C=N-Containing Azaarenes as Activating Groups in Enantioselective Catalysis

Daniel Best and Hon Wai Lam*

EaStCHEM, School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, United Kingdom,and

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom.

hon.lam@nottingham.ac.uk

ABSTRACT: Nitrogen-containing aromatic heterocycles (azaarenes) are of widespread chemical significance, and chiral compounds containing azaarenes feature prominently in pharmaceuticals, agrochemicals, and natural products. This Perspective highlights the use of a relatively underdeveloped strategy to prepare chiral azaarene-containing compounds: exploitation of the C=N bond embedded within certain azaarenes to activate adjacent functionality in catalytic asymmetric reactions. Work in this area has resulted in the development of several different types of catalytic enantioselective processes, including reductions, nucleophilic additions, and reductive couplings. It is hoped that this Perspective will encourage more researchers to work in this promising area.

INTRODUCTION

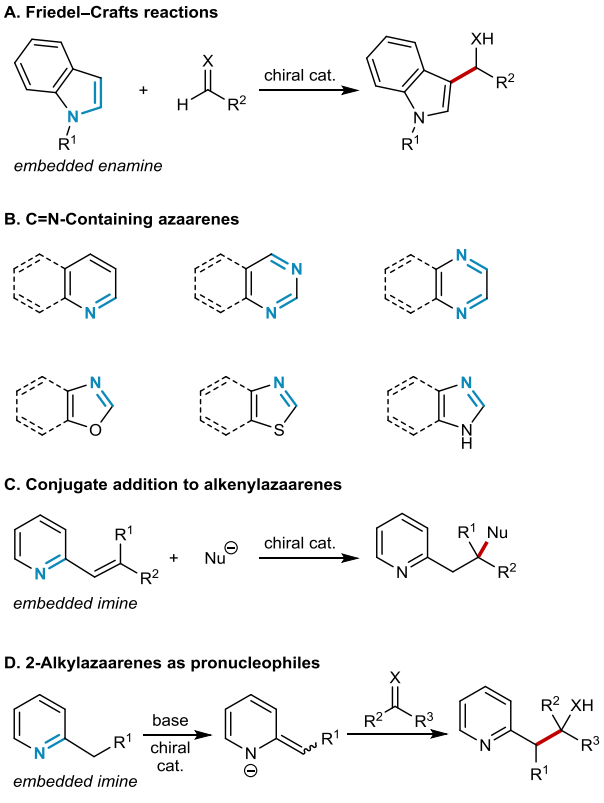
Nitrogen-containing aromatic heterocycles (azaaarenes) are common structures in chiral biologically active molecules such as pharmaceuticals, agrochemicals, and natural products. Consequently, the development of catalytic enantioselective reactions for the synthesis of chiral azaarene-containing building blocks is a valuable objective. Although such compounds may be prepared using established catalytic enantioselective reactions of azaarene-containing substrates where the azaarene acts as a non-participating bystander, *the development of methods that exploit the chemical properties of the azaarene itself to promote the reaction* should provide powerful, complementary tools for synthesis. Catalytic enantioselective Friedel-Crafts additions of π-excessive azaarenes to π-electrophiles are a well-established class of reactions

that fulfil this criterion (Scheme 1A).[1] These reactions rely upon the enamine embedded within π-excessive azaarenes such as indoles or pyrroles to impart nucleophilic character onto the azaarene.

However, many classes of azaarenes do not contain embedded enamines; rather, they contain an embedded imine (Scheme 1B). This C=N moiety exhibits electron-withdrawing properties resembling those of the carbonyl group, and this similarity raises a fundamental question: can the C=N group of an azaarene facilitate catalytic enantioselective transformations normally associated with carbonyl groups? For example, could a prochiral 2-alkenylpyridine be a viable substrate for a catalytic enantioselective conjugate addition by virtue of the C=N bond activating the adjacent alkene (Scheme 1C)? Similarly, could the ability of the C=N bond of an azaarene to acidify the protons of an adjacent methylene group be exploited in catalytic enantioselective additions of 2-alkylazaarenes to π-electrophiles (Scheme 1D)?

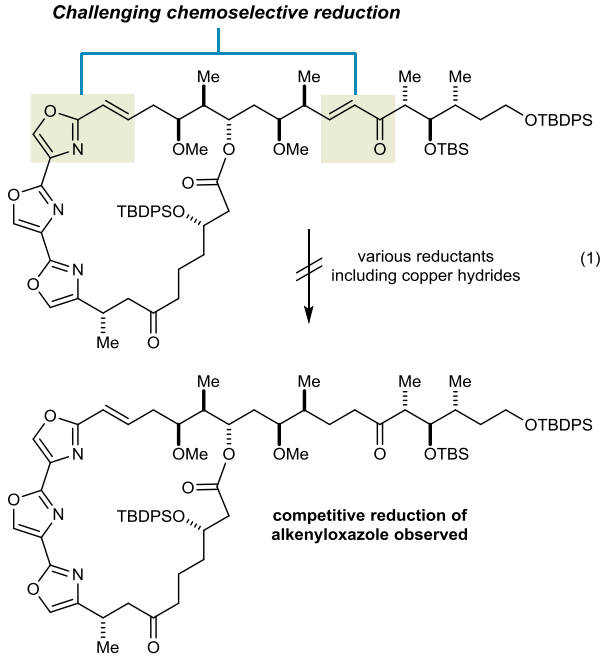
Despite the apparent simplicity of these concepts, catalytic enantioselective reactions exploiting these modes of activation only recently began to appear in the literature. This Perspective provides an overview of these developments from our laboratory and from others. The discussion is limited to reactions where the azaarene moiety in the substrate remains intact in the final product. Reactions such as catalytic enantioselective hydrogenations of C=N-containing azaarenes to produce (partially) saturated nitrogen heterocycles are not covered.

Scheme 1. Azaarenes as Activating Groups for Enantioselective Catalysis



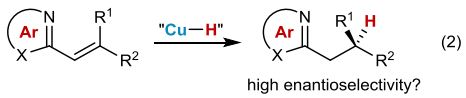
PERSONAL PERSPECTIVE

Our decision to explore C=N-containing azaarenes as activating groups in enantioselective catalysis originally stemmed from a research seminar given by one of the authors of this Perspective (H.W.L.) at the School of Chemistry, University of Nottingham on the 7th of November 2007. This seminar described (among other topics) our work on copper hydride-catalyzed reductive aldol[2] and Michael[3] cyclizations. At the end of the lecture, Professor Gerald Pattenden asked a question that went something along the lines of "What do you think the prospects are of using copper hydride chemistry to reduce α,*β*-unsaturated carbonyl compounds selectively in the presence of 2-alkenyloxazoles?" This question arose because of work conducted in the Pattenden group toward the total synthesis of the *tris*-oxazole-containing natural product ulapualide A. During those studies, attempts were made to reduce the alkene of an α,*β*-unsaturated ketone in the presence of a 2-alkenyloxazole (eq 1).[4] Despite numerous efforts to achieve this transformation with a variety of reducing agents (including those based upon copper hydrides), the α,*β*-unsaturated ketone could not be reduced chemoselectively.[5] Although H.W.L. now cannot remember what his answer to Professor Pattenden's question was, this synthetic problem led us to ponder whether the ability of copper hydrides to reduce 2-alkenyloxazoles could be developed into a useful synthetic method. In turn, the question of whether C=N-containing azaarenes could provide multiple modes of substrate activation in a range of catalytic enantioselective reactions began to feature more prominently in our research.



CATALYTIC ENANTIOSELECTIVE NUCLEOPHILIC ADDITIONS TO ALKENYLAZAARENES

Given that copper-hydride-based reagents can reduce 2-alkenyloxazoles (eq 1), the asymmetric copper-catalyzed reduction of *β*,*β*-disubstituted alkenylazaarenes (eq 2) was selected as our first target in the area of C=N-containing azaarenes as activating groups in enantioselective catalysis. Our work on this project began in 2008, and before describing our results, a brief discussion of what was already known about nucleophilic additions to alkenylazaarenes at that time is warranted.



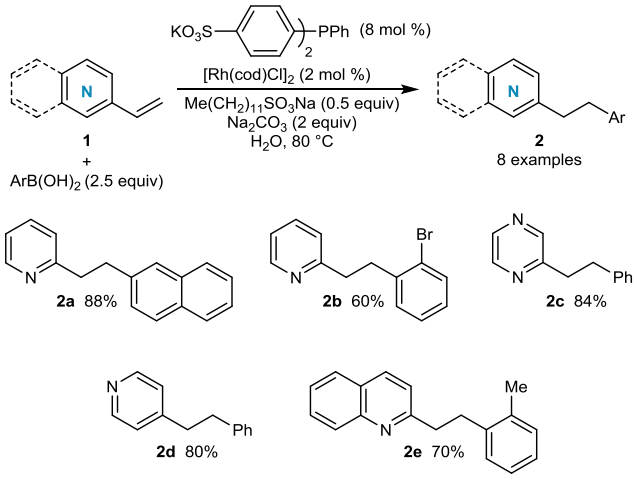
(2)

State of the Field *ca.* 2008. The 1,4-addition of nucleophiles to electron-deficient alkenes is one of the most important and commonly used synthetic methods. Although this transformation is normally associated with alkenes activated by carbonyl, nitrile, nitro, sulfonyl, or phosphonyl groups, imines have also been used for this purpose.[6] The ability of a C=N moiety of an azaarene to function in a similar manner has also long been recognized; the addition of Grignard reagents to 2-alkenylquinolines, for example, was demonstrated in 1933.[7]

The overwhelming majority of nucleophilic additions to alkenylazaarenes involve vinylazaarenes. There are numerous examples of the addition of nitrogen-, oxygen-, sulfur-, and carbon-centered nucleophiles to a range of vinylazaarenes, and developments in this area have been summarized in a recent review by Klumpp.[8]

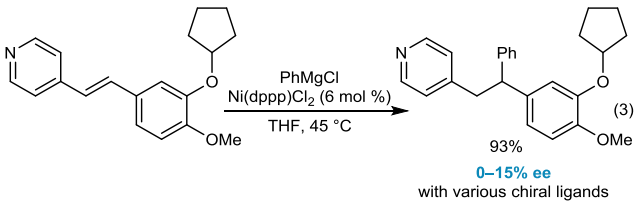
Transition-metal-catalyzed additions of carbon-centered nucleophiles to vinylazaarenes were also known. For example, in 2001, Lautens and co-workers described the rhodium-catalyzed addition of arylboronic acids to vinylazines **1** in water, using a rhodium complex containing water-soluble phosphine ligands, in the presence of 0.5 equivalents of sodium dodecyl sulfate (Scheme 2).[9] The scope of the acceptor included 2-vinylpyridine (**2a**,**b**), vinylpyrazine (**2c**), 4-vinylpyridine (**2d**), and 2-vinylquinoline (**2e**), and a range of arylboronic acids were effective. In addition, competitive insertion of rhodium into the carbon–bromine bond of 2-bromophenylboronic acid was not observed (**2b**). The use of water as the reaction medium was essential, as other solvents resulted in significantly lower conversions.[10] The group of Genêt and Michelet reported closely related additions to 2-vinylpyridine one year later.[11]

Scheme 2. Rhodium-Catalyzed Addition of Arylboronic Acids to Vinylazines



Compared with vinylazaarenes, nucleophilic additions to *β*-substituted alkenylazaarenes are less common, a fact that is perhaps unsurprising given the greater steric hindrance and hence lower reactivity of these substrates. Nevertheless, several examples of non-asymmetric additions of nitrogen-[12] and carbon-centered[7,13,14] nucleophiles to these substrates had been reported.[8]

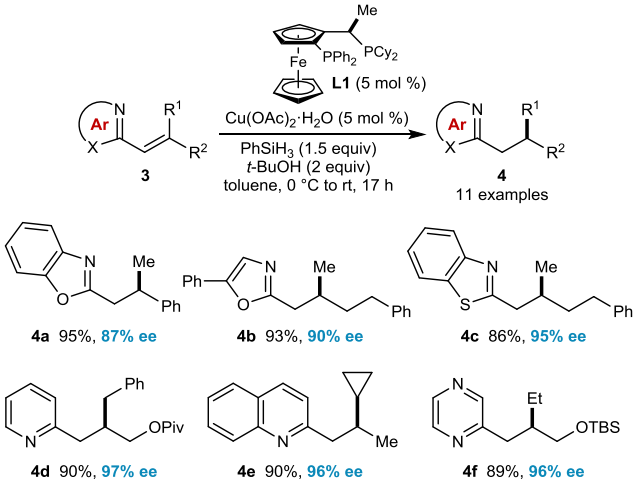
With respect to transition-metal-catalyzed reactions, Houpis and co-workers described the nickel-catalyzed addition of Grignard and organozinc reagents to 4-alkenylpyridines in 1998.[14] For example, reaction of a 4-alkenylpyridine with PhMgCl in the presence of Ni(dppp)Cl_2 (6 mol %) gave the phenylation product in 93% yield (eq 3). Importantly, this work also described efforts toward a catalytic enantioselective variant. Although these attempts met with limited success (use of various chiral ligands led to products in 0–15% ee),[14] this work provided a tantalizing suggestion that effective catalytic enantioselective nucleophilic additions to alkenylazaarenes might be possible.[15]



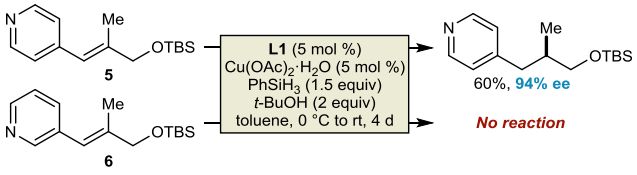
Work in the Field Since 2008. In 2008, work on the catalytic asymmetric reduction of *β*,*β*-disubstituted alkenylazaarenes **3** began in our group. The Cu-catalyzed enantioselective 1,4-reduction of electron-deficient alkenes using silicon hydride reagents is a powerful and well-established method in organic synthesis,[16,17] and numerous examples of this process using α,*β*-unsaturated carbonyls,[18] nitriles,[19] sulfones,[20] phosphonates,[21] and nitro compounds[22] now exist. Although the reaction presented in eq 1 showed that a C=N-containing azaarene provided sufficient activation to an adjacent *β*-substituted alkene for it to undergo reduction by copper-hydride-based reagents, it was uncertain whether the level of activation would be sufficient for the reduction of more sterically hindered *β*,*β*-disubstituted alkenylazaarenes.

In the event, we found that these substrates were indeed effective (Scheme 3).[23] In the presence of $Cu(OAc)_2 \cdot H_2O$ (5 mol %), the Josiphos ligand **L1** (5 mol %), $PhSiH_3$ (1.5 equiv), and *t*-BuOH (2.0 equiv), a range of *β*,*β*-disubstituted alkenylazaarenes **3** were reduced in generally good yields with high enantioselectivities. Azaarenes that are effective activating groups include (benz)oxazoles (**4a**,**b**), benzothiazole (**4c**), pyridine (**4d**), quinoline (**4e**), and pyrazine (**4f**), and the reaction is tolerant of functional groups such as esters (**4d**), cyclopropanes (**4e**), and silyl ethers (**4f**). Conjugation of the C=N moiety of the azaarene with the alkene was shown to be essential; while the 4-alkenylpyridine **5**, in which the C=N bond is still conjugated with the alkene, successfully underwent reduction in 60% yield and 94% ee, the 3-alkenylpyridine **6** was unreactive (Scheme 4).

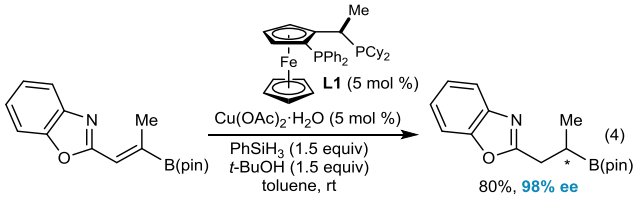
Scheme 3. Enantioselective Cu-Catalyzed Reduction of *β*,*β*-Disubstituted Alkenylazaarenes



Scheme 4. Comparision of the Reactivities of 4- and 3-Alkenylpyridines.



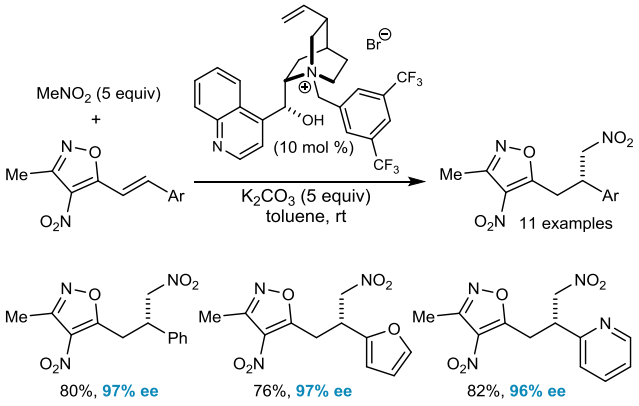
Yun and co-workers subsequently demonstrated that a 2-alkenylbenzoxazole containing a pinacol boronic ester at the *β*-position also underwent copper-catalyzed reduction in good yield and enantioselectivity (eq 4).[24]



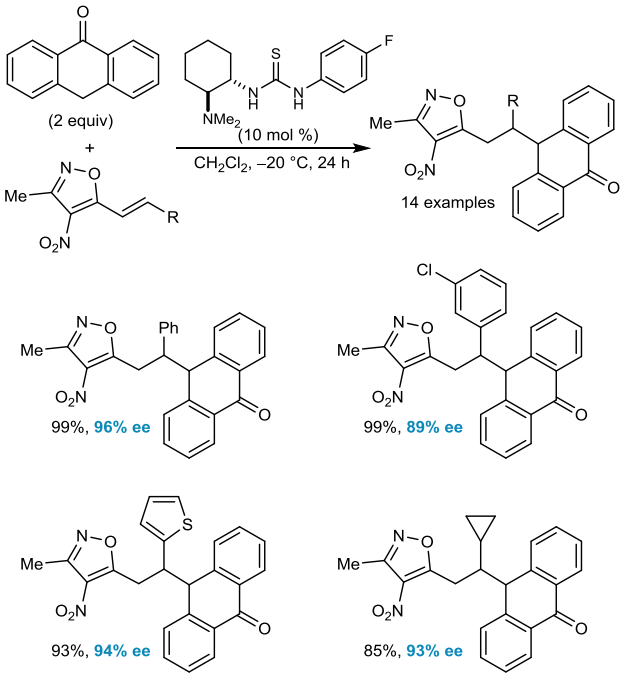
In late 2009, our attention turned to the challenge of enantioselective addition of carbon-centered nucleophiles to *β*-monosubstituted alkenylazaarenes. Compared with the reactions presented in Scheme 3, such a process would be more convergent and hence more suitable for the generation of compound libraries. In addition, the preparation of *β*-monosubstituted *E*-alkenylazaarenes would be much simpler compared to the synthesis of *β*,*β*-disubstituted alkenylazaarenes.

Earlier in 2009, the groups of Bernadi and Adamo had reported the only example of highly enantioselective additions of carbon-centered nucleophiles to alkenylazaarenes (Scheme 5).[25] These reactions involved the addition of nitromethane to 4-nitro-5-styrylisoxazoles, promoted by a chiral phase transfer catalyst. A range of aryl or heteroaryl substituents were tolerated at the *β*-position, and the use of longer chain nitroalkanes was also possible (not shown).[25] Building upon this work, the Yuan group subsequently described the enantioselective addition of anthrone to 4-nitro-5-alkenylisoxazoles, catalyzed by a chiral thiourea (Scheme 6).[26]

Scheme 5. Catalytic Enantioselective Addition of Nitromethane to 4-Nitro-5-styrylisoxazoles



Scheme 6. Catalytic Enantioselective Addition of Anthrone to 4-Nitro-5-styrylisoxazoles



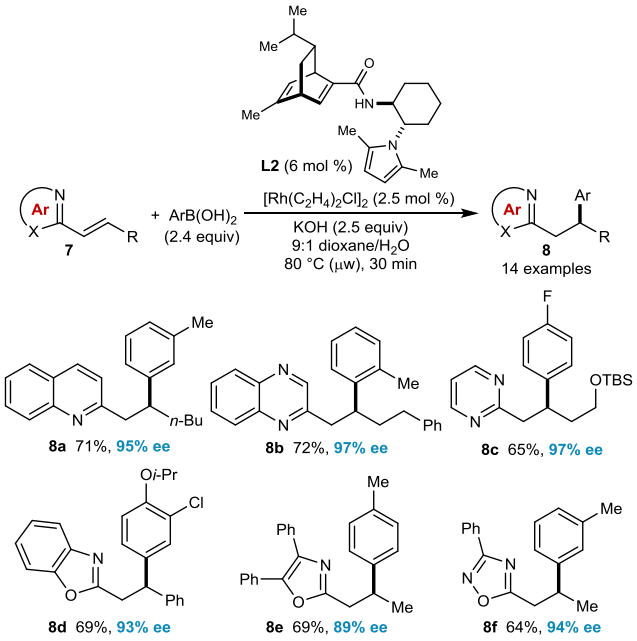
These studies demonstrated that the catalytic enantioselective addition of carbon-centered nucleophiles to alkenylazaarenes is possible. However, only one type of azaarene was employed; the 4-nitroisoxazole unit was selected for its ability to serve as a carboxylate surrogate (it is hydrolyzed into the carboxylic acid using 1 M aqueous NaOH in THF at 100 °C).[25] Therefore, we were interested in whether a wider range of azaarenes (including those not substituted with the highly electron-withdrawing nitro group) could be effective activating groups in other catalytic enantioselective carbon–carbon bond forming reactions.

The enantioselective rhodium-catalyzed 1,4-addition of organoboron compounds to electron-deficient alkenes is now well-established as a valuable method for the preparation of enantioenriched chiral compounds.[27−30] Advantages of these reactions include: (i) the wide availability, stability, low toxicity, and functional group tolerance of arylboron reagents; (ii) the broad range of effective chiral ligands that are available, and (iii) the often mild reaction conditions. Furthermore, Lautens and co-workers had demonstrated that vinylazines are effective acceptors in non-asymmetric rhodium-catalyzed additions of arylboronic acids (Scheme 2).[9] These results suggested that, at least in principle, a catalytic enantioselective variant employing *β*-monosubstituted alkenylazaarenes might be possible, which would be a useful route to *β*-stereogenic 2-alkylazaarenes.

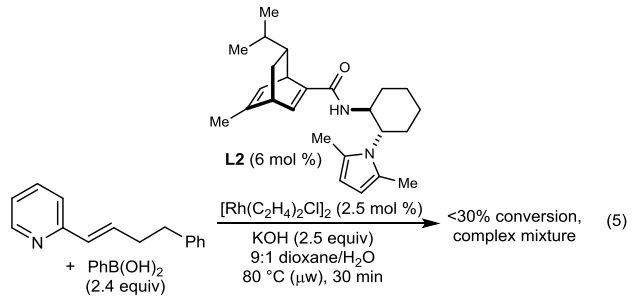
Efforts to achieve this objective in our laboratory resulted in the development of the enantioselective rhodium-catalyzed 1,4-arylation of 2-alkenylaazaarenes **7** (Scheme 7).[31] The catalyst was generated from $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol %) and the chiral diene **L2** (6 mol %), which is derived from the natural product α-phellandrene and (*S*,*S*)-2-(2,5-dimethyl)pyrrol-1-ylcyclohexylamine. The reactions were conducted by microwave irradiation of a mixture of the 2-

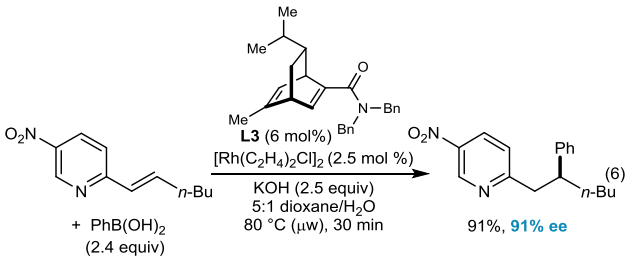
alkenylazaarene **7** with the arylboronic acid (2.4 equiv) in a 9:1 mixture of dioxane and H_2O in the presence of KOH (2.5 equiv) at 80 °C for 30 min. Under these conditions, a range of 2-alkenylazaarenes underwent arylation with various arylboronic acids in moderate to good yields and with high enantioselectivities. Substrates containing quinoline (**8a**), quinoxaline (**8b**), pyrimidine (**8c**), benzoxazole (**8d**), 4,5-diphenyloxazole (**8e**), or 3-phenyl-1,2,4-oxazadiazole (**8f**) were effective, and both *β*-alkyl and *β*-aryl substituents were tolerated.

Scheme 7. Enantioselective Rh-Catalyzed Arylation of Alkenylazaarenes with Arylboronic Acids

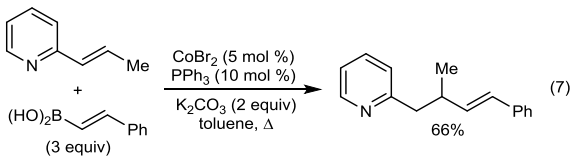


Simple 2-alkenylpyridines were arylated with low conversion under these conditions (<30%), accompanied by the formation of side-products (eq 5). This observation is in contrast to the enantioselective copper-catalyzed 1,4-reduction of *β*,*β*-disubstituted alkenylazaarenes, where 2-alkenylpyridines were effective substrates (Scheme 3).[23] We subsequently demonstrated that incorporation of the strongly electron-withdrawing nitro group at the 5-position of the pyridine dramatically increases the reactivity, allowing 1,4-arylation to proceed in good yield and high enantioselectivity using a dibenzylamide-containing chiral diene **L3** (eq 6).[32]

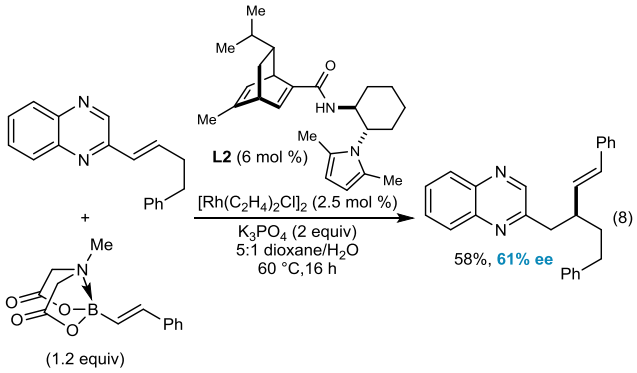




During the final stages of our work, the group of Yorimitsu and Oshima reported the cobalt-catalyzed alkenylation of vinylazines with styrylboronic acids.[33] This study also included one example of a racemic 1,4-addition to a *β*-substituted substrate (eq 7).

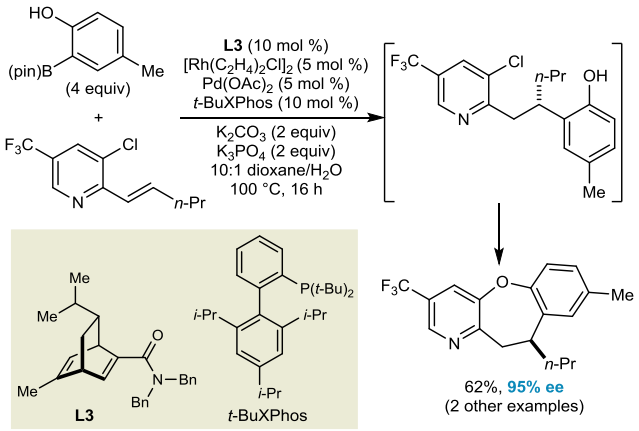


We have demonstrated that an enantioselective variant of this process is possible with rhodium catalysis. Using 5 mol % of a complex of rhodium bound to the chiral diene **L2**, a 2-alkenylquinoxaline underwent alkenylation with (*E*)-2-phenylvinyl MIDA boronate (1.2 equiv) in 5:1 dioxane/H_2O in the presence of K_3PO_4 (2 equiv) at 60 °C, though the yield and enantioselectivity of this reaction were modest (eq 8).[31] The use of an alkenyl MIDA boronate as a slow-release surrogate for the corresponding alkenylboronic acid was essential. Use of the alkenylboronic acid itself (2.4 equiv) under otherwise identical conditions led to only ~25% conversion, primarily because alkenylboronic acids undergo rapid protodeboronation under the aqueous, basic reaction conditions typically required for rhodium-catalyzed 1,4-additions.



Recently, the Lautens group reported the asymmetric synthesis of azadihydrobenzoxepines using the enantioselective rhodium-catalyzed arylation of an alkenylpyridine followed by a palladium-catalyzed C–O coupling in the same pot (Scheme 8).[34] A survey of various chiral ligands established that the chiral diene **L3**[32] provided optimal results.

Scheme 8. Application of Enantioselective Rh-Catalyzed Arylation of an Alkenylpyridine in the Asymmetric Synthesis of Azadihydrobenzoxepines

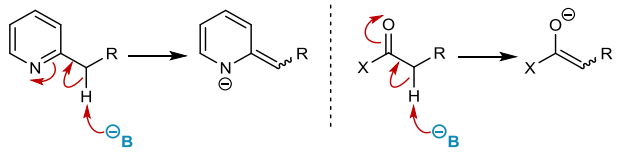


2-ALKYLAZAARENES AS PRONUCLEOPHILES IN CATALYTIC ENANTIOSELECTIVE C–C BOND-FORMING REACTIONS VIA α-DEPROTONATION

Having demonstrated that C=N-containing azaarenes are able to activate adjacent, conjugated alkenes toward catalytic enantioselective nucleophilic additions (see previous section), in 2011 our attention turned to the use of these structures in reactions requiring complementary modes of substrate activation. Specifically, we targeted the development of catalytic enantioselective processes that exploit the ability of C=N-containing azaarenes to acidify the α-protons of a 2-alkyl substituent, thus enabling the nucleophilic addition of the resulting azaallyl anion[35] to a π-electrophile (Scheme 1D).

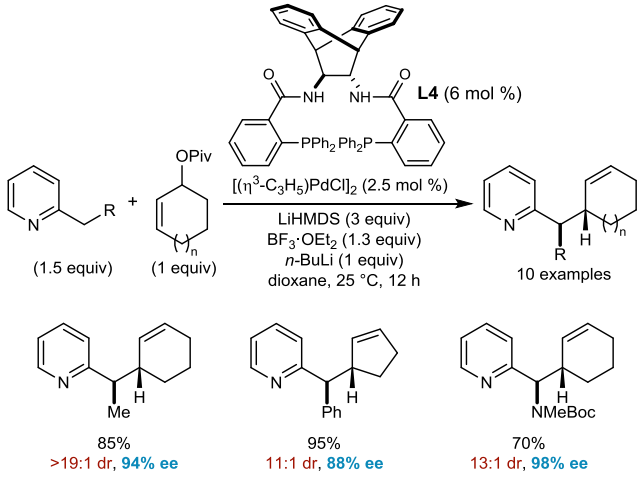
State of the Field *ca.* 2011–2012. The α-deprotonation of 2-alkylazaarenes draws strong parallels with the enolization of carbonyl compounds (Scheme 9). Although the latter process has been exploited in a variety of *direct* catalytic enantioselective aldol, Mannich, and Michael reactions (i.e. those not requiring prior preparation of activated derivatives such as enol silanes), the use of 2-alkylazaarenes in analogous processes was almost non-existent. The main barrier in the development of such reactions is the lower acidity of 2-alkylazaarenes compared with carbonyl compounds. As a result, more basic conditions are generally required, and the higher nucleophilicity/basicity of the resulting azaallyl anions are likely to present significant challenges in the development of catalytic enantioselective addition reactions.

Scheme 9. Parallel Between α-Deprotonation of 2-Alkylazaarene and Enolization of Carbonyl Compounds.



Nevertheless, there was encouraging precedent for the use of 2-alkylazaarenes as pronucleophiles in catalytic enantioselective additions to π-electrophiles in the work of Trost and co-workers.[36] In these reactions, 2-methylpyridines,[36a] 2-alkylpyridines,[36b] and polynitrogen-containing 2-alkylazaarenes[36c] underwent highly enantioselective allylic alkylations with mainly cyclic allylic carbonates or esters in the presence of a chiral palladium complex derived from the chiral bisphosphine **L4** (representative examples using 2-alkylpyridines[36b] are shown in Scheme 10). In the case of 2-methyl[36a] or 2-alkylpyridines,[36b] the reactive nucleophiles were generated by coordination to $BF_3{\cdot}OEt_2$ followed by deprotonation with excess LiHMDS. In the case of 2-alkylpyridines,[36b] one equivalent of *n*-BuLi was required to drive the deprotonation to completion. With polynitrogen-containing 2-alkylazaarenes, neither $BF_3{\cdot}OEt_2$ nor *n*-BuLi were required.[36c]

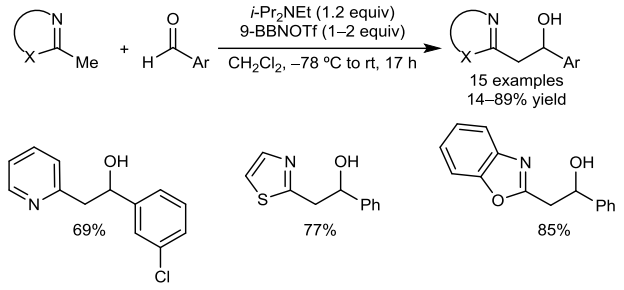
Scheme 10. Diastereo- and Enantioselective Palladium-Catalyzed Allylic Alkylation of 2-Alkylpyridines with Cyclic Electrophiles



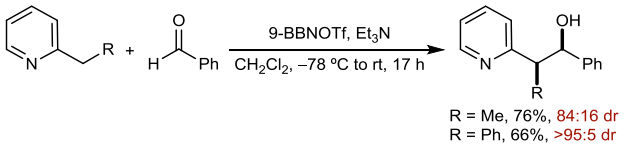
The reactions described by Trost and co-workers are important demonstrations of the use of 2-alkylazaarenes as pronucleophiles in enantioselective catalysis. However, processes that generate the nucleophilic species without employing strong bases would also be of value.

To facilitate the α-deprotonation of alkylazaarenes under relatively mild conditions, Hamana and Sugasawa exploited the combined action of dialkylboron triflates and a tertiary amine base to generate azaallylboron species, which underwent nucleophilic addition to aromatic aldehydes (Schemes 11 and 12).[37] Although these reactions proceeded successfully without requiring strong bases, stoichiometric quantities of the dialkylboron triflate and amine were required, and only racemic reactions were reported.

Scheme 11. Addition of Methylazaarenes to Aromatic Aldehydes

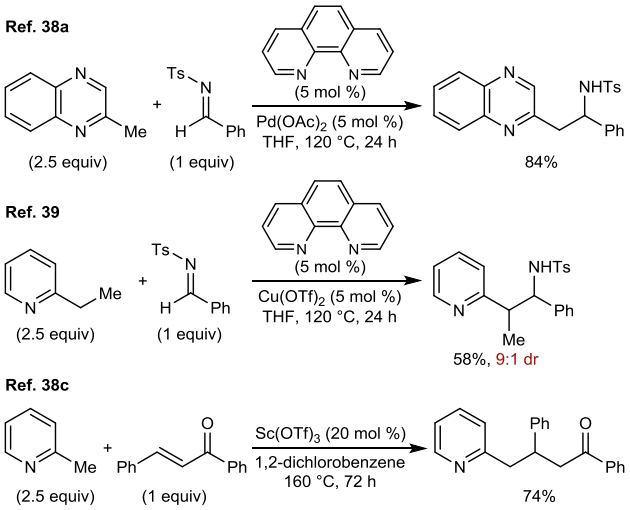


Scheme 12. Diastereoselective Additions of 2-Alkylpyridines to Benzaldehyde



Avoiding stoichiometric quantities of promoters in these reactions has been addressed recently with the development of additions of alkylazaarenes to π-electrophiles using substoichiometric quantitites of Lewis acids.[38–40] For example, the Huang and Rueping groups, as well as the group of Kanai and Matsunaga, have reported palladium-,[38a] scandium-,[38b] iron,[38c] or copper-catalyzed[39,40b] additions of alkylazaarenes to *N*-sulfonylimines. Scandium-[40] and ytterbium-catalyzed[38d] additions of alkylazaarenes to various α,*β*-unsaturated carbonyl compounds have also been reported. Selected examples of these reactions are shown in Scheme 13. The use of Brønsted acid catalysis to promote the addition of 2-methylazines to isatins has also been described.[41]

Scheme 13. Lewis Acid-Catalyzed Additions of 2-Alkylazaarenes to Imines and Enones

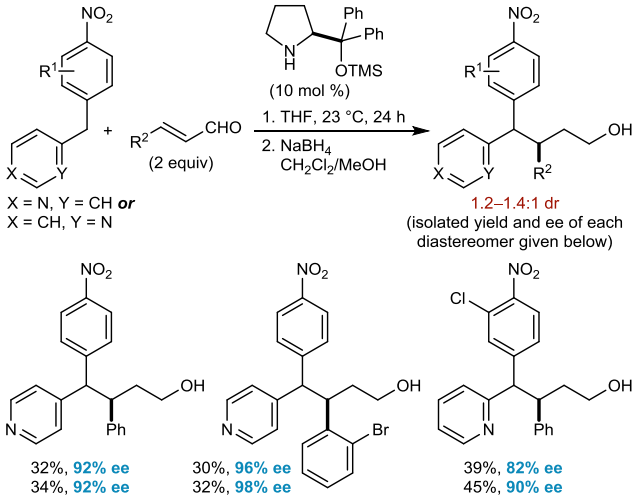


Although the processes depicted in Scheme 13 represent encouraging progress, a catalytic enantioselective variant had not been developed. Furthermore, the addition of alkylazaarenes to *N*-sulfonylimines has been shown to proceed in tol-

uene at reflux *in the absence of a catalyst*, and under these conditions the addition step is most likely reversible. These two observations present challenges for enantioselective catalysis, since the racemic background reaction and the reversibility of the process would erode enantioselectivity.[42]

Another strategy to overcome the low acidity of alkylazaarenes is placement of second activating group at the reactive center. As a demonstration of this approach, Melchiorre and co-workers reported the enantioselective addition of various nitrobenzyl pyridines to α,*β*-unsaturated aldehydes using a chiral secondary amine catalyst (Scheme 14).[43] In this process, the combination of the electron-withdrawing nitrophenyl and pyridine groups renders the protons at the benzylic position sufficiently acidic for the reactions to proceed under mild conditions.[44] The products were obtained with generally high enantioselectivities, though the diastereoselectivities were very low.

Scheme 14. Enantioselective Addition of Nitrobenzylpyridines to α,β-Unsaturated Aldehydes



Work in the Field Since 2012. Our group initially became interested in the use of 2-alkylazaarenes as pronucleophiles in catalytic enantioselective Michael additions to nitroalkenes. To overcome the low reactivity of alkylazaarenes, substrates containing a second activating group at the α-carbon, such as ethyl 2-pyridylacetate, were employed (Figure 1).[45] In addition to further acidifying the methylene protons, the presence of the ester results in a strong structural similarity of the azaarylacetate with 1,3-dicarbonyl compounds. Given that numerous catalytic enantioselective additions of 1,3-dicarbonyl compounds to nitroalkenes have been described,[46,47] it appeared likely that existing chiral catalyst systems could be successfully applied to azaarylacetates.

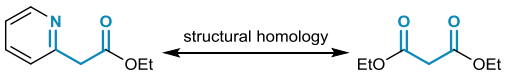
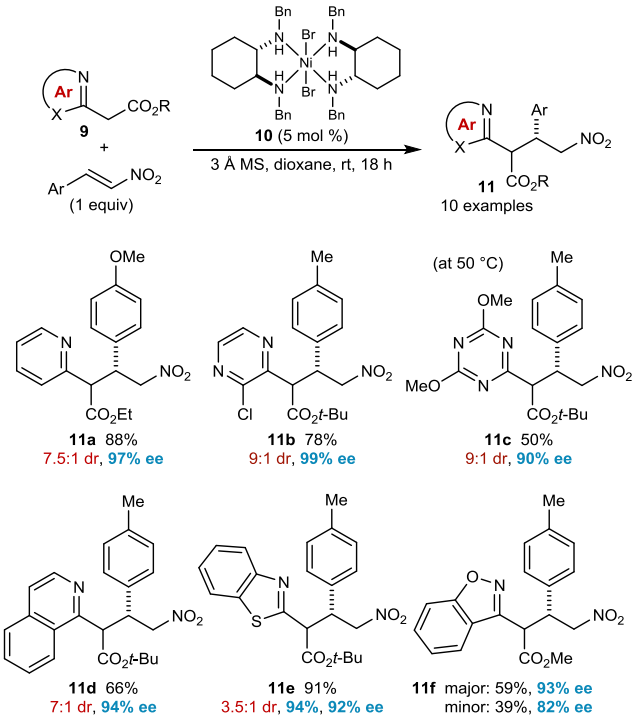


Figure 1. Structural homology between azaarylacetates and 1,3-dicarbonyl compounds.

We first examined the additions of azaarylacetates **9** to *β*-(hetero)aryl-substituted nitroalkenes, and found that the nickel(II)-bis(diamine) complex **10** described by Evans and co-workers[46d,e] was effective. Stirring an equimolar mixture of the α-azaarylacetate and the nitroalkene with 5 mol % of **10** in dioxane in the presence of 3 Å molecular sieves at room temperature led to Michael addition products with high enantioselectivities (Scheme 15). Many of these products were isolated as inseparable mixtures of diastereoisomers due to configurational instability at the stereocenter α to the ester.

The process is tolerant of a range of azaarenes in the pronucleophile, including pyridine (**11a**), chloropyrazine (**11b**), dimethoxytriazine (**11c**), isoquinoline (**11d**), benzothiazole (**11e**), and benzisoxazole (**11f**).

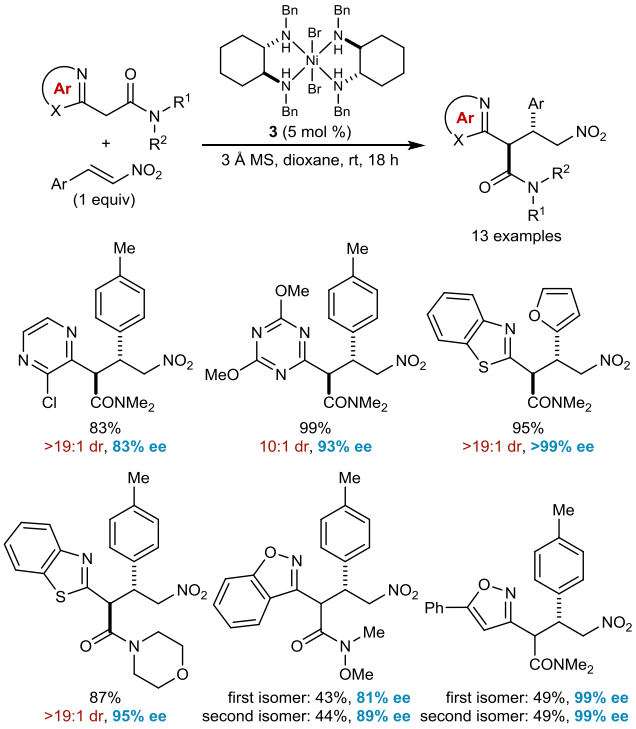
Scheme 15. Enantioselective Nickel-Catalyzed Michael Additions of Azaarylacetates to Nitroalkenes



Azaaryl tertiary acetamides are also competent substrates in this process (Scheme 16). In contrast to the products resulting from azaarylacetates (Scheme 15), the relative configurations of the amide products are stabilized by the well-recognized unfavorable $A_{1,3}$ strain accompanying the enolization of α-stereogenic tertiary amides.[48] Therefore, the diastereomeric ratios of the products indicated in Scheme 16 most likely reflect the inherent kinetic diastereoseletivities of the Michael reactions. Again, a variety of azaarenes in the pronucleophile were accommodated, and the range of amides

tolerated included *N*,*N*-dimethyl, morpholinyl, and Weinreb amides. Many of these reactions were highly diastereoselective, but diastereoselectivies were low to non-existent with substrates containing benzisoxazole or isoxazole groups.

Scheme 16. Enantioselective Nickel-Catalyzed Michael Additions of Azaarylacetamides to Nitroalkenes



Based upon a model described for related Michael additions,[46e] a stereochemical model to rationalize the diastereo- and enantioselectivity of these reactions can be proposed (Figure 2).[45] In this model, it is assumed that: (i) binding of the deprotonated pronucleophile to the nickel center of the catalyst occurs through the enolate oxygen and azaarene nitrogen atoms, and (ii) the nitroalkene is bound to nickel to stabilize the developing negative charge of the nitronate anion. Using a benzothiazole-containing *N*,*N*-dimethylacetamide substrate for illustrative purposes, four distinct transition state models appear reasonable. **TS 1** and **TS 2** (which involve C–C bond formation at one particular prochiral face of the nitroalkene) appear to be disfavored on the basis of steric interactions of the nitro group with a benzyl substituent of the ligand. These interactions are absent in **TS 3** and **TS 4**, but in **TS 3**, there is an unfavorable interaction of the nitro group with the benzene ring of the benzothiazole. Reaction through **TS 4**, which is relatively free of unfavorable interactions, is consistent with the stereochemical outcome observed. The low to non-existent diastereoselectivities observed with (benz)isoxazole-containing pronucleophiles can be rationalized by the relatively open space in the vicinity of the oxygen atom of the (benz)isoxazole rings, which reduces the unfavorable NO_2–azaarene interaction in **TS 3** and thus the energy difference between **TS 3** and **TS 4**.

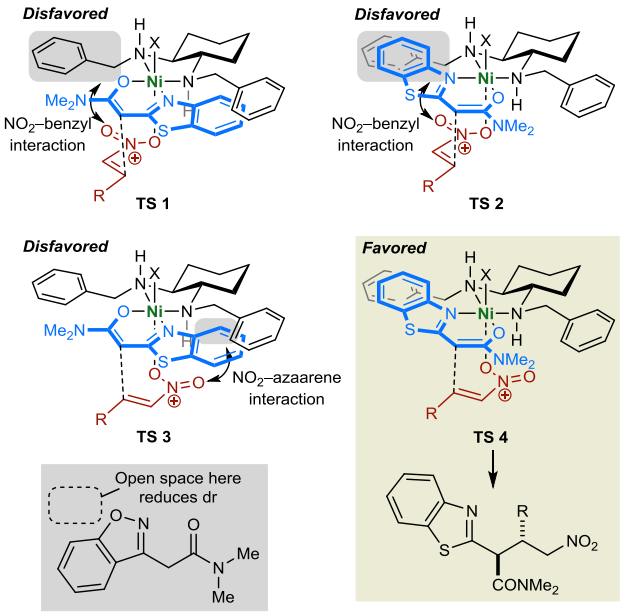
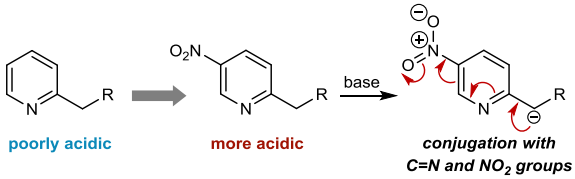


Figure 2. Model for stereochemical induction.

Despite the success of the reactions shown in Schemes 14–16, the development of processes that do not require an additional activating group at the α-carbon would be valuable since this would allow this position to be functionalized with other groups.

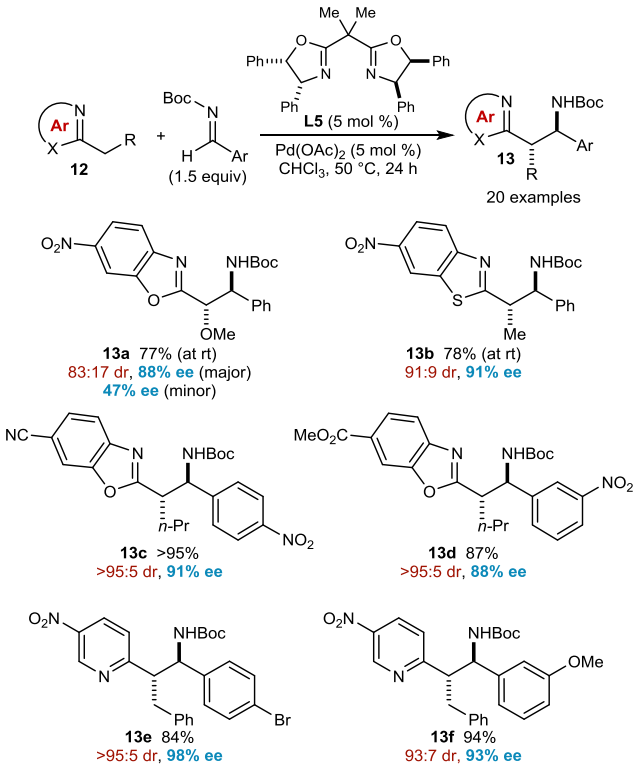
An alternative approach for the activation of alkylazaarenes is the use of an electron-withdrawing group *on the azaarene itself* that is conjugated with the C=N bond, and which can therefore stabilize the development of negative charge on the nitrogen atom (Scheme 17). 4-Alkyl-5-nitroisoxazoles, for example, have been shown to undergo deprotonation and subsequent addition to aldehydes under mild conditions (using tertiary amine bases).[49]

Scheme 17. Acidification of the α-Protons of Alkylazaarenes with an Electron-Withdrawing Group on the Heterocycle



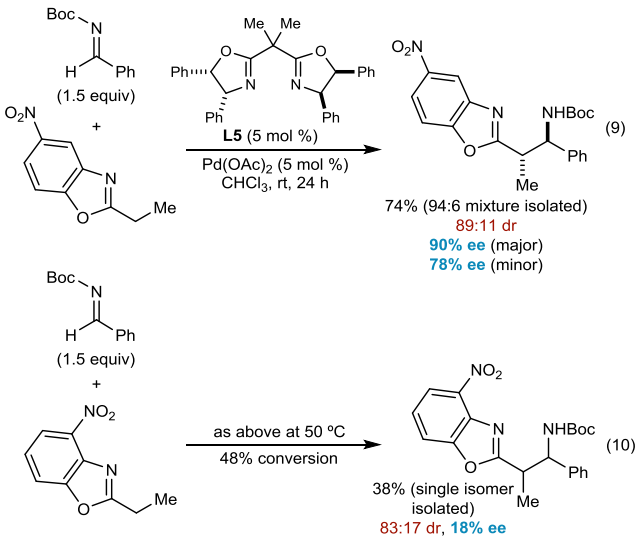
In accordance with this strategy, our group has developed the diastereo- and enantioselective addition of various 2-alkylazaarenes to *N*-Boc imines derived from aromatic aldehydes to provide *anti*-products (Scheme 18).[50] These reactions are promoted by 5 mol % of a complex consisting of $Pd(OAc)_2$ bound to the chiral tetraphenyl bis(oxazoline) ligand

Scheme 18. Enantioselective Pd-Catalyzed Addition of Alkylazaarenes to *N*-Boc Imines



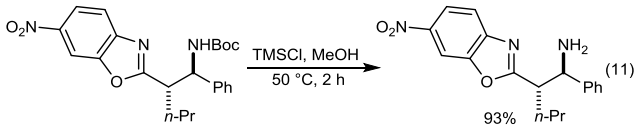
L5, and the reactivities of the 2-alkylazaarenes **12** were increased by the placement of electron-withdrawing groups such as nitro, ester, or cyano groups at a suitable position on the azaarene. In contrast with related reactions reported previously (Scheme 13),[38-40] these additions occur under mild conditions (generally room temperature or 50 °C). Substrates containing benzoxazole (**13a**,**c**,**d**) or benzothiazole (**13b**) with nitro (**13a**,**b**), ester (**13d**), or nitrile (**13c**) groups at the 6-position were effective, as were 2-alkyl-5-nitropyridines (**13e**,**f**). A range of simple alkyl substituents at the α-position were tolerated, as was a methoxy group (**13a**), though in this case the ee of the minor diastereomer of the product was only 47%. With respect to the imine, various substituents such as methyl, halo (**13e**), nitro (**13c**,**d**), cyano, or methoxy (**13f**) groups could be accommodated on the phenyl ring.

2-Ethyl-5-nitrobenzoxazole was also effective in this process, providing the addition product as a 94:6 inseparable mixture of diastereomers in 74% yield with 90% ee and 78% ee for the major and minor diastereomers, respectively (eq 9). The reactivity of this substrate was unexpected since mesomeric stabilization (–M effect) of the conjugate base by the 5-nitro substituent is not possible. It would appear that in this case, the inductive electron-withdrawing nature of the nitro group (–I effect) is sufficient for good reactivity.



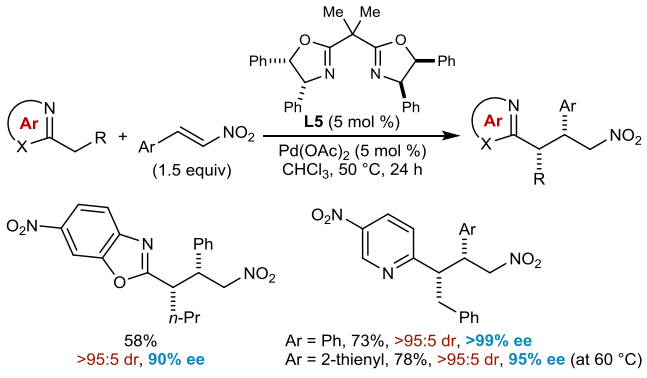
In contrast, the reaction of 2-ethyl-4-nitrobenzoxazole provided the product in low yield with poor diastereo- and enantioselectivity, even though a nitro group at the 4-position is able to provide mesomeric stabilization of the conjugate base (eq 10). We speculate that unproductive interactions between the nitro group and the substrate-bound palladium complex are responsible for the poor performance of this substrate.

A further benefit of the use of *N*-Boc imines in these reactions as opposed to the use of *N*-sulfonyl imines (Scheme 13) is that deprotection of the products to reveal the corresponding amines may be accomplished readily by treatment with mild acid (eq 11).[50]



Nitroalkenes are also effective electrophiles using the same catalyst system, providing conjugate addition products as single diastereomers with high enantioselectivities (Scheme 19).[50]

Scheme 19. Enantioselective Pd-Catalyzed Addition of Alkylazaarenes to Nitroalkenes



A tentative stereochemical model for these reactions is presented in Figure 3. Coordination of the alkylazaarene to the palladium complex **14** and subsequent α-deprotonation by an acetate ligand leads to the azaallylpalladium intermediate **15** or **16**. We believe the azaallyl ligand possesses *E*-stereochemistry to minimize unfavorable interactions between the R-substituent and the other ligands. Binding of the *N*-Boc imine to an axial coordination site can then occur from the relatively unhindered top face of **15**, activating it toward nucleophilic attack. In species **16**, in which the azaallyl ligand adopts an alternative conformation, approach of the imine from the top face is hindered by the acetate ligand, whereas approach from the bottom face is hindered by the phenyl groups of the chiral ligand.

Four distinct transition state models resulting from conformation **15** can then be envisaged. Reaction through **TS 7** and **TS 8**, in which the imine possesses an s-*cis* geometry, appear to be disfavored due to eclipsing interactions. In **TS 5** and **TS 6**, the imine adopts an s-*trans* geometry, which results in more favorable staggered conformations. However, an unfavorable steric interaction between the *tert*-butyl group of the imine with one of the methyl groups of the bis(oxazoline) ligand exists in **TS 6**. Therefore, reaction through **TS 5** is favored. The stereochemical outcome of the nitroalkene additions can be explained by similar arguments (**TS 9**).

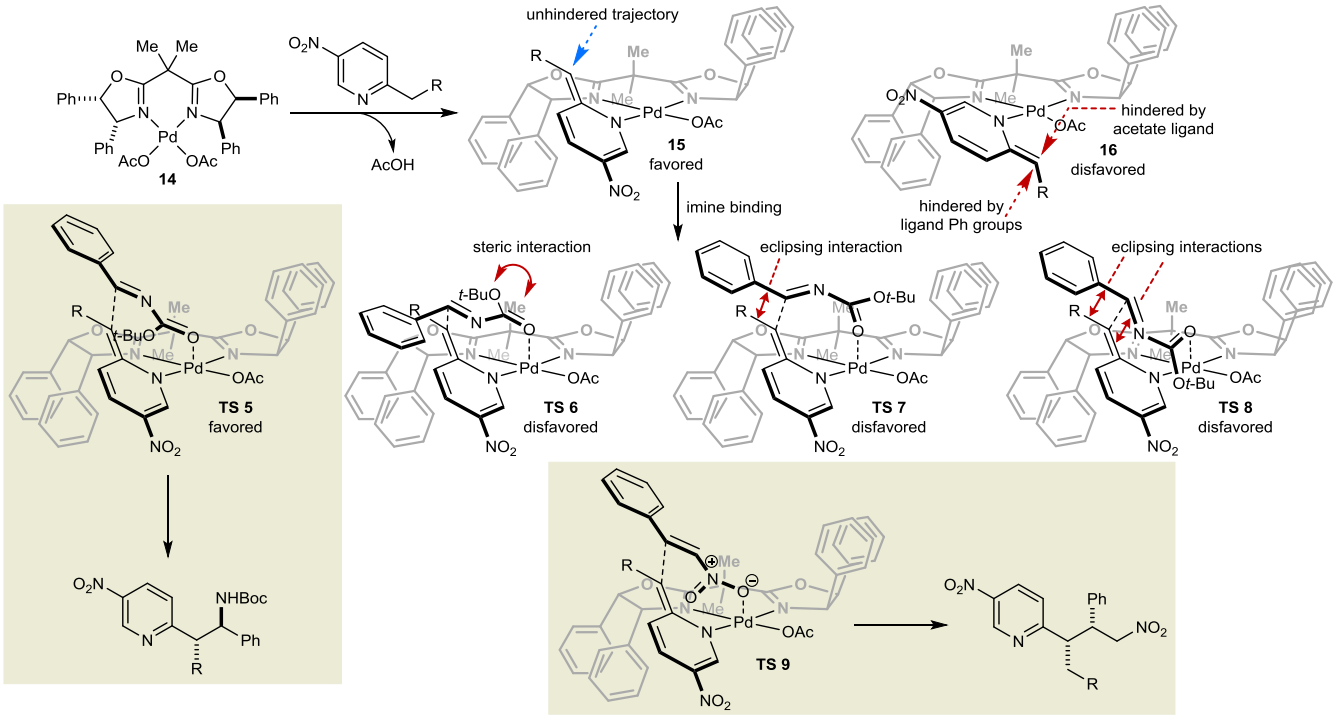
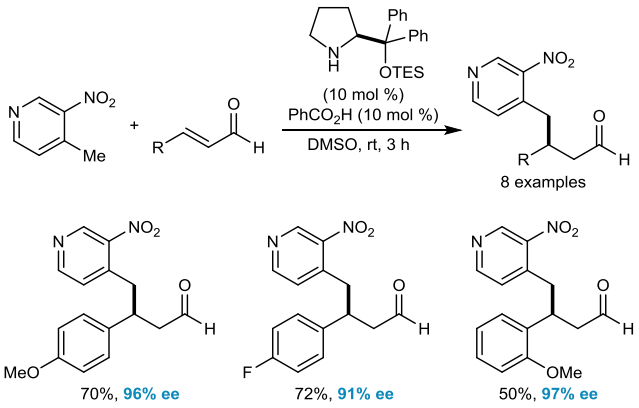


Figure 3. Stereochemical model.

The ability of nitro groups to acidify the α-protons of alkylpyridines was later exploited by the groups of Li and Wang, who described the enantioselective Michael addition of 4-methyl-3-nitropyridine to α,*β*-unsaturated aldehydes, catalyzed by a chiral secondary amine (Scheme 20).[51]

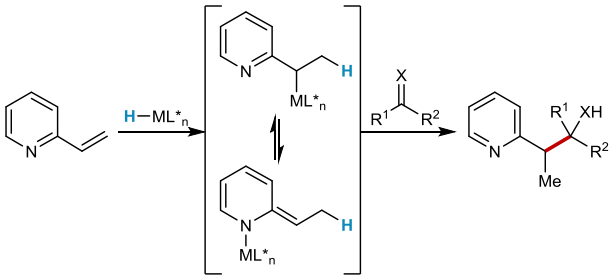
Scheme 20. Organocatalytic Conjugate Addition of 4-Methyl-3-nitropyridine to Enals



ALKENYLAZAARENES AS LATENT NUCLEOPHILES IN C–C BOND-FORMING REACTIONS

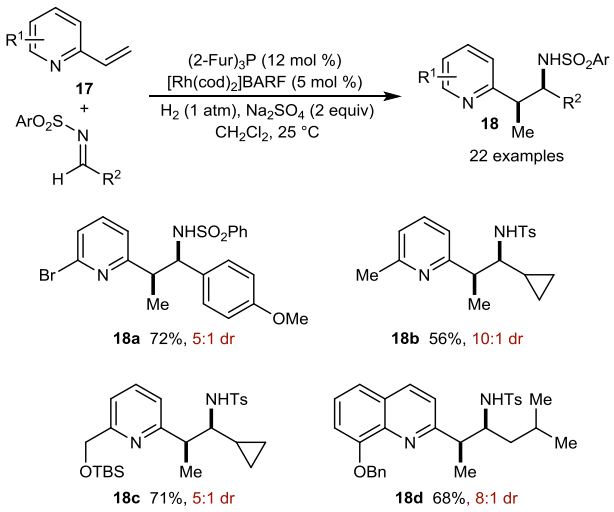
As discussed in the previous section, the relatively low acidity of 2-alkylazaarenes provides the main challenge in their use as pronucleophiles in catalytic enantioselective processes. However, the α-deprotonation of 2-alkylazaarenes is not the only method by which azaallylmetal intermediates can be prepared. The hydrometalation of 2-alkenylazaarenes offers a complementary access to these species under mild conditions, which can then be trapped in situ with π-electrophiles (Scheme 21). Such a reductive coupling process is well-precedented in reductive aldol and Mannich reactions involving α,*β*-unsaturated carbonyl compounds as latent enolate equivalents.[52,53] However, the use of alkenylazaarenes in similar processes is comparatively undeveloped.

Scheme 21. Reductive Coupling of Alkenylazaarenes



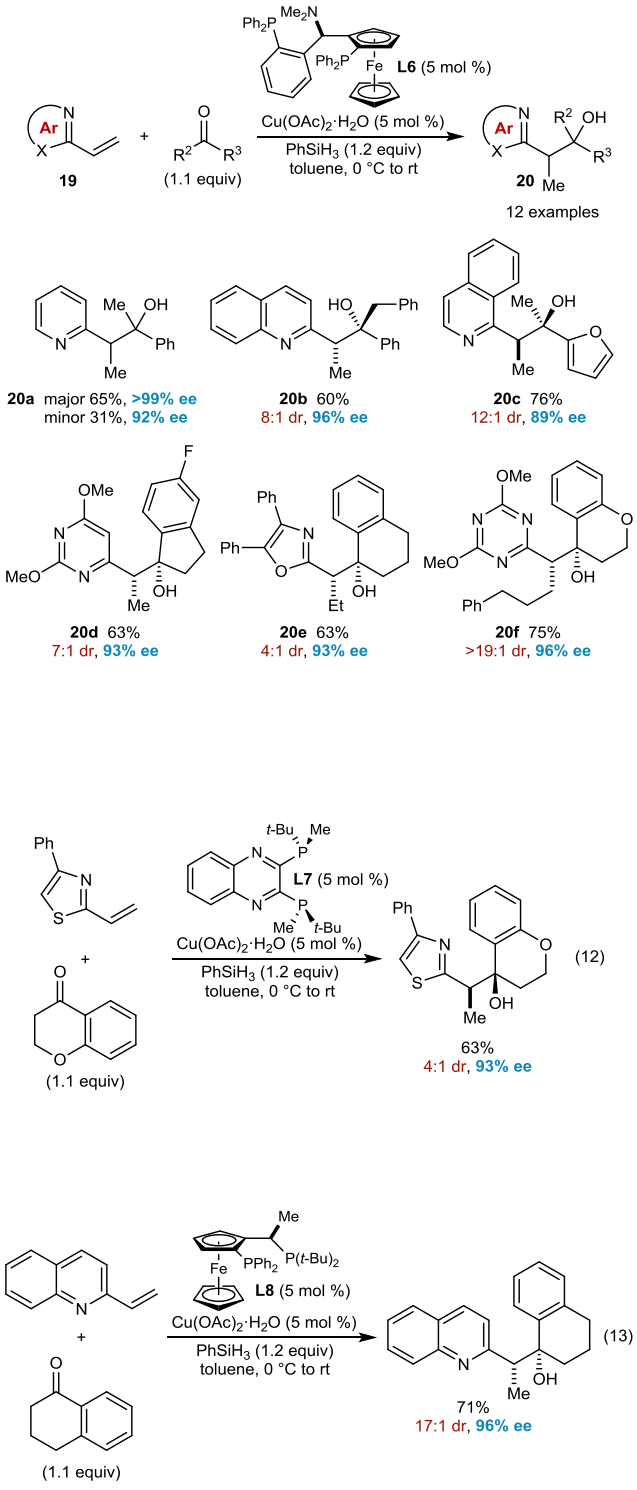
Prior to our investigations in this area, Krische and co-workers reported the diastereoselective reductive coupling of vinylazines with imines using hydrogen as the stoichiometric reductant, catalyzed by a $(2\text{-Fur})_3P$–rhodium complex (Scheme 22).[54] The inclusion of Na_2SO_4 was found to be beneficial for suppressing hydrolysis of the imine. Under these conditions, a range of 6-substituted 2-vinylpyridines **17** underwent reductive coupling to various *N*-sulfonylimines derived from aryl (**18a**), heteroaryl, alkenyl, and aliphatic (**18b-d**) aldehydes in generally good yields and with moderate to high levels of *syn*- diastereoselectivity. The presence of a 6-substituent at the pyridine was important, as demonstrated by the failure of the parent 2-vinylpyridine to participate in reductive coupling, presumably due to strong binding of rhodium to the nitrogen atom. 8-Benzyloxy-2-vinylquinoline was also effective (**18d**).

Scheme 22. Rh-Catalyzed Reductive Coupling of Vinylazines with N-Sulfonyl Imines



Given the successful enantioselective copper-catalyzed reduction of alkenylazaarenes developed in our laboratory (Scheme 3),[23] our attention turned to processes whereby the copper intermediates are trapped not by a protic additive, but by a π-electrophile. Initial investigations revealed that copper-bisphosphine complexes are effective in catalyzing the reductive coupling of vinylazaarenes to ketones, using $PhSiH_3$ as the stoichiometric reductant (Scheme 23).[55] Among the various chiral bisphosphines tested, the Taniaphos ligand **L6** gave the highest diastereo- and enantioselectivities. The scope of this process with respect to the azaarene is broad, with pyridine (**20a**), (iso)quinoline (**20b**,**c**), quinoxaline, dimethoxypyrimidines (**20d**), diphenyloxazole (**20e**), dimethoxytriazine (**20f**), and 4-phenylthiazole all being accommodated. Regarding the ketone partner, acetophenones (**20a**,**b**), indanones (**20d**), tetralone (**20e**), and chromanone (**20f**) were tolerated. Notably, *β*-substituted alkenylazaarenes are also competent substrates (**20e**,**f**). In certain cases, the use of alternative bisphosphines such as (*R*,*R*)-Quinox-P* (**L7**) or the Josiphos ligand **L8** provided better results (eq 12 and 13).

Scheme 23. Enantioselective Cu-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones



The stereochemical outcome of these transformations is dependent on the nature of the substrates. For example, the reactions of 2-vinylquinoline and 2-vinylisoquinoline provide products of the opposite absolute stereochemistry (**20b** and **20c**, respectively) using the same enantiomer of **L6**. Furthermore, cyclic ketones result in different diastereochemi-

cal outcomes compared with acyclic ketones (compare products **20b**,**c** with **20d-f**). The reasons for these differences are not clear at the present time.

CATALYTIC ENANTIOSELECTIVE NUCLEOPHILIC ADDITIONS TO ALKENYLARENES

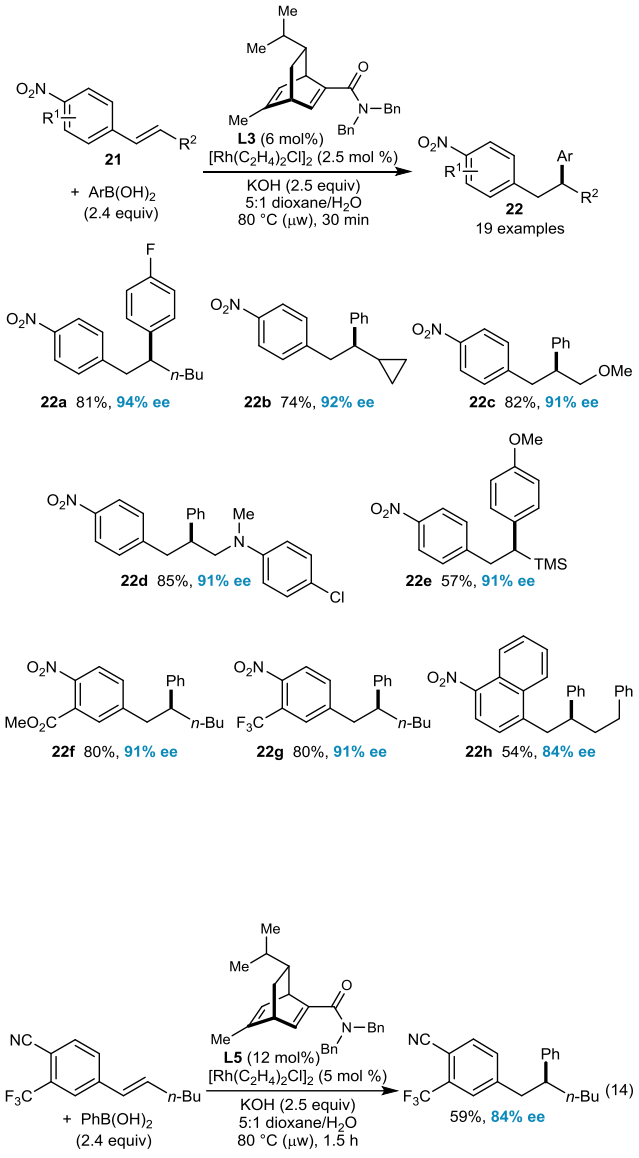
As shown previously, there are now several examples of catalytic enantioselective nucleophilic additions to alkenylazaarenes where activation of the alkene by the C=N moiety in the azaarene is critically important. This raised the question of whether the azaarene could be replaced with a simple benzene ring, or one substituted with an electron-withdrawing group. Styrenes are well-established substrates in enantioselective, α-selective, metal-catalyzed hydroborations,[56,57] but until recently, their use as electrophiles in other types of catalytic enantioselective processes had been somewhat underdeveloped. Although falling just outside of the main topic of this Perspective, it is felt a discussion of such reactions will nevertheless be useful.

Following on from our development of enantioselective rhodium-catalyzed arylation of alkenylazaarenes (Scheme 4),[31] we became interested in the corresponding reactions using alkenylarenes as the electrophiles. Given the reduced activation conferred by simple arenes compared to azaarenes, it is unsurprising that the addition of carbon-centered nucleophiles to simple alkenylarenes is relatively uncommon,[58] and often requires highly reactive organometallic reagents.[59,60] Several groups have reported stoichiometric and catalytic enantioselective carbolithiation of alkenylarenes,[61] but a limitation of this approach is the low functional group tolerance of the organolithium reagents employed.

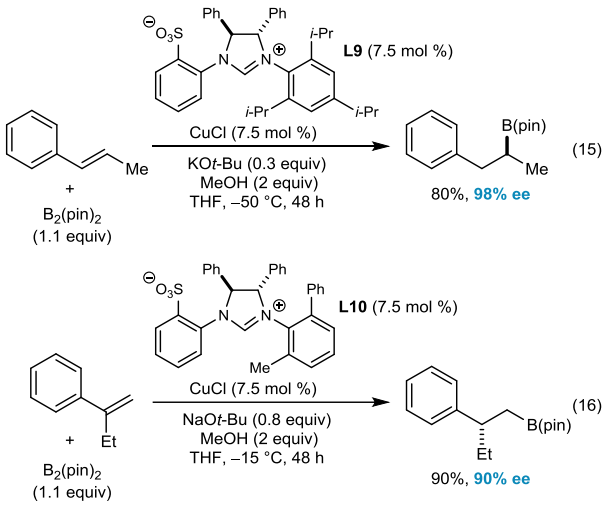
Lautens and co-workers had also shown that under rhodium catalysis, styrenes reacted with arylboronic acids to provide Heck-type products rather than hydroarylation products.[9] We envisaged that placement of highly electron-withdrawing groups at the *para*-position of the alkenylarene might lead to sufficient electrophilic activation of the alkene to enable hydroarylation, rather than Heck-type reactions, to occur. Indeed, alkenylnitrobenzenes have been shown to be viable electrophiles for the addition of stabilized carbon-centered nucleophiles.[62] However, prior to our investigations, no catalytic enantioselective variants existed.

Our studies resulted in the successful enantioselective arylation of *β*-substituted alkenyl-4-nitrobenzenes (Scheme 24).[32] The conditions employed were similar to those used in the corresponding reactions of alkenylazaarenes (Scheme 7),[31] with the main difference being that the optimal ligand among those examined was the dibenzyl amide-containing chiral diene **L3**. Regarding the *β*-substituent of the alkene, the reaction is tolerant of simple alkyl groups (**22a**,**f**–**h**), a cyclopropane (**22b**), an ether (**22c**), an amine (**22d**), and a trimethylsilyl group (**22e**). Additional substituents on the nitrobenzene are tolerated (**22f**,**g**), and a substrate containing a 4-nitronaphthyl group was also successfully arylated (**22h**). The reactions are successful using electron-rich, electron-poor, and *ortho*-substituted arylboronic acids. While arylation did not proceed with 3- or 2-alkenylnitrobenzenes, a substrate containing a 4-cyano group in combination with 3-trifluoromethyl group was also sufficiently reactive (eq 14).

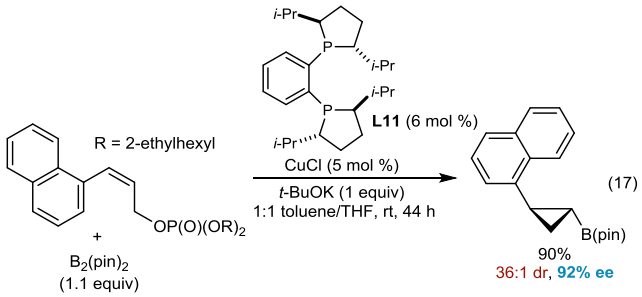
Scheme 24. Enantioselective Rh-Catalyzed Arylation of Alkenylazaarenes with Arylboronic Acids



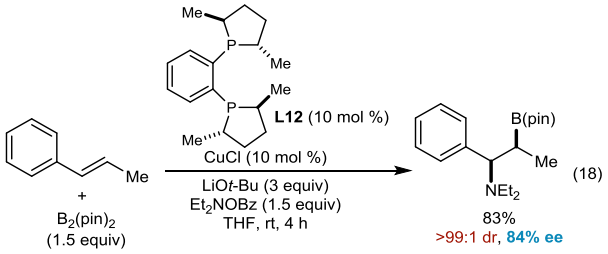
It should be noted that recent work from other groups has greatly expanded the utility of alkenylarenes as electrophiles in catalytic enantioselective reactions. For example, Hoveyda and co-workers have demonstrated that copper complexes formed from chiral *N*-heterocyclic carbene precursors such as **L9** and **L10** catalyze highly site-selective, enantioselective hydroborations of both *β*-[63] (eq 15) and *α*-substituted[64] styrenes (eq 16) with $B_2(pin)_2$ (1.1 equiv) in the presence of MeOH (2 equiv) as a proton source.

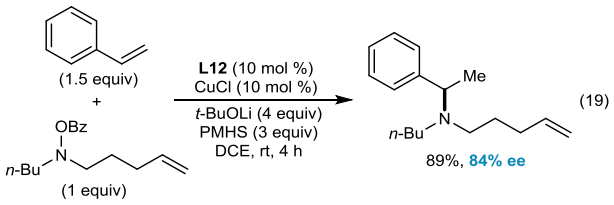


Trapping the intermediate benzylcopper species with electrophiles other than a proton has been demonstrated by the group of Ito, who reported the diastereo- and enantioselective copper-catalyzed synthesis of cyclopropylboronates by the addition of $B_2(pin)_2$ to *Z*-configured, aryl-substituted allylic phosphates (eq 17). In these reactions, the benzylcopper intermediates undergo an intramolecular S_N2 reaction with the alkyl phosphate.

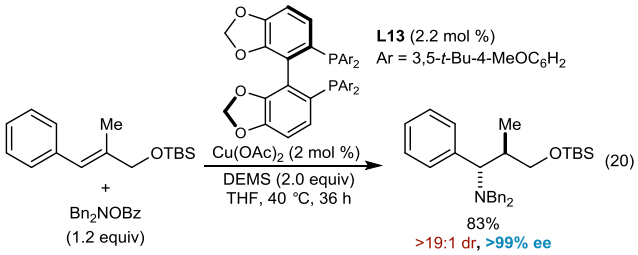


Hirano, Miura, and co-workers have recently reported the copper-catalyzed aminoboration (eq 18)[65] and hydroamination (eq 19)[66] of alkenylarenes using $B_2(pin)_2$ or polymethylhydrosiloxane (PMHS), respectively. Following enantioselective borocupration or hydrocupration, the resulting benzylcopper species are trapped with various *O*-benzoylhydroxylamines.





The Buchwald group has also recently described enantioselective copper-catalyzed hydroaminations of alkenylarenes that are very similar to those reported by Hirano, Miura, and co-workers.[67] In this work, diethoxymethylsilane (DEMS) was used as the hydride source. Notably, one example of using β,β-disubstituted alkenylarene was also described (eq 20).



CONCLUSIONS AND OUTLOOK

The activating properties of C=N-containing azaarenes and electron-deficient arenes have long been known to facilitate nucleophilic additions to adjacent, conjugated alkenes, and to enable the generation of carbanions *via* α-deprotonation of a 2-alkyl group. Despite this recognition, it is only within the last few years that such reactivity has been exploited in the catalytic enantioselective construction of chiral azaarene-containing compounds. The carbonyl-like reactivity arising from the embedded imine functionality of certain azaarenes has been utilized in various enantioselective conjugate addition, aldol-, and Mannich-like reactions, providing a range of potentially useful chiral building blocks. It is our hope and expectation that the current limitations of these reactions, many of which originate from the more modest electron-withdrawing properties of (aza)arenes compared with carbonyl groups, will be addressed in the future by researchers worldwide to result in more generally applicable synthetic methods.

AUTHOR INFORMATION

Corresponding Author

hon.lam@nottingham.ac.uk

BIOGRAPHY

Hon Wai Lam received an M.Chem. degree in chemistry from the University of Oxford in 1998. He then moved to the University of Nottingham to carry out his Ph.D. under the direction of Gerald Pattenden. In January 2002, he moved to Harvard University as a GSK Postdoctoral Fellow to work with David A. Evans. In October 2003, he joined the School of Chemistry at the University of Edinburgh where he became a Reader in Organic Chemistry. In October 2013, Hon took up the GSK Chair of Sustainable Chemistry at the University of Nottingham. His group's research interests are based around the development of new synthetic methodology, including enantioselective catalysis and C–H functionalization chemistry.

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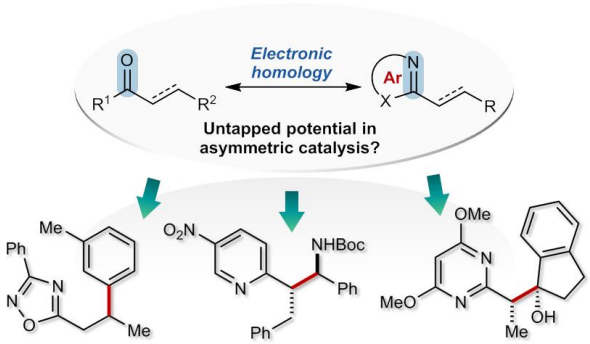
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O
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