substituted allylic systems are used as starting materials (eqn (1)). In fact, chiral iridium-based catalysts can afford highly enantiomerically enriched branched products (**3**) from a wide range of easily accessible substrates **1** and **2**, whilst Pd complexes tend to favour linear products (**4**). Molecules of general formula **3** are of particular interest as chiral building blocks for the synthesis of natural products and pharmaceuticals and as fine chemicals for other industrial applications.



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In this perspective article, we provide an overview of the use of iridium complexes as catalysts for asymmetric allylic substitutions. Other reviews dealing with the general scope and

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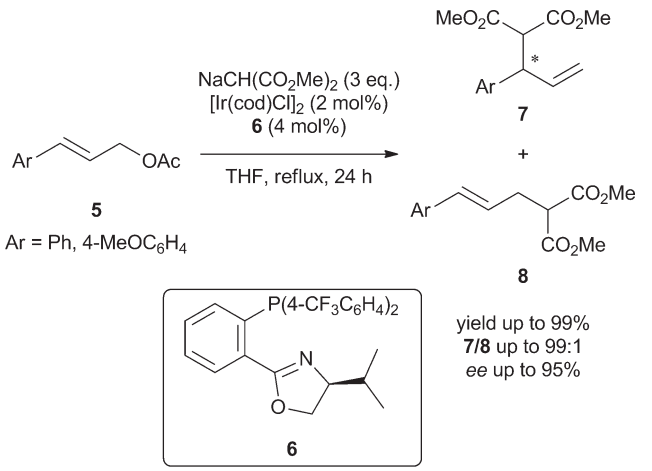
Paolo Tosatti graduated cum Laude *in 2007 from the University of Genoa (Italy). After a short period as a graduate research assistant at the same institution, he moved to the UK to pursue his doctoral studies under the joint supervision of Professors Steve Marsden and Adam Nelson. During this time he applied metal-catalysed asymmetric allylic substitutions to the array synthesis of lead-like molecules as part of a collaborative project between the University of Leeds and GlaxoSmithKline. In 2011, he joined the group of Professor Andreas Pfaltz at the University of Basel as a postdoctoral researcher, investigating transition metal-free catalytic hydrogenations.*

Adam Nelson was appointed at the University of Leeds in 1998, and is currently Professor of Chemical Biology. He was Director of the Astbury Centre for Structural Molecular Biology between 2009 and 2011. Professor Nelson was awarded the RSC Meldola medal (in 2001), the Pfizer academic award (in 2002), an EPSRC advanced research fellowship (2004–2009), the AstraZeneca award in organic chemistry (in 2005) and the RSC Corday–Morgan medal (in 2008). He has diverse research interests at the interface between chemistry and biology.



Scheme 1 First regio- and enantioselective Ir-catalysed allylic alkylation.

mechanism of the reaction have been published recently,[5a–d] we focus on the recent applications of iridium catalysed AAS for the synthesis of natural products, biologically relevant molecules and unusual molecular scaffolds.

2. General reactivity, mechanistic investigations and ligand effect

2.1. First results, isolation of a reactive chiral iridacycle species

The first examples of Ir-catalysed allylic substitution were reported by Takeuchi and Kashio in 1997[6] who observed that allylic acetates and carbonates undergo regioselective alkylation at the more hindered position of the allylic system using sodium malonate in the presence of $[Ir(cod)Cl]_2$ and a phosphite ligand. Shortly after, Janssen and Helmchen described the first Ir-catalysed asymmetric allylic alkylation using a phosphine–oxazoline ligand (Scheme 1).[7] Following these two seminal publications, there has been a growing interest in the development of Ir-catalysed AAS, mainly driven by the groups of Helmchen and Hartwig with important contributions from Alexakis, Carreira, Takeuchi and You *inter alia*.

After a series of studies by Helmchen and Takeuchi aimed at unveiling the general reactivity of Ir-catalysts formed with different chiral ligands,[8–11] a major breakthrough in the field was reported by Ohmura and Hartwig who accomplished the first Ir-catalysed asymmetric allylic amination of linear allylic carbonates using $[Ir(cod)Cl]_2$ and a chiral Feringa–Alexakis-type phosphoramidite **9**.[12] The reaction was characterised by very promising levels of regio- and enantioselectivity in favour of branched products. This result was underpinned by another coeval investigation by Helmchen, who attained interesting results for the alkylation of linear allylic acetates using very similar conditions to those published by Hartwig (Scheme 2).[8]

On the basis of a thorough investigation on the active catalyst system for the allylic amination reaction, Hartwig *et al.* confirmed previous observations[9] that square planar complexes like **10** are not reactive towards allylic carbonates. The same study also revealed that addition of a base promotes C–H insertion of one methyl group of phosphoramidite **9**, converting the ligand from mono- to bidentate and therefore allowing the formation of the trigonal bipyramidal iridacycle **11** (Scheme 3). Reactions carried out with pre-formed **11** proceeded with higher rate and without the induction period that was instead observed with the metallacycle generated *in situ* by the nucleophile. Reactions carried out with a 2 : 1 mixture of **11** and $[Ir(cod)Cl]_2$ were even faster, in accordance with the hypothesis that $[Ir(cod)Cl]_2$ plays a role in the catalytic cycle, liberating a binding site of **11** by sequestering monodentate **9**.[13] A further advantage of complex **11** (or its mixture with $[Ir(cod)Cl]_2$) is that it can be generated with a base such as TBD,[14] *n*-propylamine,[15,16] or DABCO[16] and then used for asymmetric allylic substitutions involving weakly basic nucleophiles that are not able to promote cyclometallation (*e.g.* anilines, see Scheme 4).[16–25] Despite giving excellent initial results for amination and etherification, iridacycle **11** displayed low catalytic activity for the alkylation of linear allylic carbonates with malonates. Helmchen and co-workers attributed the low catalytic activity of the iridacycle to the saturated binding site on the metal and used additives to displace **9** from **11** more efficiently.[26] A combination of tetrahydrothiophene (THT) and CuI proved to be successful, generating a highly reactive species for alkylations that were carried out at room temperature, with low catalyst loading and were characterised by high regio- and enantioselectivity (Scheme 5). For aminations, $Pb(OAc)_2$ was used in place of CuI, given the tendency of the latter to complex the nucleophile.[26,27]

2.2. Origin of the enantioselectivity: chiral ligands

Iridium-phosphoramidite complexes like **11** are the most widely used chiral systems for Ir-catalysed allylic substitution reactions. The impact of phosphoramidite ligands on the enantioselectivity of the reaction has been revealed thanks to the fine tuning of their chiral elements and substituents. These studies, conducted by the groups of Alexakis,[28] Hartwig[15,29,30] and Helmchen[27,31] were made possible by the nature of Feringa–Alexakis-type phosphoramidites that are easily prepared in a modular fashion using straightforward transformations.[32]

It has been demonstrated that the origin of the enantioselectivity in allylic substitutions catalysed by iridacycle complexes like **11** can be ascribed mainly to the chiral centre in the β-position to the metal. In fact, Hartwig *et al.* have shown that comparable results of linear allylic carbonates, can be achieved even with ligands bearing only two or even one stereodefined

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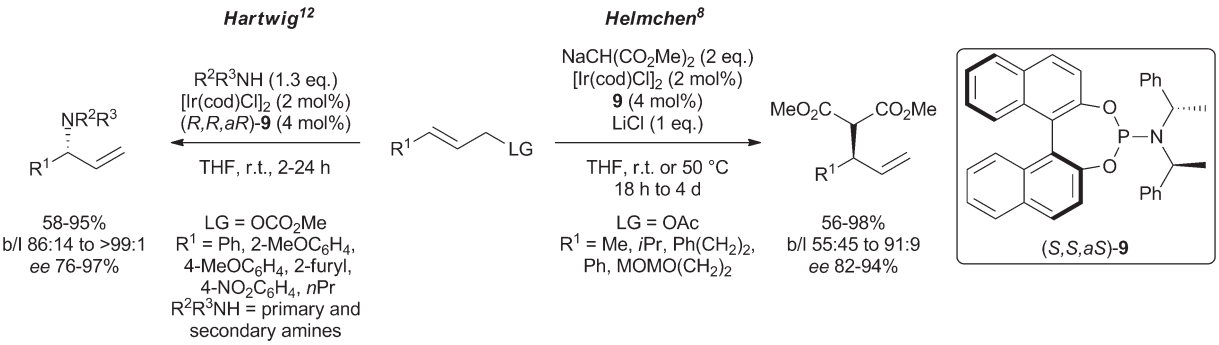
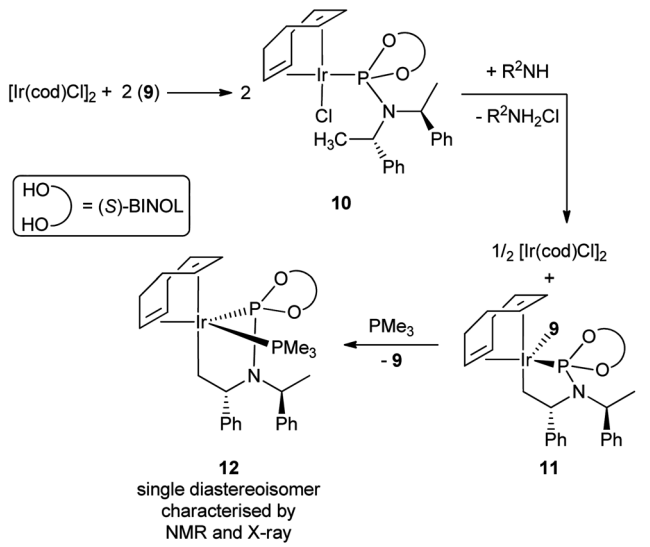
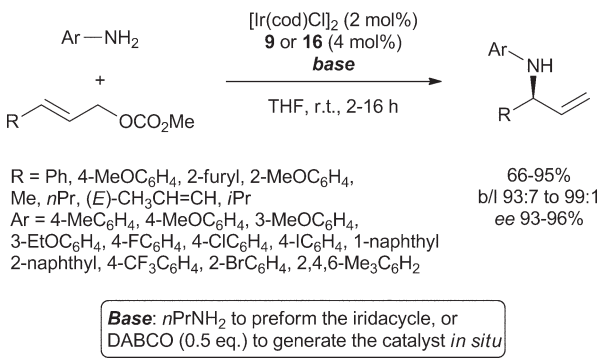


Scheme 2 Ir-catalysed allylic amination and alkylation of linear substrates using the first generation catalyst system ($[Ir(cod)Cl]_2$ and phosphoramidite **9** – no added base). The notation b/l indicates the ratio of branched (b) and linear (l) product.

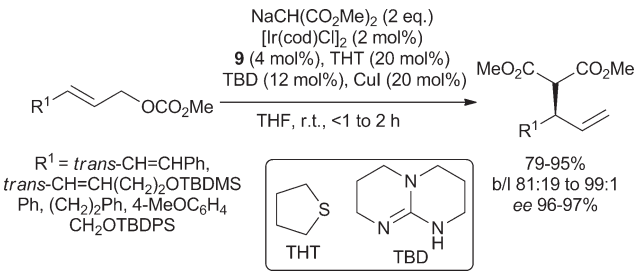


Scheme 3 Formation of the active iridacycle **11** and its derivative **12**.



Scheme 4 Anilines as nucleophiles for Ir-catalysed AAS.

element as in **13** and **14** (Fig. 1) respectively.[29,30] However, the ease of access to enantiopure BINOL and the straightforward assembly of phosphoramidites posed no limitation to the preparation of more elaborate phosphoramidites. A vast library of such ligands has been tested in a series of studies by Alexakis *et al.*[28c] who identified phosphoramidites **15**–**17** as particularly efficient (both in terms of reaction rate and selectivity) for the



Scheme 5 Improved methodology for Ir-catalysed asymmetric allylic alkylations.

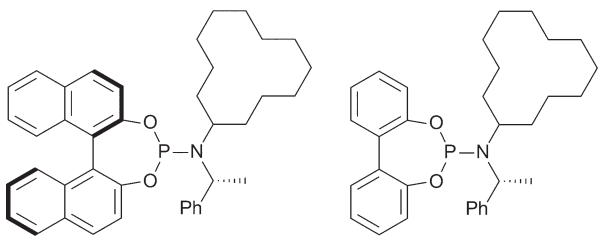
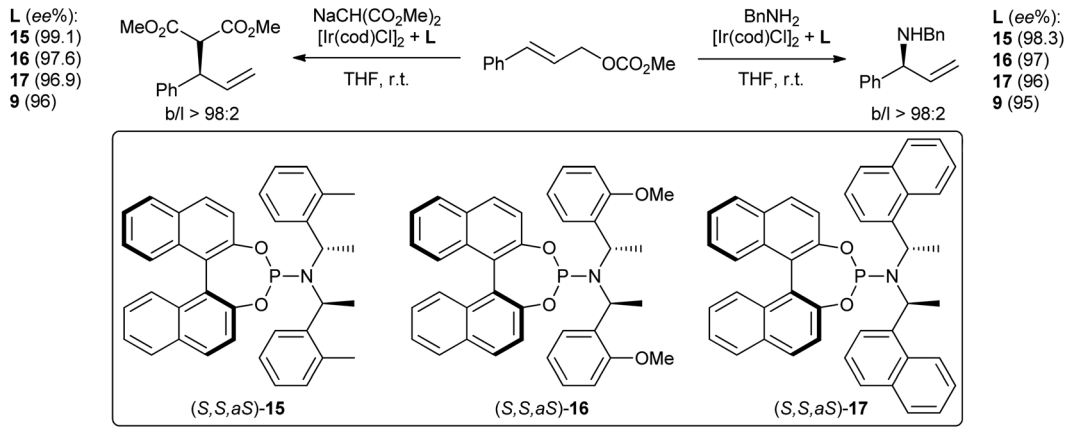


Fig. 1 Phosphoramidite ligands bearing only two or one stereodefined elements.

alkylation and amination of allylic carbonates in the presence of $[Ir(cod)Cl]_2$ (Scheme 6). These findings paralleled independent studies by Hartwig *et al.*[16,33] and Helmchen *et al.*[27,31] and further to these results, phosphoramidites **9**, **16** and **17** are now the most used chiral ligands for Ir-catalysed AAS. Although steric effects have been hypothesised to be the reason for the improved activity and selectivity of ligands **15**–**17**,[27] this rationale remains tentative.[70] Modification of the biaryl moiety of the phosphoramidite ligands as in **18**, **19** and **20** was briefly investigated, but proved deleterious.[27,34] Recently, Takeuchi *et al.* introduced new phosphoramidites **21**, containing an oxazolidine moiety, as effective ligands for allylic alkylations. In this case, no explicit pre-activation of the catalyst with a base was carried out and the use of LiCl as an additive was found to be superfluous. It is postulated that phosphoramidites such as **21** act as bidentate ligands and the planarity of the amide group enhances the rigid conformation about the metal, but further mechanistic



Scheme 6 Use of ligands **9** and **15–17** for Ir-catalysed AAS.

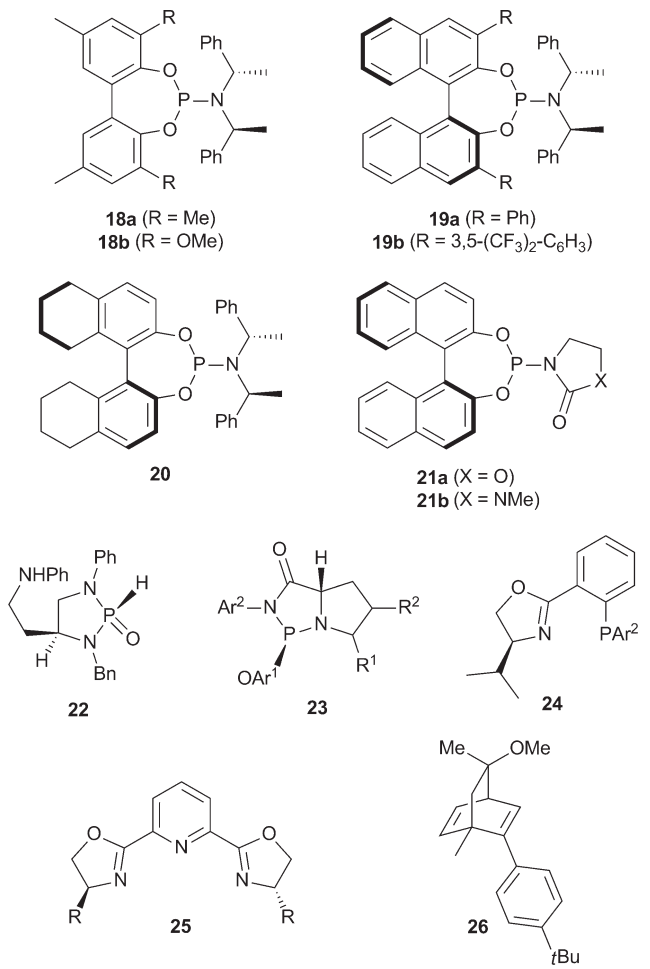
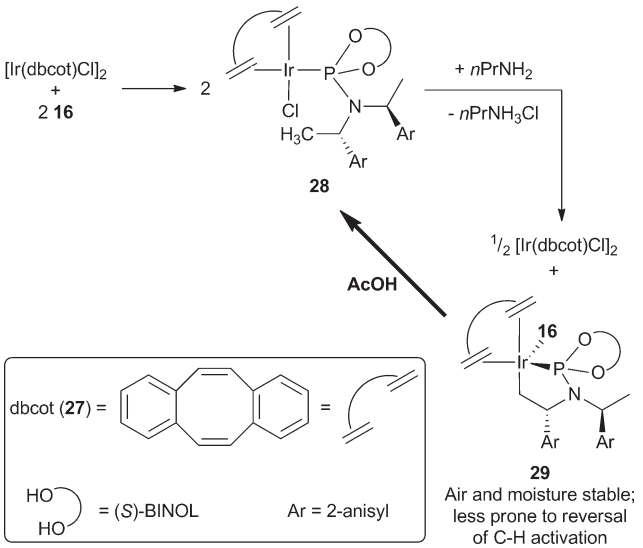


Fig. 2 Structure of alternative ligands used for Ir-catalysed AAS.

studies are needed to clarify the improved performances of these ligands.[35] Other ligands including diaminophosphine oxides (DIAPHOX) **22**,[36] more complex phosphoramidite ligands **23**,[37] phosphinooxazolines (PHOX) **24**,[7,38] bisoxazolinylpyridines (PyBox) **25**[39] and [2.2.2]bicyclooctadiene **26**[40] (Fig. 2) have been used for Ir-catalysed asymmetric substitutions, but to a much more limited extent.



Scheme 7 Formation of iridacycle **29** containing dbcot diene ligand.

2.3. Diene ligand

Although $[Ir(cod)Cl]_2$ is the most popular pre-catalyst for Ir-catalysed allylic substitutions, catalysts derived from this binuclear species and a chiral phosphoramidite have to be prepared under an inert atmosphere (typically under Ar or in a glovebox) and using dry solvents, as the species present in the activating cyclometallation step are oxygen and moisture sensitive.[5e] In 2008 Helmchen *et al.* demonstrated that the replacement of the standard cod ligand by dibenzo[*a*,*e*]cyclooctatriene (dbcot) (**27**) is highly beneficial to the stability and the performances of the resulting iridacycle **29** (Scheme 7). In fact, amination and alkylation of allylic carbonates in the presence of complex **29** showed higher regioselectivity than those carried out using its parent complex prepared with $[Ir(cod)Cl]_2$. More importantly, **29** worked efficiently under air affording products with comparable yield and selectivity to those obtained under a protective atmosphere, whilst reactions performed using the cod-containing iridacycle failed to react under air. Furthermore, iridacycle **29** proved highly stable to reversal of the C–H activation that can occur for complexes like **11** upon evaporation of the *n*-propylamine

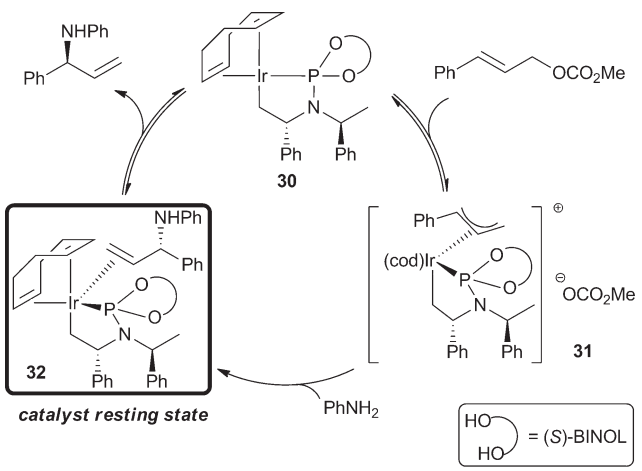
needed to drive their formation (presumably, the HCl required for reverse C–H activation derives from the remaining nPrNH$_3$Cl). Indeed, the conversion of complex **29** into **28** is only possible by deliberate addition of acetic acid (Scheme 7).[41]

Our own work has also demonstrated that the iridacycle derived from [Ir(dbcot)Cl]$_2$ and ligand **9** can be formed and used in polar aprotic solvents like DMSO, allowing reactions to be run with highly polar substrates. The same reaction conditions were not applicable to catalysts derived from [Ir(cod)Cl]$_2$.[42]

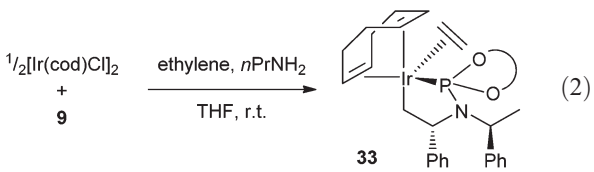
2.4. Reaction kinetics, catalyst resting state and (π-allyl)iridium complexes

The first chiral (π-allyl)Ir complexes were isolated and characterised by Helmchen *et al.* in 2004 employing a phosphine–oxazoline ligand.[38] However, the mechanism of Ir-catalysed AAS that employ this class of chiral ligands remained unclear.

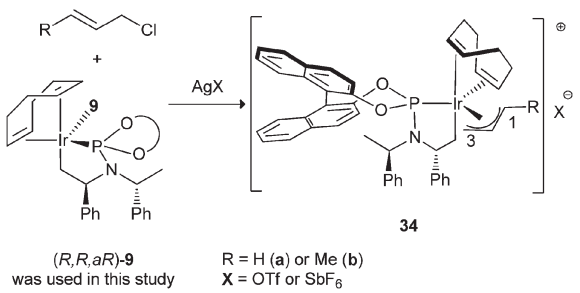
It was only three years later that a mechanism for the Ir-catalysed asymmetric amination of allylic carbonates was proposed by Marković and Hartwig, who studied the allylation of aniline in the presence of a mixture of [Ir(cod)Cl]$_2$ and iridacycle **11**.[43] According to the catalytic cycle proposed by Marković and Hartwig (Scheme 8), the reactive 16-electron species **30** reacts reversibly with the allylic carbonate to form the (π-allyl)Ir system **31** that undergoes irreversible nucleophilic attack of aniline to give iridacycle **32** and subsequent dissociation of the allylic amine re-forms **30** to complete the catalytic cycle. The iridacycle **32** has been isolated as the major iridium species in the reaction mixture and identified as the resting state of the catalyst; furthermore, **32** could be pre-formed and successfully used as a catalyst for allylic aminations. Following these observations, an ethylene analogue of **32** (complex **33** in eqn (2)) has been prepared and used as a particularly stable and active catalyst for allylic substitutions (see Section 4).[43]



Scheme 8 Proposed catalytic cycle for asymmetric allylic amination.



As no reaction was observed between cinnamyl carbonate and metallacycles **32** or **33**, they were treated with more reactive allyl chlorides in the presence of silver salts to allow isolation and characterisation of (π-allyl)Ir complexes **34** (eqn (3)). X-ray analysis showed that iridacycles **34** are highly distorted octahedra with an Ir–C1 distance longer than Ir–C3 (in the case of **34b**), moreover they react with a series of C, N, and O nucleophiles to give the desired branched allylic products in high yield, regio- and enantioselectivity, proving that they are real intermediates in the catalytic cycle of Ir-catalysed asymmetric allylic substitutions. Importantly, it was noted that nucleophilic attack takes place on the more distant carbon from the metal centre and *anti* to the iridium.[44]



Helmchen *et al.* have recently reported an alternative method for the synthesis of (π-allyl)Ir complexes: in this case, allyl iridium complexes **38** were obtained by mixing [Ir(cod)Cl]$_2$, a chiral phosphoramidite ligand (**L***), allylic carbonate and a silver salt with a weakly coordinating anion (Scheme 9). Interestingly, complexes **38** were found to be particularly stable to oxygen and were even purified by column chromatography.[45] According to this study and previous observations,[41] if the formation of metallacycle **37** is promoted by a base such as *n*-propylamine or TBD, the ammonium salt that is present in the reaction mixture is sufficient to promote reversal of C–H activation and the consequent formation of an inactive square planar complex **35** that, in this case, constitutes the resting state of the catalyst. Scheme 10 gives a summary of the proposed catalytic cycle for Ir-catalysed asymmetric allylic substitutions using iridacycles derived from [Ir(cod)Cl]$_2$ and a phosphoramidite ligand in the presence of a base that induces C–H activation. It is important to note that the catalyst resting state depends on the protocol used for the preparation of the metallacycles and the use of pre-formed metallacycles such as **32** or **33** is supposed to maximise the amount of active catalyst species present in the reaction mixture.[5c] Surprisingly, when the allylic alkylation of carbonates was carried out using dimethyl malonate and complexes **38** as catalysts under conditions that excluded the possibility of reversal of C–H activation, the resting state of the catalyst was found to be the (π-allyl)Ir complex, in contrast to the observation of Hartwig using complex **32** without a non-coordinating counterion.[45] Therefore, some further investigations on the factors that affect each single step of the catalytic cycle are probably still needed.

3. Reaction scope and applications to the total synthesis of biologically relevant compounds

A full account of the whole scope of Ir-catalysed AAS goes beyond the aim of this perspective article. We aim instead to

summarise important classes of C, N and O nucleophiles that have been used hitherto to generate interesting chiral intermediates for the synthesis of biologically relevant products. In terms of electrophiles, the general features observed for Ir-catalysed AAS can be summarised as it follows:

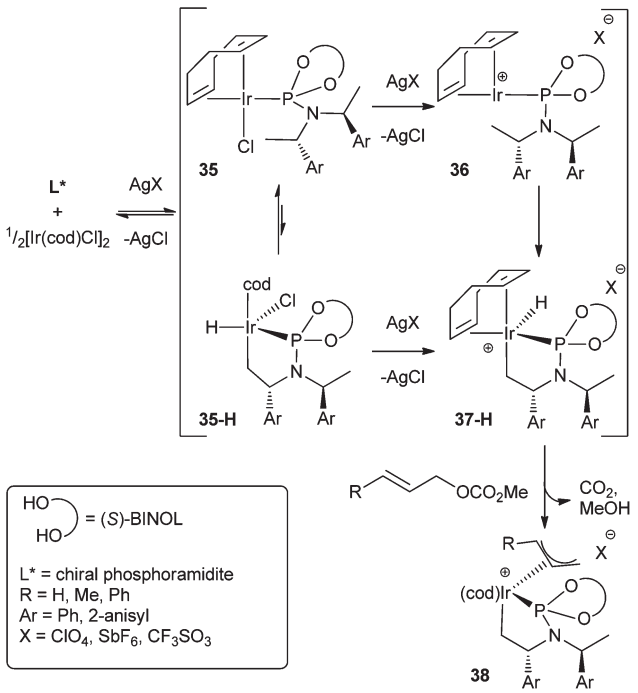
• Allylic carbonates are generally more reactive than allylic carboxylates

• The geometry of the double bond of the allylic substrates plays an important role in the reactivity of the substrate and *E*-configured systems are best suited for Ir-catalysed AAS[46]

• Aromatic allylic carbonates usually show higher reactivity than aliphatic ones

• *ortho*-Subtituted aromatic allylic carbonates normally afford products with reduced enantiopurity regardless of the nucleophile employed.

The following subsections deal with the total synthesis of selected natural products and pharmaceuticals featuring an Ir-catalysed AAS as the key step of the synthetic sequence.

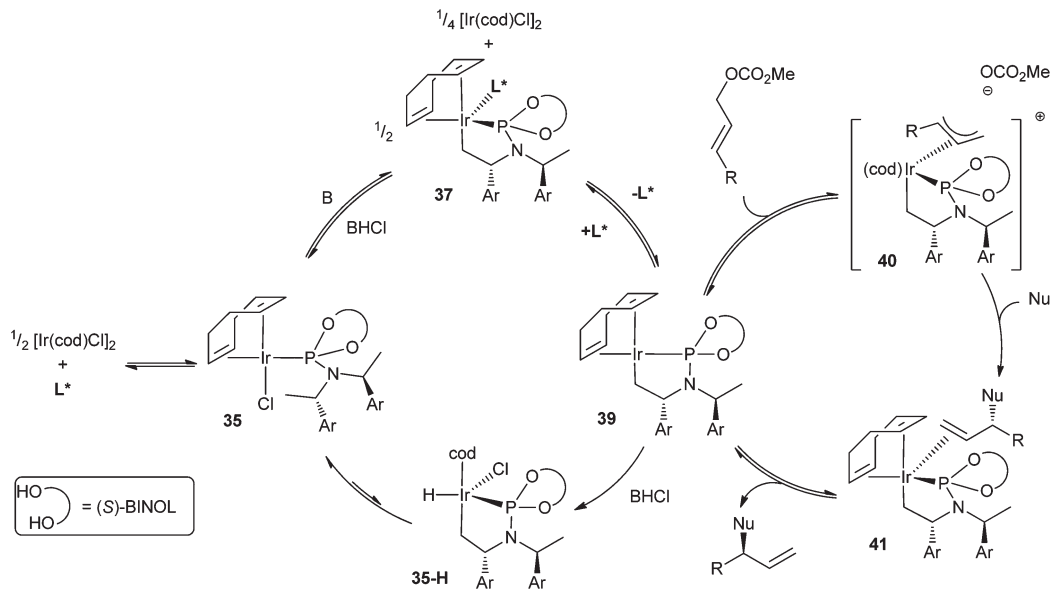


Scheme 9 Direct preparation of (π-allyl)Ir complexes using Helmchen's protocol.

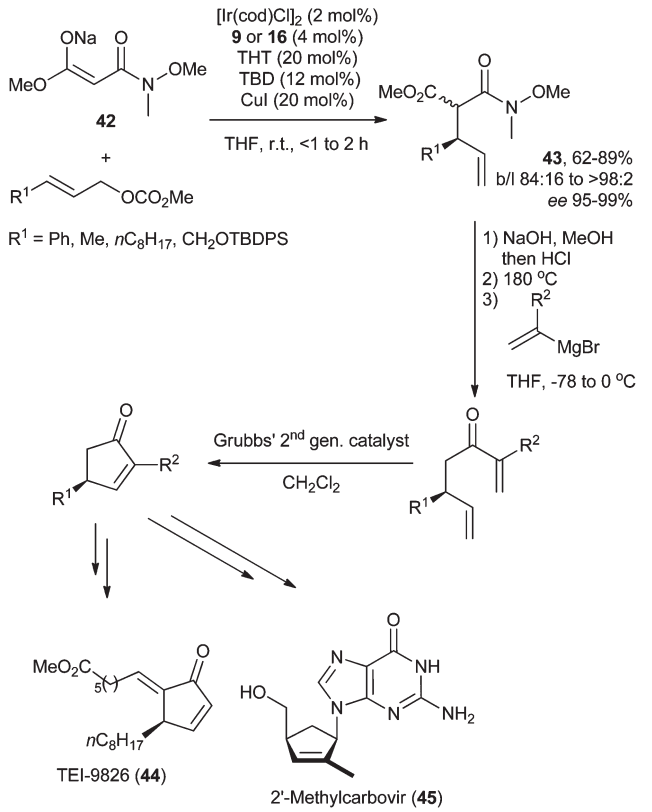
3.1. Carbon nucleophiles

Although much attention over the past decade has been focussed on the use of malonates, several other C-nucleophiles including malononitrile,[20,22] amino acid derivatives,[47] nitro compounds,[18] enamines[21] and ketone[17] enolate, half-amides of malonic ester,[48] phenols,[49a] pyrroles[49b] and indoles[23,25,50] have been successfully employed. It is worth highlighting that in the case of C-nucleophiles several variants of the reaction conditions have been studied[5a,e] and often the use of additives such as THT, CuI (*cf.* Scheme 5) and LiCl is found necessary to attain good results. Nevertheless, Helmchen has demonstrated that the use of deprotonated nucleophiles (*e.g.* sodium malonate) and additives can be circumvented in some cases and alkylations can be carried out under salt-free conditions.[18,20,22]

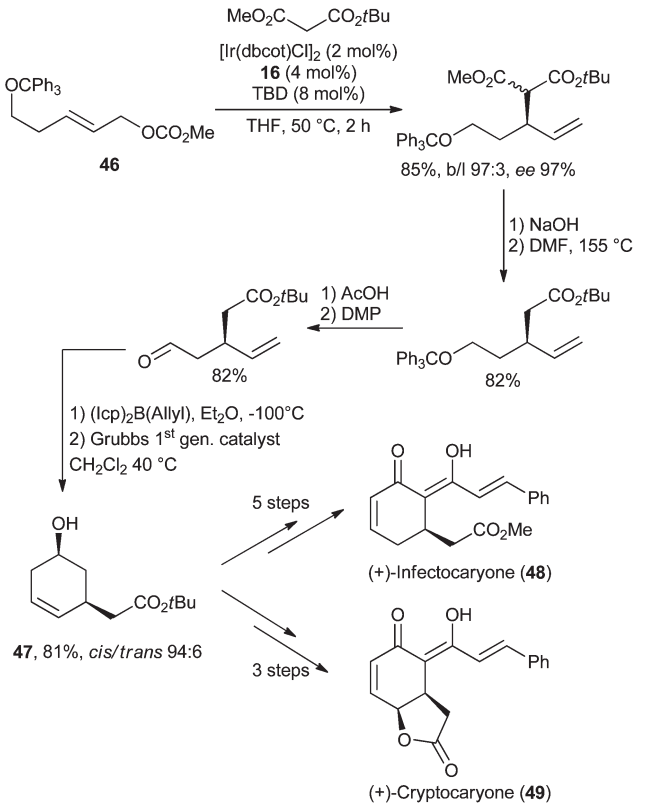
Half-amides of malonic ester have found application as nucleophiles for Ir-catalysed allylic alkylations giving similar results to those obtained with sodium malonates, but salt-free conditions could not be successfully applied in this case. Scheme 11 describes the general reaction conditions applied to alkylations carried out with malonic half-amide **42**. No diastereoselectivity was observed in the formation of products **43** that were generated in good yield and generally high regioselectivity



Scheme 10 Proposed catalytic cycle for Ir-catalysed allylic substitutions carried out with iridacycle generated *in situ* by reaction of $[Ir(cod)Cl]_2$ and chiral phosphoramidite in the presence of a base.



Scheme 11 Use of malonic half-amide **42** for the synthesis of TEI-9826 and 2′-methylcarbovir.

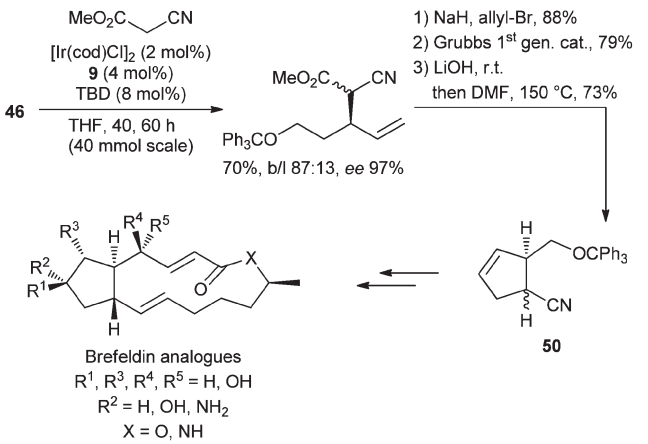


Scheme 12 Overview of the total synthesis of (+)-infectocaryone and (+)-cryptocaryone.

and excellent enantioselectivity. Sterically encumbered carbonates (R^1 = $CH_2OTBDPS$) gave lower regioselectivity and in those cases the use of chiral ligand **9** was more effective than the usually superior **16** (this behaviour of hindered carbonates has been generally observed in other cases[20,22,27,51]). Compounds **43** were elegantly employed as intermediates for the assembly of chiral cyclopentenones *via* saponification followed by decarboxylation, addition of vinyl Grignard reagents and subsequent ring closing metathesis. The utility of the resulting cyclopentenones has been demonstrated by the total synthesis of the prostaglandin analogue TEI-9826 (**44**) (active against cisplatin-resistant tumors) and the carbonucleoside 2′-methylcarbovir (**45**).[48]

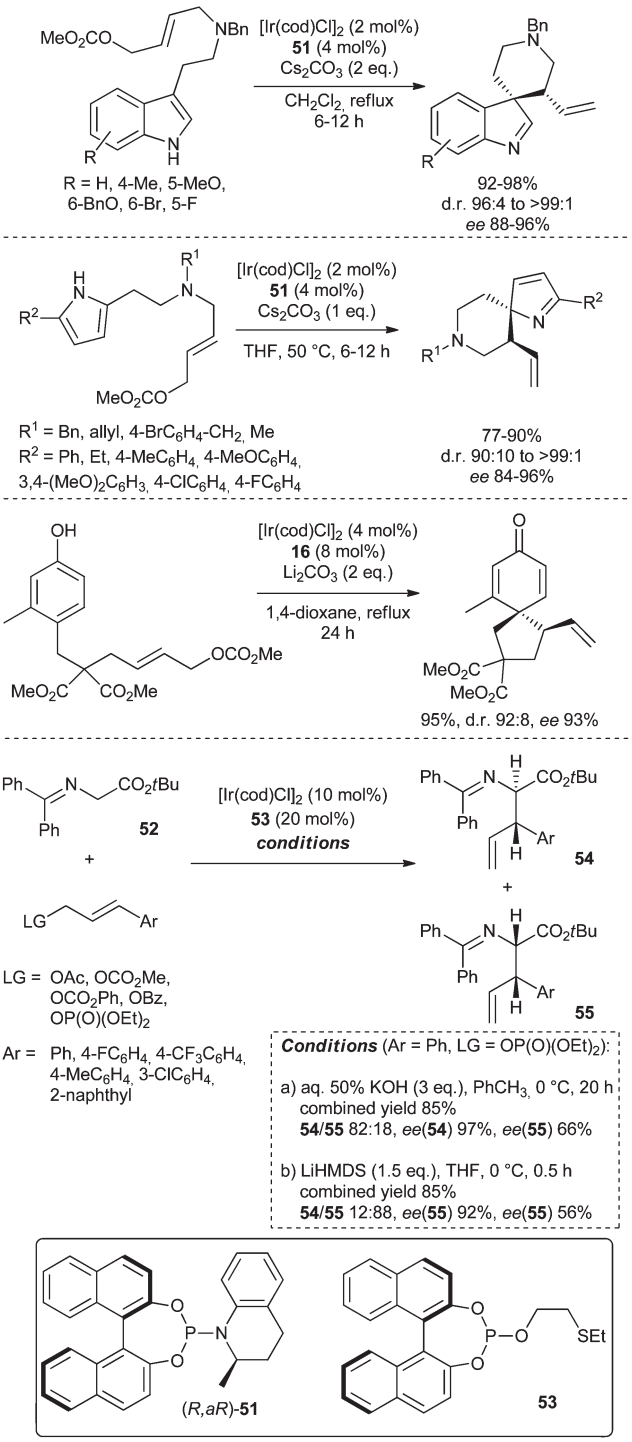
More recently, a similar approach has been devised for the preparation of chiral cyclohexenones deploying the Ir-catalysed allylic alkylation of carbonate **46** as the stereodetermining step of the reaction sequence. This strategy allowed Helmchen and co-workers to access the key intermediate cyclohexene **47** in seven steps, which was then used for the total synthesis of (+)-infectocaryone **48** and (+)-cryptocaryone **49** (Scheme 12).[52] It should be noted that in this synthesis, the use of $[Ir(dbcot)Cl]_2$ as the pre-catalyst allowed the allylic alkylation to be performed with high levels of both regio- and enantioselectivity in favour of the desired branched product.

Alkylation of carbonate **46** with methyl cyanoacetate was also reported by Förster and Hemchen under salt free conditions to give a chiral building block (on a 40 mmol scale) for the synthesis of cyclopentene **50**, that was used in the synthesis of various brefeldin analogues (Scheme 13).[53]



Scheme 13 Synthesis of cyclopentene **50** by Ir-catalysed asymmetric allylic alkylation and its use for the synthesis of a series of brefeldin analogues.

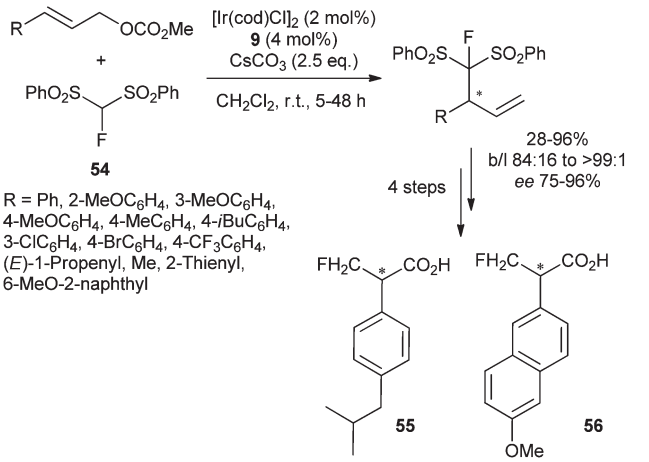
The use of nucleophiles containing a prostereogenic centre (*e.g.* methyl cyanoacetate) usually results in no diastereoselectivity.[18,20,28c,48] Rare exceptions to this observation have been recently reported by You *et al.* in the intramolecular allylation of indoles[50] and in the intramolecular dearomatisation of pyrroles and phenols[49] (see Scheme 14). To date, the only successful example of diastereoselective intermolecular Ir-catalysed allylic substitution employing a C-nucleophile bearing a prostereogenic centre has been accomplished by Takemoto *et al.* who used



Scheme 14 Successful examples of diastereoselective Ir-catalysed allylic alkylations using prostereogenic nucleophiles.

diphenyliminoglycinate **52** and found that different bases used for the generation of the nucleophile affect the stereochemical outcome of the reaction (Scheme 14).[47]

Recently, the scope of C-nucleophiles has been further expanded to include fluorobis(phenylsulphonyl)methane **54**. This nucleophile gave access to fluorinated products with high regio- and enantioselectivity. Cs_2CO_3 was found to be the



Scheme 15 Use of fluorobis(phenylsulphonyl)methane for the synthesis of monofluorinated ibuprofen and naproxen.

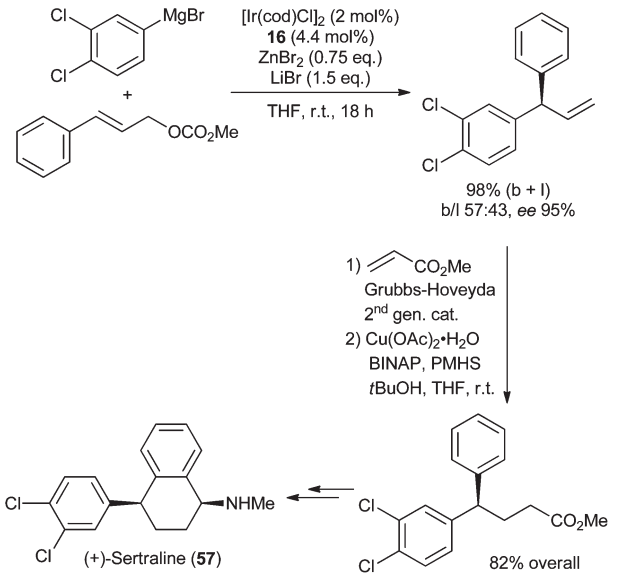
optimal base in this case and large scale reactions were carried out successfully (up to 1 g of allylic carbonate). The method has been used for the synthesis of both enantiomers of fluorinated ibuprofen (**55**) and naproxen (**56**) (Scheme 15).[34b]

Attempts to use hard C-nucleophiles (pK_a of the conjugated acid > 25) have been reported by Alexakis *et al.* who studied reactions of arylzinc reagents. Although promising initial results were observed for the asymmetric arylation of allylic carbonates under standard conditions ($[Ir(cod)Cl]_2$ and ligand **16**), low regioselectivities in favour of the desired branched products (typically b/l ratios just above 50%) posed a limitation to further developments. In addition, only allylic carbonates bearing an aromatic ring at one allylic terminus were successful, whereas linear aliphatic substituents gave products with very low enantioselectivity. Nevertheless, the utility of this strategy was exemplified by the formal synthesis of the pharmaceutical (+)-sertraline **57** (Scheme 16).[54]

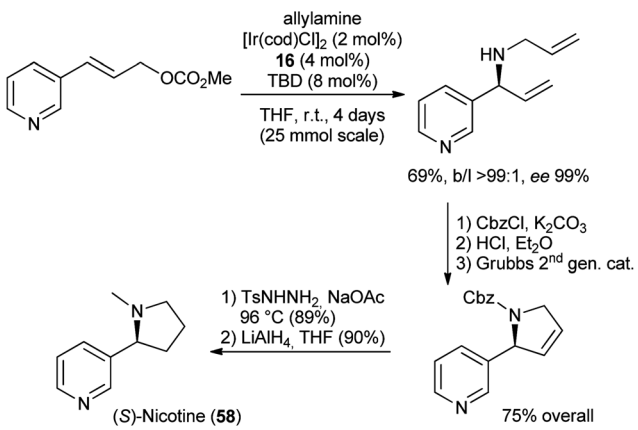
4. Nitrogen nucleophiles

The evolution of iridium-based catalysts for allylic substitution has allowed the use of a remarkably broad range of amines and other N-nucleophiles. An early example of the use of Ir-catalysed asymmetric allylic amination for the synthesis of natural products was reported in 2005 by Helmchen and co-workers who prepared (*S*)-nicotine **58** in five steps as summarised in Scheme 17.[55]

A more elaborate example of the potential of Ir-catalysed AAS has been reported by Helmchen *et al.* who accomplished the remarkable synthesis of a series of piperidine alkaloids by intramolecular amination of carbonates.[46a,56] Helmchen and co-workers showed that the key 2,6-disubstituted piperidine cores **61–64** in Scheme 18 could be obtained in high yield and with excellent catalyst-controlled diastereoselectivity. Substrates **59** and **60** were obtained by cross-metathesis and used as mixtures of *E* and *Z* isomers with good results. The same reaction on pure *E*-substrates was also examined and gave nearly perfect diastereoselectivity, whereas pure *Z*-carbonates reacted slowly and gave drastically reduced d.r. values. Access to the final natural



Scheme 16 Ir-catalysed asymmetric allylic arylation and formal synthesis of (+)-sertraline.



Scheme 17 Enantioselective synthesis of (*S*)-nicotine *via* Ir-catalysed asymmetric allylic amination.

products was made possible by elaboration of the resulting olefin, mainly by cross-metathesis.[46a,56]

Our own recent studies on a similar reaction sequence for the amination of chiral allylic carbonates, paralleled Helmchen's results in showing predominant catalyst control over substrate effects even in the intermolecular variant of the reaction. This allowed for the synthesis of a pair of *N*,*N*-diprotected unnatural branched α-amino acids bearing two contiguous stereocentres (Scheme 19).[57]

The use of more acidic protected amines has also been examined extensively. Helmchen was the first to report the use of tosylamine salts and more acidic *p*-nosylamines as ammonia equivalents for Ir-catalysed inter- and intramolecular allylic amination with excellent results. The resulting protected allylic amines were also successfully used for metathesis reactions.[58] Later on, the Helmchen group showed that a variety of ammonia equivalents could be successfully employed under salt-free conditions. In fact, it was found that the methoxide generated from the allylic carbonate during the course of the reaction was a sufficient base for the reaction to proceed and, therefore, addition of anionic amide derivatives or external bases was often not essential. This novel methodology allowed for the synthesis of doubly-protected chiral primary amines that could be selectively transformed into mono-protected equivalents or, upon cleavage of both protecting groups, be used as nucleophiles for a second allylic amination. A variety of protecting groups were employed under salt-free conditions (Scheme 20).[19,58]

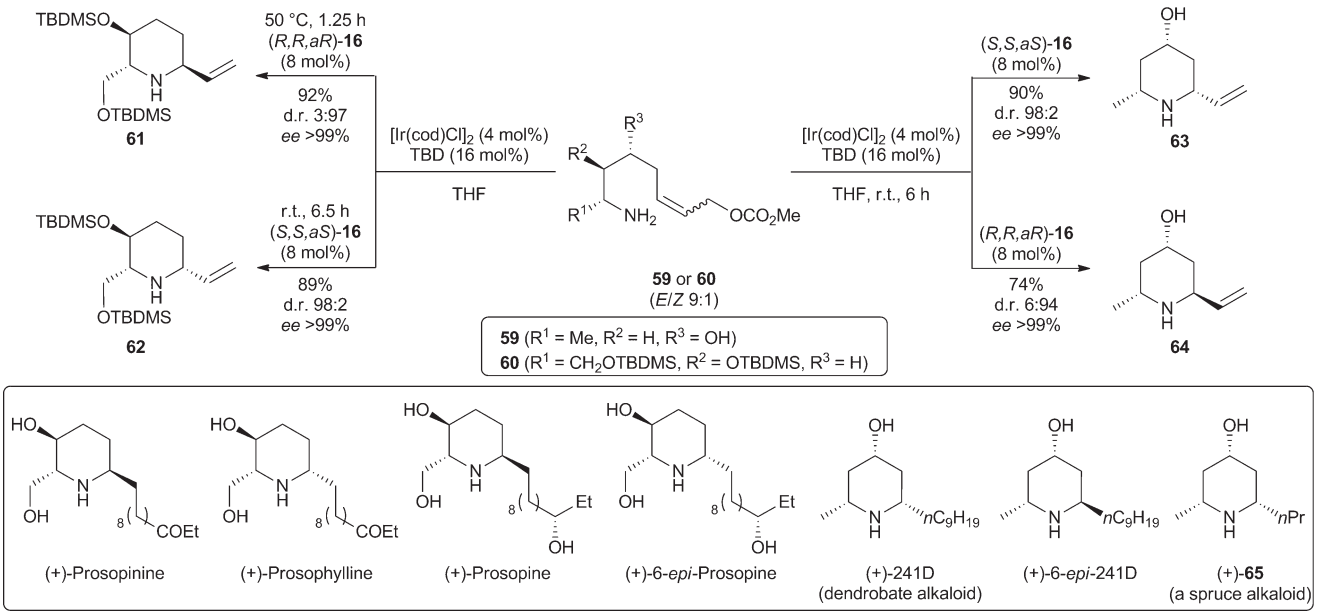
A variety of ammonia equivalents have been tested by Hartwig *et al.*,[59] Carreira *et al.*[60] and Singh and Han[61] but it was in 2009 that Hartwig *et al.* reported on the direct use of ammonia as a competent nucleophile for the synthesis of chiral primary amines by Ir-catalysed AAS. In this case the use of the ethylene complex **33** proved essential. In fact, in order to achieve selectivity for the formation of primary amines over secondary ones, high concentrations of ammonia were necessary and a robust catalyst that could survive under these conditions was required. The presence of primary amines at the end of the reaction allowed for a second allylic substitution or formation of amides upon ammonia evaporation (Scheme 21).[62]

Of course, Ir-catalysed AAS produces molecules bearing a terminal alkene, therefore many applications of these products rely on metathesis to generate key scaffolds and/or elaborate intermediates for total synthesis. Recently though, more original applications have been shown. For instance, Farwick and Helmchen reported on the use of propargylic amines as nucleophiles for Ir-catalysed AAS. A subsequent Pauson–Khand reaction then generated a key intermediate towards the total synthesis of (−)-α-kainic acid **68** (Scheme 22).[63]

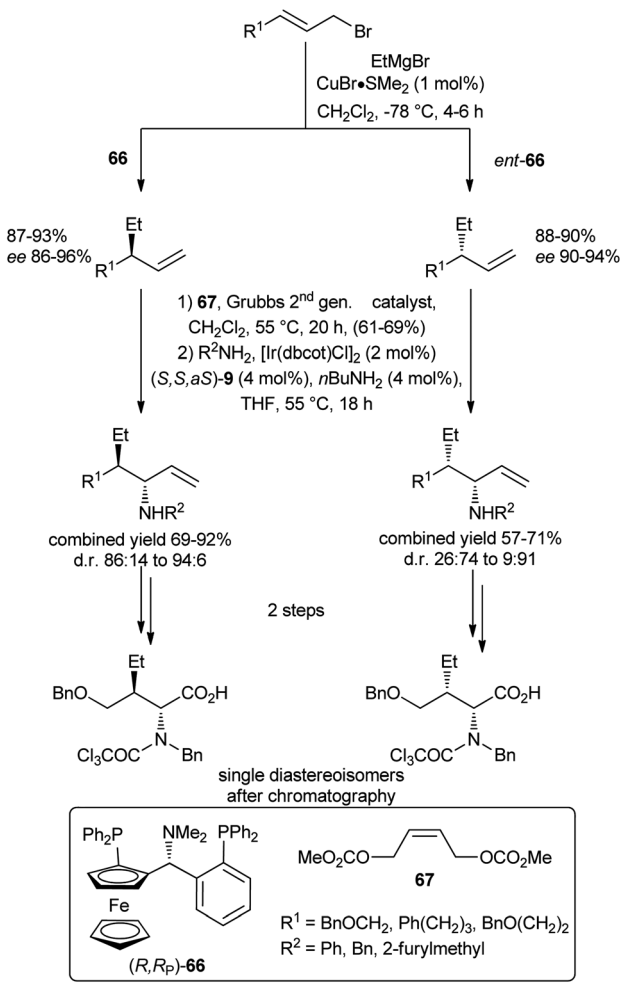
Recently, the group of You has applied *N*-tosyl propynylamines as nucleophiles for Ir-catalysed AAS and deployed the resulting products for the synthesis of exotic heterocyclic scaffolds *via* Pt-catalysed cycloisomerisation reactions. Different architectures of the final products could be obtained depending on the substituents on the C≡C bond (Scheme 23).[64] The use of 1,6-enynes deriving from Ir-catalysed AAS has also been reported by Helmchen *et al.* who exploited a Pt-catalysed domino enyne isomerisation/Diels–Alder sequence for the synthesis of complex heterocycles.[65]

An elegant strategy for the systematic synthesis of 2,5-disubstituted pyrrolidines has been developed by Helmchen and coworkers. This methodologies relies on the Ir-catalysed asymmetric allylic amination of carbonates with *N*,*N*-diacylamines and the subsequent conversion of the resulting alkene functionality into an alkylborane to be used for Suzuki–Miyaura couplings with iodoacrylate **70**. Access to pyrrolidines and subsequent synthesis of a series of pyrrolidine, pyrrolizidine and indolizidine alkaloids was accomplished by intramolecular aza-Michael addition (Scheme 24).[66] In earlier work, the same group had shown that the synthesis of α,β-unsaturated esters **71** and cyclisation to afford β-proline derivatives can also be achieved *via* domino hydroformylation/Wittig olefination of protected amines deriving from Ir-catalysed AAS.[67]

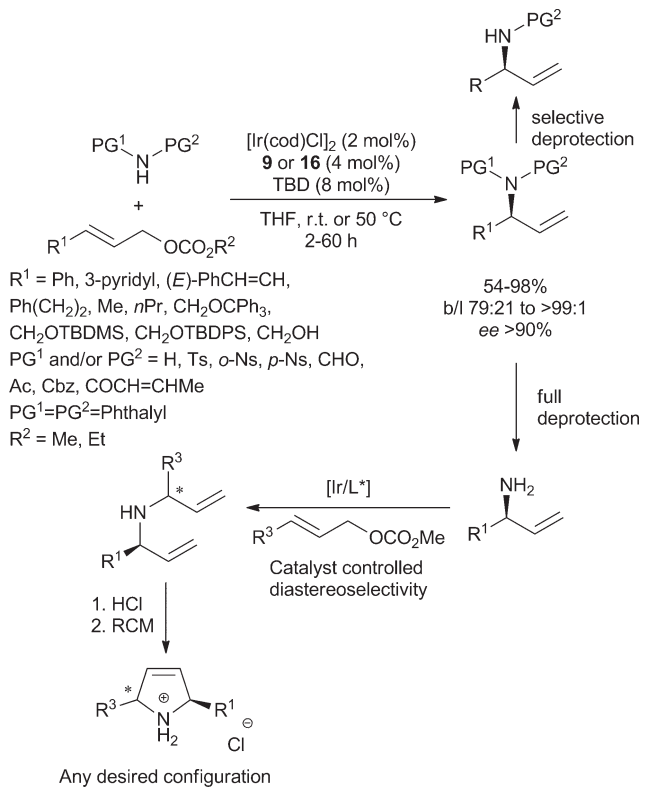
The sequence of hydroboration and subsequent Suzuki–Miyaura coupling has also been exploited for products deriving from the Ir-catalysed asymmetric allylic amination of carbonates with *o*-haloanilines. Unfortunately, the reactions of these nucleophiles were characterised by lower yields than those typically



Scheme 18 Diastereo- and enantioselective intramolecular allylic aminations and their application in the synthesis of a range of piperidine alkaloids.

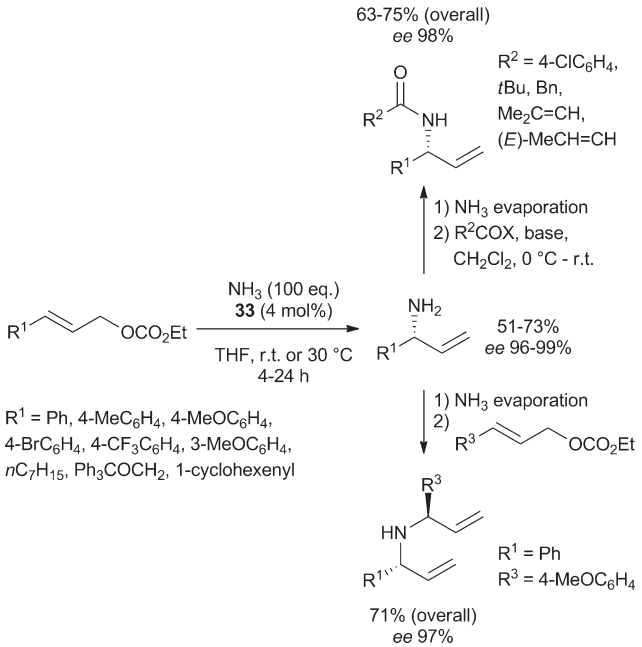


Scheme 19 Intermolecular diastereoselective allylic amination for the synthesis of unnatural α-amino acids bearing two vicinal stereocentres.

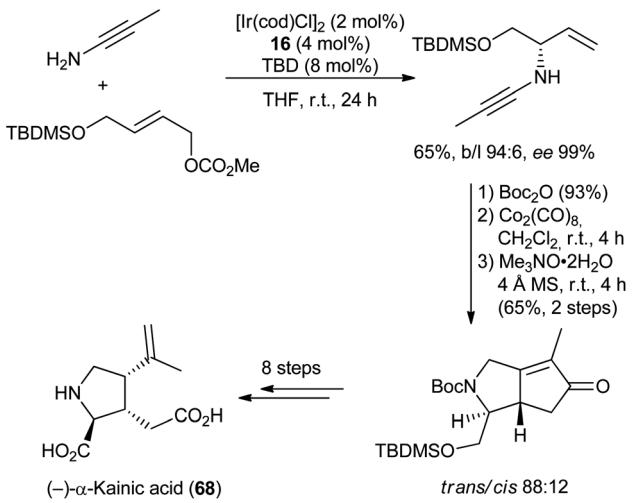


Scheme 20 General use of activated N-nucleophiles for Ir-catalysed AAS.

observed for Ir-catalysed AAS. However, this method proved useful for the synthesis of enantioenriched 2-substituted tetrahydroquinolines that are usually accessed *via* asymmetric hydrogenation of quinolines. The synthetic utility of this strategy has



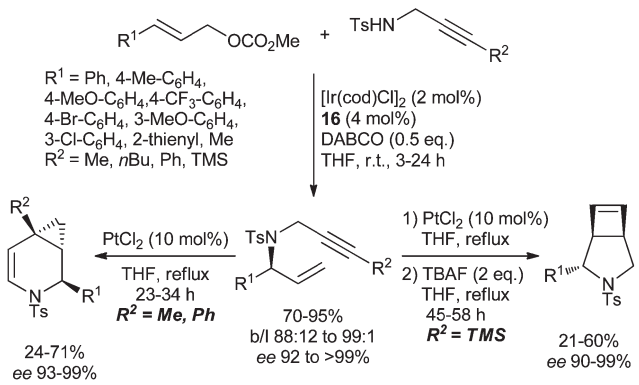
Scheme 21 Ir-catalysed asymmetric allylation of ammonia.



Scheme 22 Overview of the total synthesis of (−)-α-kainic acid *via* Ir-catalysed AAS and Pauson–Khand reaction.

been demonstrated by Helmchen *et al.* with the synthesis of (+)-angustureine **72** and (−)-cuspareine **73** (Scheme 25).[68]

An important expansion of the scope of N-nucleophiles was achieved by Hartwig *et al.* who used the ethylene complexes **74** and **75** to implement a method for the *N*-allylation of heteroaromatic substrates. The scope of heteroaromatic N-nucleophiles encompasses indoles,[69] imidazole, benzimidazole and purine derivatives.[70] Performing the reaction on benzimidazoles, it was observed that the presence of K_3PO_4 is required to suppress isomerisation of the product to the corresponding enamine. Although the reactions could be carried out using a combination of metallacycle **11** and $[Ir(cod)Cl]_2$, complexes **74** and **75** could be used in lower loadings and also facilitate operational



Scheme 23 Application of *N*-tosyl propynylamines to Ir-catalysed AAS and subsequent Pt-catalysed cycloisomerisation.

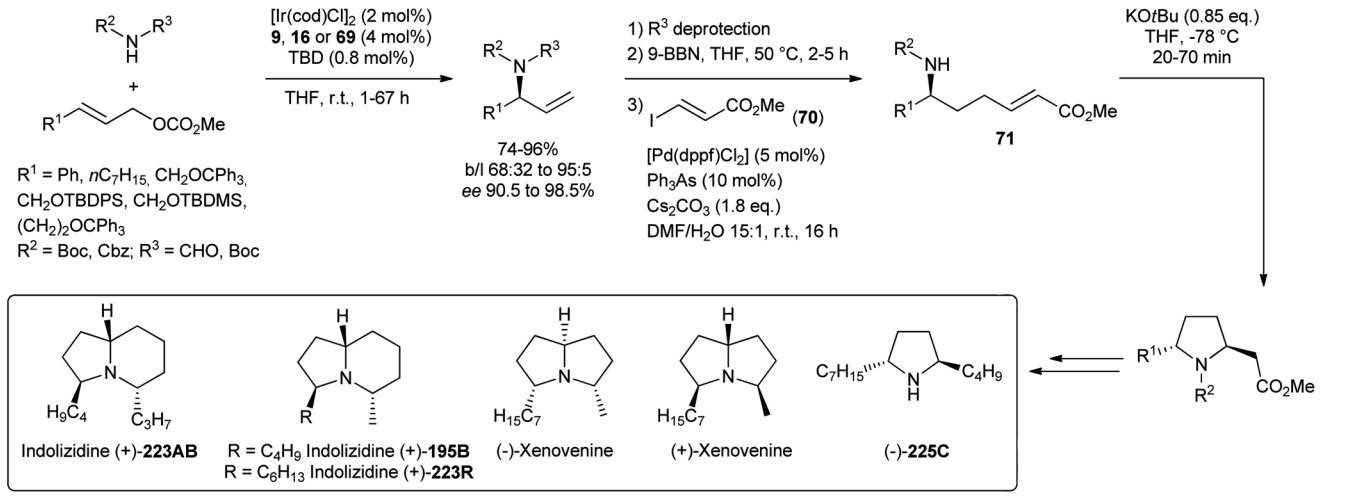
procedures since they can be prepared as single components on large scale, rather than being formed *in situ* using additives like *n*-propylamine. Allylation of benzimidazole occurred with excellent results as summarised in Scheme 26. Cinnamyl carbonates with strong electron-withdrawing groups were more prone to C═C isomerisation and in this case the use of an internal alkyne additive prevented the undesired process. Importantly, after allylation the resulting terminal olefin could be conveniently elaborated to give useful building blocks.

The same reaction conditions were also successful for imidazoles, although only complex **74** was successful for these nucleophiles, since reactions carried out in the presence of **75** furnished mixtures of the desired terminal olefins and the corresponding enamine. Two examples of reactions of substituted imidazoles were also reported and good regioselectivity was observed for the N1-allylated product (N1/N3 72 : 28 and 87 : 13). The importance of *N*-allylated imidazoles was demonstrated by the formal synthesis of a c-jun N-terminal kinase 3 inhibitor (**76**) (Scheme 27).[70]

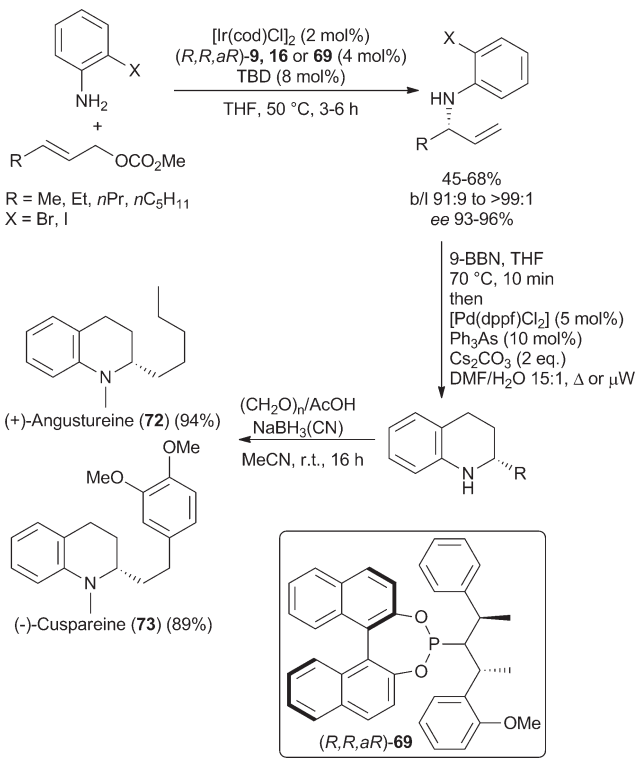
Purine nucleophiles also reacted at the N9 position under these conditions although in some cases higher catalyst loadings were required. Excellent selectivities were again attained and even biologically important adenine was allylated. Again, products from all these reactions could be easily derivatised by standard oxidation of the final terminal olefin (Scheme 28).[70]

Chiral Ir-ethylene complexes **74** and **75** were also successfully used for the *N*-allylation of substituted indoles. In this case electron-withdrawing substituents at the C2 position, C3-substituents or both were usually required to reduce the nucleophilicity of the C3 position. Interestingly, even unsubstituted 7-azaindole was a competent nucleophile, whilst simple indole or solely alkyl-substituted indoles underwent C3-allylation. For the reaction of indoles, *tert*-butyl carbonates were the electrophiles of choice in combination with catalytic Cs_2CO_3 and generally high yields and exquisite enantioselectivities were achieved (Scheme 29). Again, functionalisation of the resulting terminal olefins afforded interesting building blocks.[69]

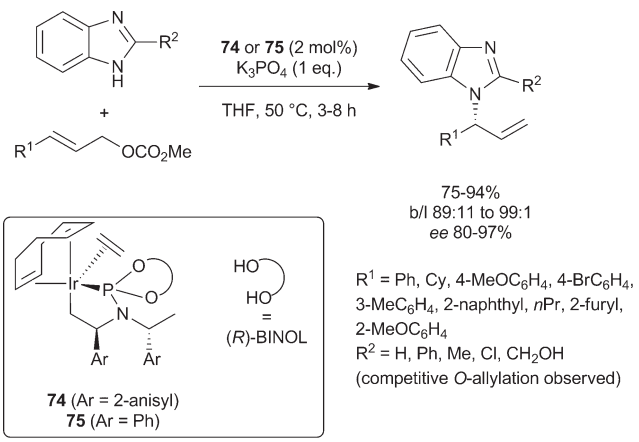
Other less developed N-nucleophiles for Ir-catalysed allylic substitutions include hydrazines (only used to produce racemic products),[71] guanidines (multiple protection of the nucleophile was needed and generally poor regiocontrol was observed)[39e] and hydroxylamines.[39a,72]



Scheme 24 Overview of the assembly of 2,5-disubstituted pyrrolidines and related alkaloids *via* Ir-catalysed AAS, Suzuki–Miyaura coupling and intramolecular aza-Michael addition.



Scheme 25 Use of ortho-haloanilines as nucleophiles for Ir-catalysed AAS and their use for the synthesis of (+)-angustureine and (−)-cuspareine.



Scheme 26 Enantioselective *N*-allylation of benzimidazoles.

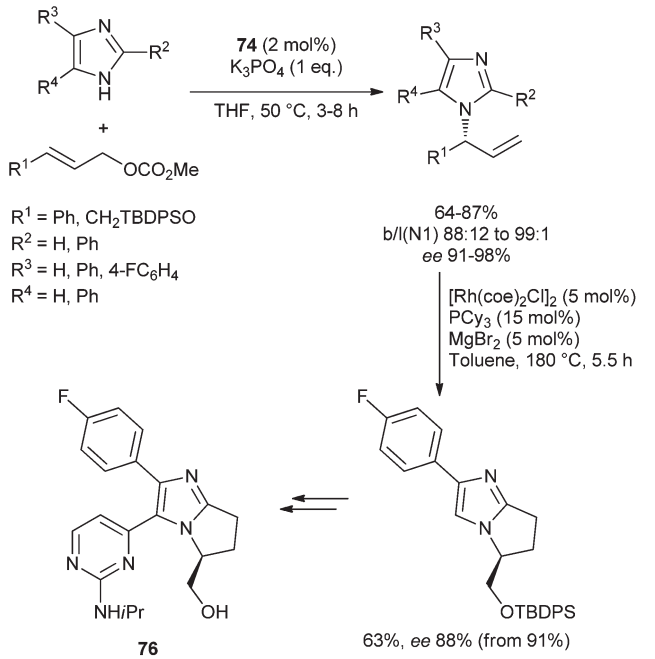
5. Oxygen nucleophiles

Oxygen nucleophiles have been successfully employed for Ir-catalysed allylic substitution, although fewer examples of their applications have been reported compared to C- or N-nucleophiles.

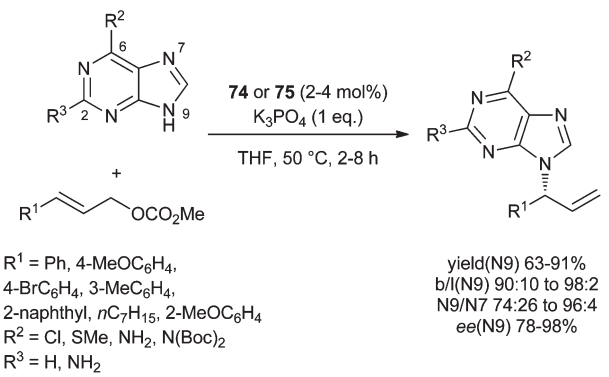
Phenoxides have been reported by Hartwig *et al.* to act efficiently as nucleophiles in Ir-catalysed asymmetric allylic etherification of carbonates as illustrated in Scheme 30. Much effort was required to establish suitable reaction conditions for this transformation: Li and Na phenoxides were found to be superior to their triethylammonium equivalents, which were more prone to giving transesterification products. In some cases, transesterification could be avoided or limited by changing the methyl carbonate for less reactive ethyl analogues.

The reaction scope was quite broad as variously substituted and even hindered phenoxides reacted successfully with aryl- and alkyl-substituted allylic carbonates. Very electron-poor (and hence non-nucleophilic) phenoxides bearing nitro or cyano groups did not react. Interestingly, extended reaction times resulted in decreased regio- and enantioselectivity, suggesting that the transformation is reversible.[73] For the intramolecular example shown in Scheme 30, the active metallacycle was generated *in situ*, but better results in terms of yield, regio- and enantioselectivity were observed later employing pre-activated metallacycles[15] that also worked for intramolecular etherifications under salt-free conditions as demonstrated by Helmchen and co-workers.[31]

Phenol has also been used as a nucleophile by Carreira and *et al.* for the Ir-catalysed kinetic resolution of racemic branched



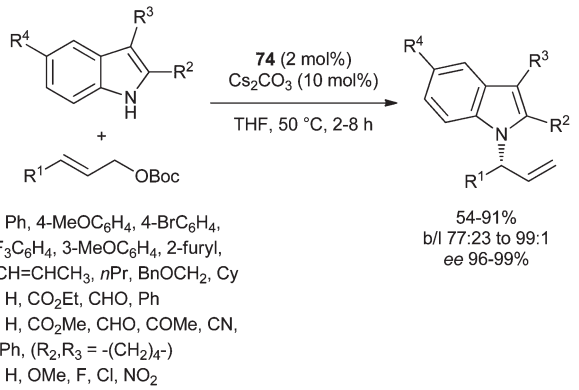
Scheme 27 *N*-Allylation of imidazoles and formal synthesis of the JNK3 inhibitor **76**.



Scheme 28 *N*-Allylation of purine heterocycles.

allylic carbonates employing a different chiral ligand (Scheme 31).[40]

The direct use of aliphatic alcohols was more complicated due to their poor nucleophilicity and the high basicity of the corresponding alkoxides, that can induce elimination and transesterification processes. Nevertheless, the application of alkoxides and even alcohols in Ir-catalysed AAS has been achieved. The first examples were reported by Shu and Hartwig who used Cu-alkoxides for the enantioselective etherification of allylic carbonates (Scheme 32). The use of more hindered *tert*-butyl carbonates was required to avoid transesterification. While Cu-alkoxides gave the best results, Zn-alkoxides also proved efficient, but alkali metal alkoxides did not form the desired products. In this case ligand screening showed that ligand **17** was considerably more efficient than the more commonly used **9**, which gave low yields. Branched ethers were formed in excellent regio- and enantioselectivities using a variety of primary and secondary

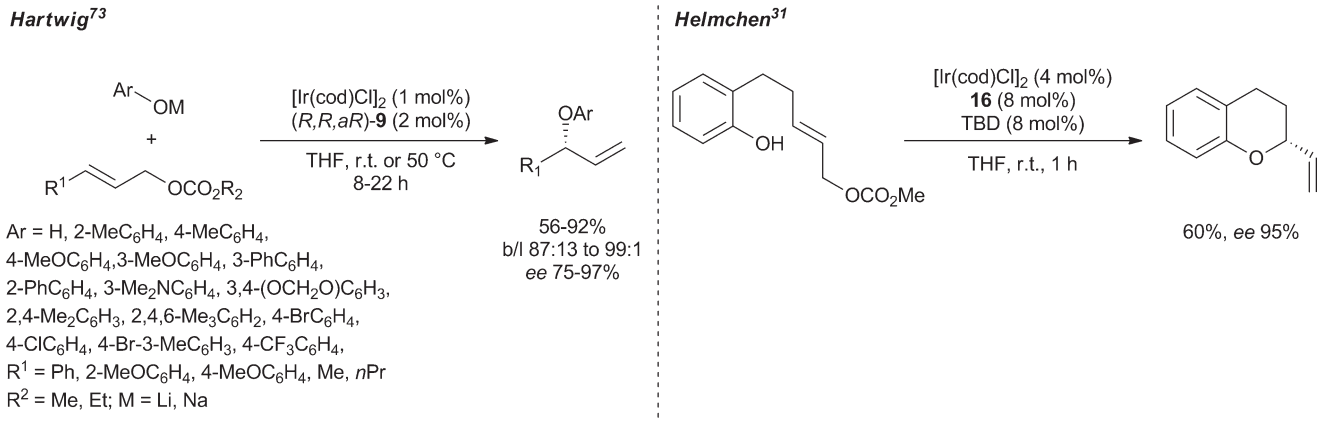


Scheme 29 *N*-Allylation of indoles.

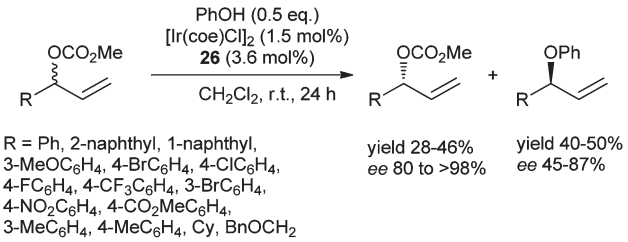
alkyl Cu-alkoxides with both aryl and alkyl-substituted allylic carbonates. Tertiary alkoxides reacted in good yield and regioselectivity but reactions in this case were sluggish and poorly enantioselective. Interestingly, the use of chiral secondary alkoxides proceeded with excellent diastereoselectivity with no appreciable matched/mismatched effects allowing for the highly selective synthesis of both *cis*- and *trans*-2,5-disubstituted dihydrofurans and 2,6-dihydropyrans upon use of alkoxides derived from unsaturated alcohols followed by a ring-closing metathesis reaction.[33] This methodology has found application as the key step in the total synthesis of natural product (−)-centrolobine (**77**) carried out by Böhrsch and Blechert (Scheme 32).[74] More complex ligands of general structure **23** (*vide supra*) were also tested by Kimura and Uozumi for the allylation of phenol, but generally low enantioselectivity was observed.[37]

An interesting class of O-nucleophiles useful for the synthesis of chiral allylic alcohols was presented by Carreira and coworkers in 2006. Potassium silanolates were efficiently used as hydroxide equivalents in the presence of a chiral iridium catalyst (Scheme 33). During the optimisation, *tert*-butyl carbonates were found to be the most reactive and a strong solvent effect was registered. While TMSOK displayed poor reactivity, good results were obtained with TESOK (easily cleaved after the reaction to give the free alcohol) and the more stable silanolates TBDMSOK and TIPSOK (that can be carried through multistep syntheses) gave very good results.[75]

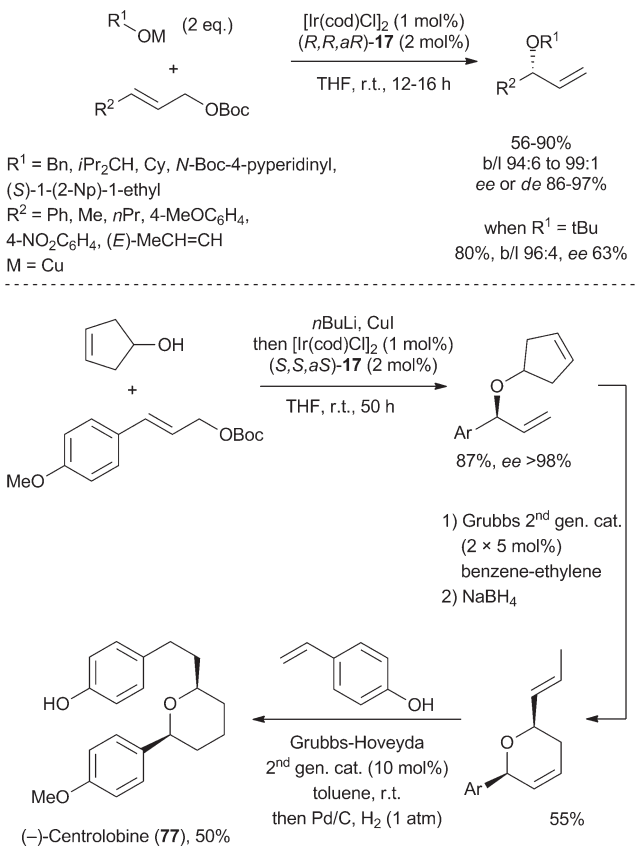
Later on, Ueno and Hartwig reported a more elaborate set of conditions for the direct use of alcohols in Ir-catalysed allylic substitutions. The use of a substoichiometric amount of an internal alkyne additive was essential to avoid the otherwise complete isomerisation of the final products to the corresponding enol ethers under the reaction conditions stated in Scheme 34. A screen of bases revealed that enantioselectivity was drastically diminished using triethylamine and after some experimentation potassium phosphate was found to give the best results. In contrast with previous examples of etherification and allylic substitution in general, acetates proved to be superior to carbonates, which were found unstable under these conditions. Excellent results were obtained with primary and secondary alcohols to give branched ethers with good yield, regio- and enantio- or diastereoselectivity. Interestingly, *tert*-butyldimethylsilanol was successfully employed so that the pre-formation of the potassium silanolates as presented by Carreira could be avoided.



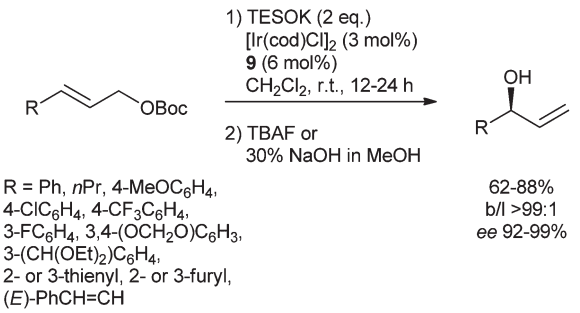
Scheme 30 First examples of use of phenoxides and phenol for Ir-catalysed allylic etherifications.



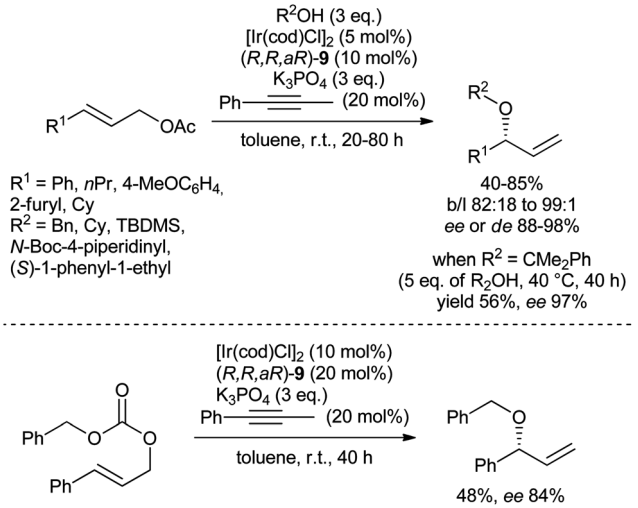
Scheme 31 Kinetic resolution of racemic branched allylic carbonates *via* Ir-catalysed etherification.



Scheme 32 Ir-catalysed allylic etherification with aliphatic alkoxides and total synthesis of (−)-centrolobine.

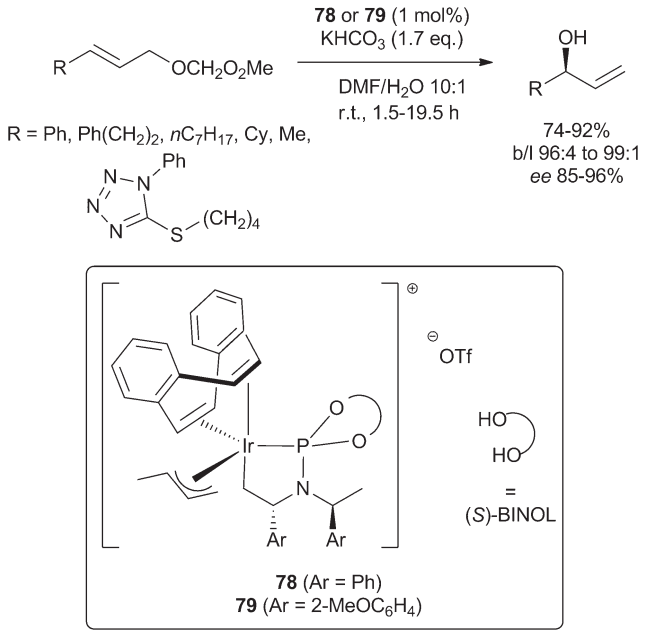


Scheme 33 Use of potassium silanolates for the synthesis of chiral allylic alcohols.



Scheme 34 Ir-catalysed allylic etherification with alkyl alcohols.

Remarkably, even tertiary alcohols reacted efficiently giving the desired ethers in relatively good yield as single regioisomers and with excellent enantioselectivity, although in this case higher temperature, long reaction time and a considerable excess of nucleophile were needed. One example of intramolecular decarboxylative etherification was also reported with interesting results.[24]

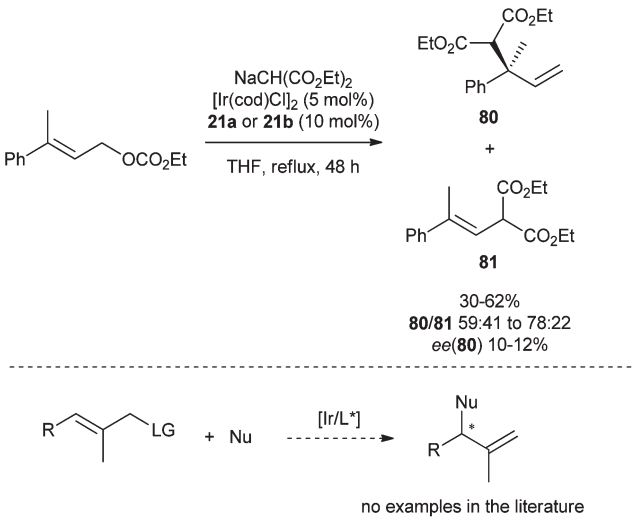


Scheme 35 Direct regio- and enantioselective Ir-catalysed allylic hydroxylation.

More recently Helmchen and co-workers used potassium bicarbonate and catalyst **78** derived from $[Ir(dbcot)Cl]_2$ for the direct hydroxylation of allylic carbonates under mild conditions. In this case complexes **78** and **79** (prepared in one step) were found to be extremely robust, allowing reactions to be run in water as solvent or co-solvent and under air, whereas their equivalents derived from $[Ir(cod)Cl]_2$ failed to give any reaction. High regio- and enantioselectivities were found for a variety of substrates using chiral phosphoramidites **9** or **16** (Scheme 35). Other inorganic bicarbonates could also be used as pronucleophiles.[76]

6. Conclusions

Iridium catalysed asymmetric allylic substitution has become a broadly applicable reaction for the synthesis of chiral molecules with an impressive scope and generality, providing access to highly enantioenriched, functionalised building blocks that can be deployed for the synthesis of natural products and pharmaceuticals. The understanding of the mechanism of this reaction and the improvement in the catalyst and ligand design have allowed an exceptional widening in the scope of the nucleophile that one could use in combination with monosubstituted linear allylic carbonates. Catalyst development has also proved successful in simplifying operational procedures, as in some case reactions can now be run with no recourse to the glovebox and using highly coordinating and even aqueous solvents. Moreover, reactions are generally highly regioselective, affording branched products characterised by enantiomeric excesses that usually exceed 90%. Another feature of allylic substitutions catalysed by iridium-phosphoramidite complexes is that the sense of the asymmetric induction and the resulting absolute configuration of the final compounds seems to be predictable on the basis of an empirical rule proposed by Helmchen *et al.*[14] Like any other synthetic



Scheme 36 Problematic trisubstituted allylic electrophiles.

methodology though, there are still some limitations to the use of Ir-catalysed AAS. For example, the use of trisubstituted allylic carbonates has only been reported once[35] with poor results and therefore the generation of quaternary stereocentres *via* Ir-catalysed AAS is not possible to date (Scheme 36). In addition, the use of prochiral nucleophiles usually results in poor diastereoselectivity, as mentioned earlier. Future developments addressing these and other issues can be anticipated to have a similarly significant impact as the methods discussed in the current review.

Notes added in proof

During the preparation of this manuscript and its review by the referees, two important studies were published by the group of You. In one case an alternative synthesis of (−)-angustureine *ent*-**72** has been accomplished in the context of an investigation into the use of α-amino styrenes as nucleophiles for Ir-catalysed asymmetric allylic substitutions.[77] In a second report, You *et al.* expanded the scope of the intramolecular Ir-catalysed dearomatisation of indoles for the synthesis of five-membered spiroindolenines. These products were then successfully converted into five-membered spiroindolines by reduction with $NaBH_3CN$, or into enantioenriched 2,3,4,9-tetrahydro-1*H*-carbazoles *via* an acid catalysed stereospecific migration.[78]

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
b/l	branched to linear ratio
BINOL	1,1′-bi-2-naphthol
cod	cycloocta-1,5-diene
coe	cyclooctene
Cy	cyclohexyl
de	diastereoisomeric excess
d.r.	diastereoisomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
dppf	1,1′-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess

LG	leaving group
MOM	methoxymethyl
Nu	nucleophile
PG	protecting group
PMHS	polymethylhydrosiloxane
TBD	1,5,7-triazabicyclo[4.4.0]dec-1-ene
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TIPS	triisopropylsilyl
THT	tetrahydrothiophene
TMS	trimethylsilyl

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