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

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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 with arylboronic acids.

As part of a program aimed at the preparation of enantioenriched chiral azaarene-containing compounds, 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. In this context, we have reported the enantioselective rhodium-catalyzed 1,4-arylation of β-substituted alkenylazaarenes with arylboronic acids using a secondary amide-containing chiral diene ligand L1 (see Table 1, entry 1), which builds upon early studies by the groups of Lautens and Genet using vinylazaarenes. Although L1 was highly effective, it was of interest to determine whether a ligand of this complexity, possessing stereocchemical elements additional to those of the chiral diene component, was actually necessary for optimal results. 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 and 92% ee in our original study. The conditions employed were identical to those we described previously. 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 dicyclohexylamidine 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 dimethylamine L6 gave high conversion but the reaction was poorly enantioselective (46% ee, entry 6). Next, ligands L7-L9 containing anilide groups were studied (entries 7–9), and of these, the 2,4,6-trisopropylanilide 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 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 alkenylboronic acid to 2a using L9 (entry 6).
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,1 underwent arylation 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 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).
Table 4 Arylation of alkenylazaarenes with various aryloboronic acids

| Entry | Product | Yield (%) | ee (%) |
|-------|---------|-----------|--------|
| 1     | 2p Ar = Ph | 89 | 99 |
| 2     | 2q Ar = 2-MeC₆H₄ | >95 | 97 |
| 3     | 2r Ar = 4-FC₂H₄ | 78 | 99 |
| 4     | 2s Ar = 4-MeOC₂H₄ | 82 | 98 |
| 5     | 2t Ar = 3-ClOC₂H₄ | 62 | 93 |
| 6     | 2u Ar = 3,5-(FC₂)₂C₆H₃ | 92 | 96 |
| 7     | 2v Ar = 4-OC₂NC₂H₄ | 85 | 94 |
| 8     | 2w Ar = 2-naphthyl | 62 | 98 |
| 9     | 2x Ar = 3,5-Cl₂C₆H₃ | 85 | 99 |
| 10    | 2y Ar = 3-Cl-4-iPrOC₂H₄ | 63 | 99 |

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

This process can also be conducted on a larger scale using lower loadings of the aryloboronic acid and catalyst. For example, arylation of alkenylpyrimidine 1h on a 5.0 mmol scale with 4-methoxy-phenoxyboronic acid (1.5 equiv.), using thermal heating at 70 °C in the presence of 2.0 mol% of the ruthenium–chiral diene complex, provided 2s in 75% yield (1.27 g) and 96% ee (eqn (1)).

In summary, a more in-depth evaluation of chiral diene ligands for the enantioselective addition of aryloboronic acids to alkenylazaarenes has resulted in the identification of a second-generation ligand L₉ containing a 2,4,6-trisopropylanilide 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 process demonstrated that the effectiveness of ligand L₉ is fairly general across a range of alkenylazaarenes and aryloboronic acids. Further experimental and theoretical investigations of anilide-containing chiral dienes in asymmetric catalysis are planned, and will be reported in due course.

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