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COMMUNICATION

A second-generation ligand for the enantioselective rhodium-catalyzed addition of arylboronic acids to alkenylazaarenes

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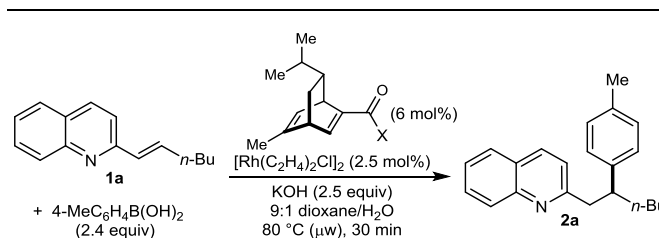
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A 2,4,6-trialkylanilide-containing chiral diene has been identified as a superior ligand for the enantioselective rhodium-catalyzed arylation of alkenylazaarenes.

As part of a program aimed at the preparation of enantioenriched chiral azaarene-containing compounds,¹ we have focused upon an underexploited strategy in asymmetric synthesis, namely the utilization of the C=N moiety within certain azaarenes to activate adjacent functionality in enantioselective catalysis.^{2–4} In this context, we have reported^{1b} the enantioselective rhodium-catalyzed 1,4-arylation^{5–8} of β -substituted alkenylazaarenes with arylboronic acids using a secondary amide-containing chiral diene^{9–11} ligand **L1** (see Table 1, entry 1), which builds upon early studies by the groups of Lautens^{12a} and Genet^{12b} using vinylazaarenes. Although **L1** was highly effective, it was of interest to determine whether a ligand of this complexity, possessing stereochemical elements additional to those of the chiral diene component, was actually necessary for optimal results.¹³ Herein, we report a simpler ligand that provides results superior to those obtained using **L1**, along with a more comprehensive evaluation of the scope of the reaction.

First, various analogues of **L1** were prepared and evaluated in the enantioselective addition of 4-methylphenylboronic acid to 2-alkenylquinoline **1a** (Table 1), a reaction that gave **2a** in 67% yield

Table 1 Ligand evaluation for arylation of **1a**^a



| Entry | Ligand | X | Conversion (%) | ee (%) |
|----------------|-----------|-----------------------------------------------------------------------|----------------|--------|
| 1 ^b | L1 | | 67% yield | 92 |
| 2 | L2 | NHCy | >95 | 90 |
| 3 | L3 | NCy ₂ | 28 | 59 |
| 4 | L4 | NHBn | >95 | 88 |
| 5 | L5 | NBn ₂ | 81 | 85 |
| 6 | L6 | NMe ₂ | 91 | 46 |
| 7 | L7 | NHPh | 58 | 76 |
| 8 | L8 | NH(2,4,6-Me ₃ C ₆ H ₂) | 33 | 96 |
| 9 | L9 | NH[2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂] | >95 | 99 |

^a Reactions were conducted using 0.10 mmol of **1a** (0.2 M). Conversions were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Ref. 1b.

and 92% ee in our original study.^{1b} The conditions employed were identical to those we described previously.^{1b} Ligand **L2**, which lacks the pyrrole moiety on the cyclohexane, provided **2a** in high conversion but the enantioselectivity was slightly lower (entry 2) compared with that obtained using **L1** (entry 1). However, the dicyclohexylamide **L3** was noticeably inferior (entry 3). Ligands **L4** and **L5**, which contain one or two benzyl groups, respectively, provided reasonable results (entries 4 and 5), but the enantioselectivities were lower compared with **L1**. The dimethylamide **L6** gave high conversion but the reaction was poorly

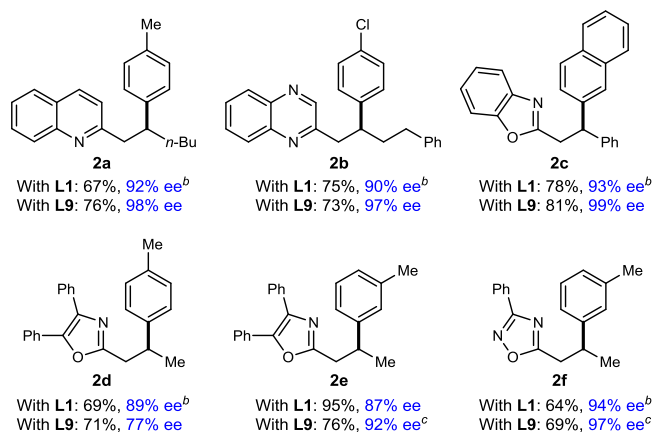
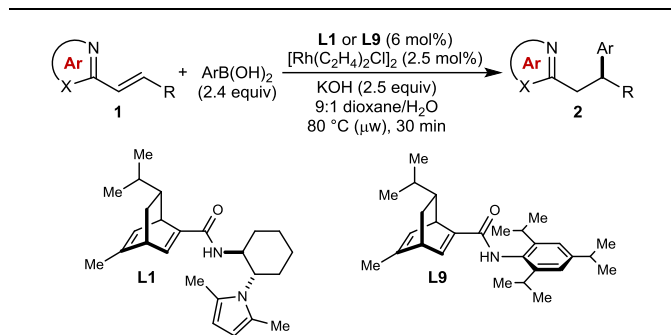
Table 2 Comparison of ligand **L9** with **L1**^a

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† Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data. CCDC 976345-976346. For ESI and crystallographic data in CIF See DOI: 10.1039/b000000x/



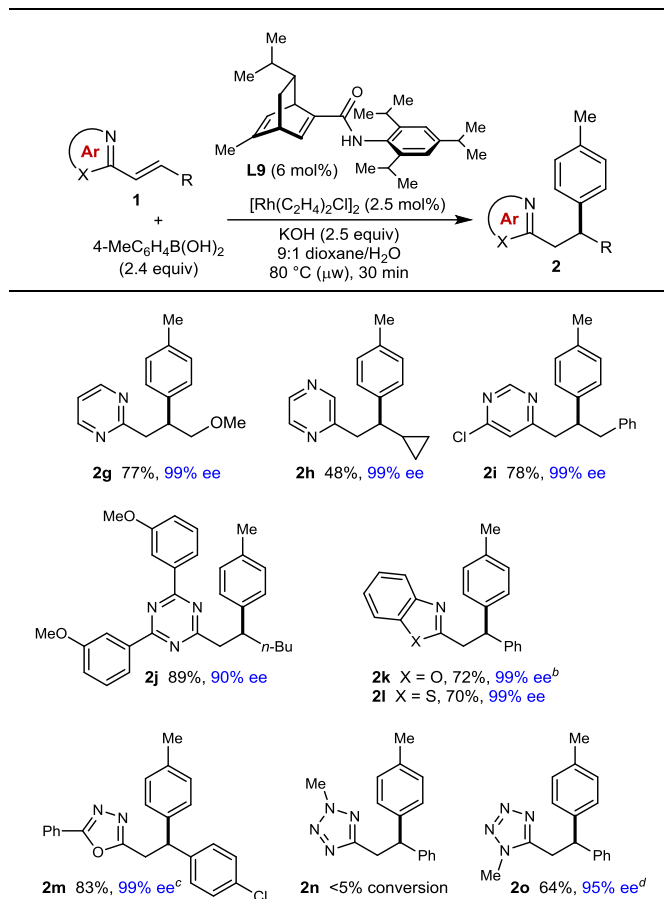
^a Reactions were conducted using 0.50 mmol of alkenylazaarene (0.2 M). Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Results taken from ref.^{1b} ^c Reaction conducted using 0.30 mmol of alkenylazaarene.

enantioselective (46% ee, entry 6). Next, ligands **L7–L9** containing anilide groups were studied (entries 7–9), and of these, the 2,4,6-triisopropylanilide **L9** provided the best results, giving **2a** in >95% conversion and 99% ee (entry 9).

Further confirmation of the superior enantioselectivities imparted by this new triisopropylanilide ligand **L9** was provided by repeating representative reactions described in our original study^{1b} using **L9** in place of **L1** (Table 2). These results indicate that while in most cases the isolated yields of the products with both ligands are comparable, the enantioselectivities are higher using **L9** (**2a**, **2b**, **2c**, **2e**, and **2f**). One exception was the addition of 4-methylphenylboronic acid to a substrate containing a 4,5-diphenyloxazole as the activating group, which gave **2d** in 77% ee using **L9**, and this result is inferior to that obtained using ligand **L1** (89% ee). Interestingly, the inferiority of **L9** compared with **L1** with this substrate appeared to be restricted to the use of 4-methylphenylboronic acid; when 3-methylphenylboronic acid was employed, **L9** provided the product **2e** in a higher enantioselectivity. The reasons for these contrasting results are not currently known.

To explore the scope of the process with the second generation ligand **L9** more comprehensively, a range of previously reported and new alkenylazaarenes were reacted with 4-methylphenylboronic acid (Table 3). While substrates containing pyrimidine or benzoxazole, azaarenes that have already been demonstrated to be efficient activating groups in our original study,^{1b} underwent arylation

Table 3 Arylation of alkenylazaarenes with 4-methylphenylboronic acid



^a Reactions were conducted using 0.30 mmol of alkenylazaarene (0.2 M). Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Enantiomeric excess determined after hydrolysis to the secondary amide. ^c The stereochemistry of **2m** was determined by X-ray crystallography, CCDC 976346. ^d The structure of the alkenylazaarene substrate **1m** was determined by X-ray crystallography, CCDC 976345.

efficiently with excellent enantioselectivities as expected (**2g** and **2k**), further examples demonstrate that other azaarenes are also effective. These examples include π -deficient azaarenes such as pyrazine (**2h**), a chloropyrimidine (**2i**), and a 4,6-bis(aryl)-1,3,5-triazine (**2j**), as well as π -excessive azaarenes such as benzothiazole (**2l**), a 1,3,4-oxadiazole (**2m**), and a tetrazole (**2o**). A pyrazine-containing substrate was only moderately reactive, providing product **2h** in 48% yield, though in 99% ee. Although alkenyltetrazole **1l** was unreactive (none of **2n** was obtained), its regioisomer **1m** provided **2o** in 64% yield and 95% ee. The difference in reactivities between **1l** and **1m** can be understood by consideration of their conjugation patterns. Whereas the alkene is conjugated only with the C=N group of the tetrazole in **1l**, it is conjugated with both the C=N and N=N

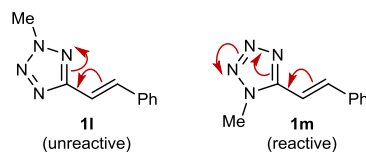
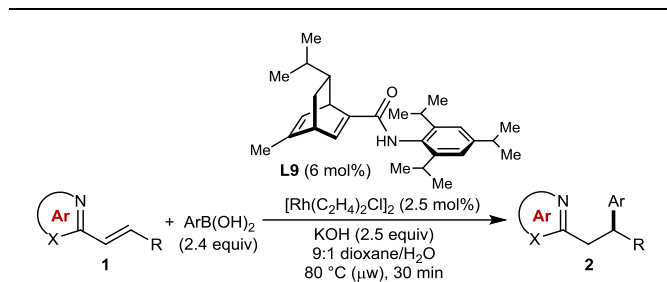


Fig. 1 Difference in conjugation between alkenyltetrazoles **1l** and **1m**.

Table 4 Arylation of alkenylazaarenes with various arylboronic acids



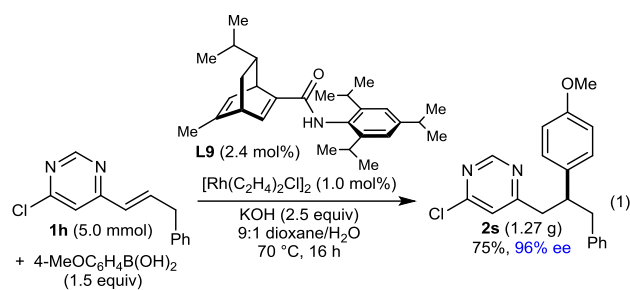
| Entry | Product | Yield (%) ^b | ee (%) ^c |
|-------|----------------------------------------------------------------------------------|------------------------|---------------------|
| 1 | 2p Ar = Ph | 89 | 99 |
| 2 | 2q Ar = 2-MeC ₆ H ₄ | >95 | 97 |
| 3 | 2r Ar = 4-FC ₆ H ₄ | 78 | 99 |
| 4 | 2s Ar = 4-MeOC ₆ H ₄ | 82 | 98 |
| 5 | 2t Ar = 3-EtO ₂ C ₆ H ₄ | 62 | 93 ^d |
| 6 | 2u Ar = 3,5-(F ₃ C) ₂ C ₆ H ₃ | 92 | 96 ^e |
| 7 | 2v Ar = 4-O ₂ NC ₆ H ₄ | 85 | 94 |
| 8 | 2w Ar = 2-naphthyl | 62 | 98 |
| 9 | 2x Ar = 3,5-Me ₂ C ₆ H ₃ | 85 | 99 |
| 10 | 2y Ar = 3-Cl-4- <i>i</i> -PrOC ₆ H ₃ | 63 | 99 |

^a Reactions were conducted using 0.30 mmol of alkenylazaarene (0.2 M). ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Enantiomeric excess determined on a derivative obtained after treatment of **2t** with LiOH in THF/MeOH/H₂O. ^e Enantiomeric excess determined after demethylation of the methoxy groups using BBr₃.

moieties in **1m**, leading to a greater degree of activation (Fig. 1). With respect to the β-substituent on the alkene, the process is tolerant of simple alkyl groups (**2i** and **2j**), a cyclopropane (**2h**), an ether (**2g**), and aryl groups (**2k**, **2l**, **2m**, and **2o**).

A range of arylboronic acids are compatible with this process, as demonstrated by the results presented in Table 4. Arylboronic acids containing substituents such as methyl (entries 2 and 9), halogen (entries 3 and 10), or alkoxy (entries 4 and 10) groups reacted smoothly with various alkenylazaarenes in good yields and high enantioselectivities. Arylboronic acids containing strong electron-withdrawing groups such as ester, trifluoromethyl, or even nitro substituents were also effective (entries 5–7). A sterically encumbering *ortho*-substituent on the arylboronic acid was also tolerated (entry 2).

This process can also be conducted on a larger scale using lower loadings of the arylboronic acid and catalyst. For example, arylation of alkenylpyrimidine **1h** on a 5.0 mmol scale with 4-methoxyphenylboronic acid (1.5 equiv), using thermal heating at 70



°C in the presence of 2.0 mol% of the rhodium–chiral diene complex, provided **2s** in 75% yield (1.27 g) and 96% ee (eq 1).

In summary, a more in-depth evaluation of chiral diene ligands for the enantioselective addition of arylboronic acids to alkenylazaarenes has resulted in the identification of a second-generation ligand **L9** containing a 2,4,6-triisopropylanilide moiety that is superior to our first generation ligand **L1**. Not only does this new chiral diene result in generally superior enantioselectivities, it is simpler in structure. A more thorough assessment of the scope of the process demonstrated that the effectiveness of ligand **L9** is fairly general across a range alkenylazaarenes and arylboronic acids. Further experimental and theoretical¹⁴ investigations of anilide-containing chiral dienes in asymmetric catalysis are planned, and will be reported in due course.

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