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# Ligand-Controlled Rhodium-Catalyzed Site-Selective Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Cyclic *N*-Sulfonyl Ketimines

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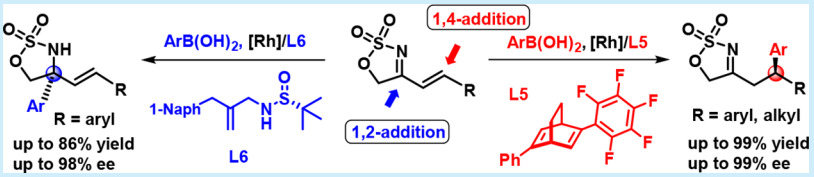
Supporting Information

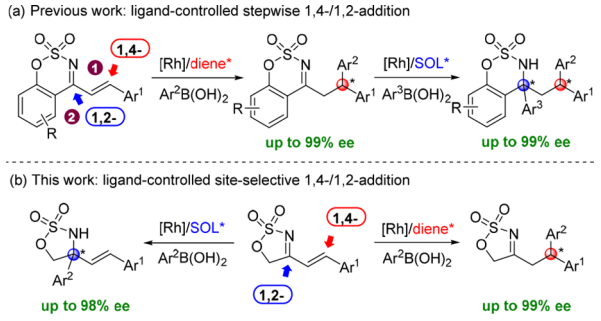



**ABSTRACT:** A site-selective rhodium-catalyzed asymmetric 1,4-/1,2-addition of arylboronic acids to challenging α,β-unsaturated cyclic ketimines was realized through a ligand-controlled strategy. By employing different chiral olefin ligands, a ligand-controlled switch in the reaction regioselectivity was attained for the first time. The reactions allow the synthesis of highly valuable α,α-disubstituted chiral allylic amines and enantioenriched 1,4-adducts. Further product transformation provided easy access to various quaternary carbon-containing chiral amines and amino acid derivatives bearing multifunctional groups.

Rhodium-catalyzed asymmetric addition of organoboron reagents to electron-deficient olefins,[1,2] imines,[3,4] and carbonyl compounds[5] constitutes an important and powerful method for the construction of carbon−carbon bonds. Among the electron-deficient conjugated substrates, α,β-unsaturated imines represent an intriguing class of substrates, as they might be subjected to 1,4-addition and 1,2-addition simultaneously under rhodium catalysis. Surprisingly, despite the fact that many beautiful examples of asymmetric 1,2-addition of imines have been realized,[3,4] to our knowledge, the utilization of α,β-unsaturated imines for stereoselective 1,2-addition to access chiral allylic amines has not been reported. On the other hand, asymmetric 1,4-addition of α,β-unsaturated imines is also rarely explored, in sharp contrast to the achievements with α,β-unsaturated ketones/esters/amides.[1,2] Only recently has a successful example of rhodium-catalyzed enantioselective 1,4-addition of arylboronic acids to α,β-unsaturated imino esters using a chiral bicyclic bridgehead phosphoramidite ligand been disclosed, which allowed the synthesis of γ,γ-diaryl-α,β-dehydroamino esters.[6] Therefore, achieving either 1,4- or 1,2-addition of α,β-unsaturated imines in a regio- and enantioselective manner remains a particularly challenging task. It would be ideal to develop a regiodivergent highly enantioselective addition of α,β-unsaturated imines through ligand/catalyst tuning.

Over the past few years, our group has been interested in rhodium-catalyzed enantioselective addition of imines using simple chiral olefins as ligands.[3c,f,g,4c,g−k,7] With challenging α,β-unsaturated cyclic *N*-sulfonyl ketimines, we recently developed a catalytic stereoselective double arylation process through rhodium-catalyzed sequential 1,4-/1,2-addition reactions with arylboronic acids by employing different chiral olefin ligands, which allowed the rapid construction of benzosulfamidates bearing two *gem*-diaryl stereocenters with high enantiopurities (Scheme 1a).[4j] Despite the notable success in achieving regio- and enantioselective 1,4-addition of these α,β-unsaturated ketimines, it is exceedingly difficult to access α,α-disubstituted chiral allylic amines via direct 1,2-addition by tuning the catalyst system. The low reactivity of the C═N may be attributed to the double conjugation with the C═C and aromatic ring in the molecule. To address this issue, we designed an unprecedented type of α,β-unsaturated cyclic ketimines[8] and wanted to achieve

**Scheme 1. Rh-Catalyzed Asymmetric 1,4-/1,2-Addition of α,β-Unsaturated Ketimines**

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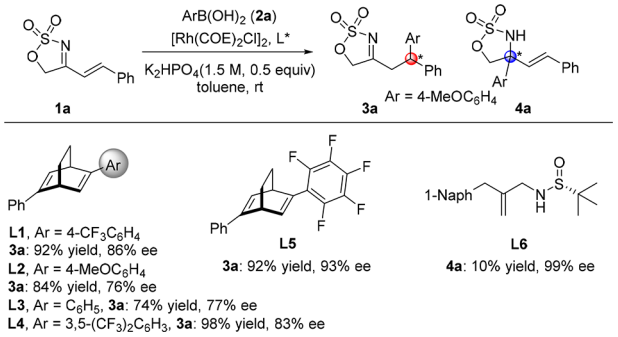
both asymmetric 1,4- and 1,2-addition through direct control of the chiral ligand. Herein, we describe the first example of rhodium-catalyzed site-selective asymmetric addition of arylboronic acids to $\alpha,\beta$-unsaturated cyclic ketimines (Scheme 1b). A ligand-controlled switch in the reaction regioselectivity was attained.

Our initial investigation was carried out by evaluating the reaction of the newly designed $\alpha,\beta$-unsaturated five-membered cyclic *N*-sulfonyl imine **1a** with *p*-methoxyphenylboronic acid **2a** under conditions similar to our previously reported ones in the presence of the optimal $C_1$-symmetric chiral diene ligand[9] and branched sulfur-olefin ligand (Scheme 2). The diene ligand

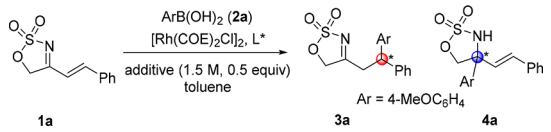
**Scheme 2. Ligand Screening**




**L1** exhibited truly excellent catalytic reactivity for 1,4-addition, giving the corresponding $\beta$-*gem*-diaryl substituted ketimine **3a** solely with commendable enantioselectivity (86% ee). For comparison, $C_2$-symmetric diene ligand **L3** was evaluated; however, a much lower ee was obtained. Gratifyingly, by examination of the substituents on the phenyl ring of chiral [2.2.2]dienes, ligand **L5** bearing a pentafluorobenzene moiety was found to be superior to the others, giving the sole 1,4-addition product in 92% yield and 93% ee. On the other hand, we were very pleased to find that the sulfur-olefin ligand **L6** showed exclusive 1,2-addition performance, which led to the formation of the desired quaternary-containing 1,2-adduct **4a** with extremely high ee (99%), albeit in low yield (10%).

Inspired by these promising results, further examination on the reaction parameters including additive, solvent, temperature, catalyst loading, and reactant ratio were subsequently carried out (Table 1). As for 1,4-addition, among the various additives (entries 1−5), the enantioselectivity remained nearly constant and KOH gave the best yield (94%) (entries 1−5). Varying the solvent did not furnish better results (entries 6−7). Lowering the catalyst loading would lead to a somewhat diminished yield, while still maintaining the enantioselectivity (entry 8). Notably, no 1,2-adducts formation was observed even with an excess amount of arylboronic acid **2a**. In the study of 1,2-addition, we investigated the effect of temperature (entries 10−14). An increase to 41% was observed at 80 °C (entry 11); however, no further improvement was attained at higher temperature (entry 12). The screening of additives indicated that KF could facilitate rhodium/sulfur-olefin **L6** in exhibiting better catalytic activity, giving the 1,2-adduct **4a** in 49% yield with 98% ee (entry 16). In the presence of 1.0 equiv of aqueous KF (1.5 M), the reaction afforded **4a** in a slightly increased yield (54%, entry 17). Fortunately, increasing the amount of *p*-methoxyphenylboronic acid was found to be beneficial to the 1,2-addition yield. With 6 equiv of arylboronic acid, the reaction proceeded with high efficiency and great

**Table 1. Optimization of Reaction Conditions**[a]




| | | | | 3a | | 4a | |
|---|---|---|---|---|---|---|---|
| entry | L | additive | $t$ (°C) | yield (%)[b,c] | ee (%) | yield (%)[b,c] | ee (%) |
| 1 | **L5** | $K_2HPO_4$ | rt | 92 | 93 | 0 | – |
| 2 | **L5** | KOH | rt | **94** | **94** | 0 | – |
| 3 | **L5** | $K_3PO_4$ | rt | 90 | 93 | 0 | – |
| 4 | **L5** | KF | rt | 76 | 92 | 0 | – |
| 5 | **L5** | $KHF_2$ | rt | 88 | 93 | 0 | – |
| 6[d] | **L5** | KOH | rt | 15 | 93 | 0 | – |
| 7[e] | **L5** | KOH | rt | 79 | 93 | 0 | – |
| 8[f] | **L5** | KOH | rt | 85 | 93 | 0 | – |
| 9 | **L6** | $K_2HPO_4$ | rt | <5 | – | 10 | 99 |
| 10 | **L6** | $K_2HPO_4$ | 50 | <5 | – | 20 | 98 |
| 11 | **L6** | $K_2HPO_4$ | 80 | <5 | – | 41 | 98 |
| 12 | **L6** | $K_2HPO_4$ | 100 | <5 | – | 40 | 97 |
| 13 | **L6** | $KHF_2$ | 80 | <5 | – | 47 | 97 |
| 14 | **L6** | $K_3PO_4$ | 80 | <5 | – | 34 | 97 |
| 15 | **L6** | KOH | 80 | <5 | – | 30 | 95 |
| 16 | **L6** | KF | 80 | <5 | – | 49 | 98 |
| 17[g] | **L6** | KF | 80 | <5 | – | 54 | 98 |
| 18[g,h] | **L6** | KF | 80 | <5 | – | 60 | 98 |
| 19[g,i] | **L6** | KF | 80 | <5 | – | **86** | **98** |

[a]The reaction was carried out with 0.1 mmol of $\alpha,\beta$-unsaturated cyclic imine **1a** and 0.2 mmol of **2a** in the presence of 5 mol % of [Rh]/**L** with 1.0 mL of solvent. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Dioxane was used. [e]DCE was used. [f]With 3 mol % of [Rh]/**L5**. [g]1.0 equiv of KF (1.5 M) was used. [h]4 equiv of **2a** were used. [i]6 equiv of **2a** were used.

stereoselectivity, providing the corresponding **4a** in good yield (86%) and enantioselectivity (98% ee) (entry 19). Under these conditions, the formation of only a trace amount of 1,4-addition products was detected, suggesting the unique site-differentiation ability of the catalyst. It is worth noting that this is the first achievement of rhodium-catalyzed enantioselective 1,2-addition of $\alpha,\beta$-unsaturated imines.

After identifying the two optimal reaction conditions, we proceeded to evaluate the scope of the reactions. As revealed in Scheme 3, 1,4-addition reactions involving $\alpha,\beta$-unsaturated cyclic *N*-sulfonyl ketimine **1a** with a wide range of arylboronic acids **2** bearing diverse steric and electronic properties were all found to be successful, affording the corresponding $\beta$-gem-diaryl substituted ketimines without any accompanying 1,2-products in high yields and excellent enantioselectivities (85−99% ee). Imines bearing diverse substituents on the phenyl ring were also tolerated in this reaction. By simply switching acceptor and donor aryl substituents, both enantiomers of the product could be smoothly accessed (**3g** vs **3g′**). Of particular note is that more challenging $\beta$-alkyl substituted substrates were also suitable for the conjugate addition (**3q−v**). Having established the highly enantioselective 1,4-addition, we turned our attention to the generality of 1,2-addition at the ketimine site using sulfur-olefin ligand **L6** (Scheme 4). In most cases, the reaction proceeded well and gave uniformly high enantioselectivities (95−98% ee). With arylboronic acid bearing an *para*-electron-donating group, the reaction of $\alpha,\beta$-unsaturated cyclic ketimine **1a** produced the desired 1,2-adducts in moderate to



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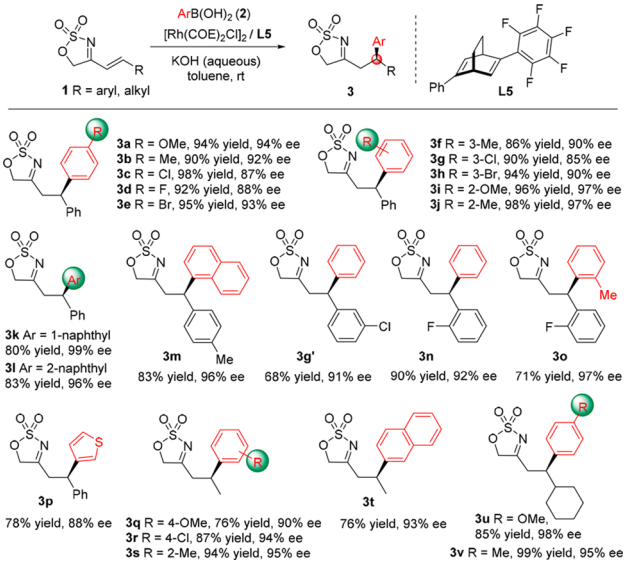
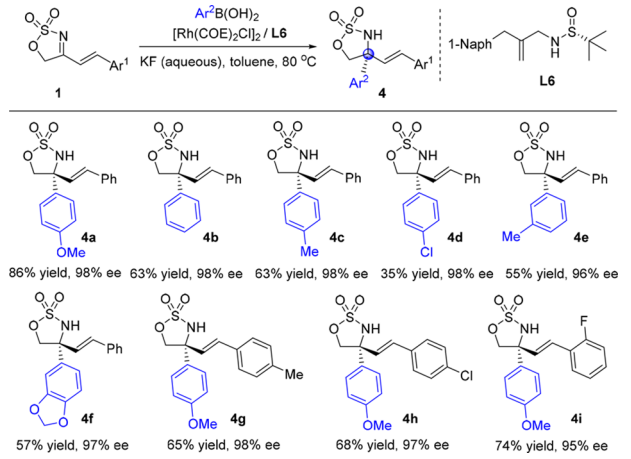
**Scheme 3. Rh-Catalyzed Asymmetric Enantioselective 1,4-Addition of α,β-Unsaturated Ketimines**[a,b,c]




[a]The reaction was carried out with 0.1 mmol of α,β-unsaturated cyclic ketimine **1**, 2.0 equiv of arylboronic acid **2** in the presence of 5.0 mol % of [Rh]/**L5**, and KOH (1.5 M, 0.5 equiv) in 1.0 mL toluene at rt for 1−8 h. [b]Isolated yield. [c]Determined by chiral HPLC.

**Scheme 4. Rh-Catalyzed Asymmetric Enantioselective 1,2-Addition of α,β-Unsaturated Ketimines**[a,b,c]

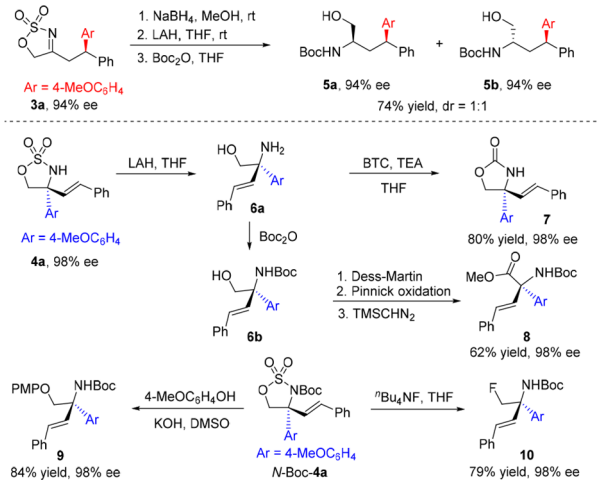



[a]The reaction was carried out with 0.1 mmol of α,β-unsaturated cyclic ketimine **1**, 2.0 equiv of arylboronic acid **2** in the presence of 5.0 mol % of [Rh], 5.0 mol % of ligand **L6**, and KF (1.5 M, 1.0 equiv) in 1.0 mL toluene at 80 °C for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC.

good yields. However, the use of arylboronic acid having an electron-withdrawing group on the phenyl ring led to an obvious yield drop, while the enantioselectivity still remained excellent (**4d**). The *meta*-substituted arylboronic acids were compatible with the 1,2-addition, and the corresponding products (**4e**, **4f**) could be obtained in moderate yields. The substitution pattern and the electronic nature of the aryl group attached to the double bond of α,β-unsaturated ketimines did not seem to affect the enantioselectivity of the products (**4g**, **4h**, **4i**). When a less reactive β-methyl substituted substrate was employed, the yield was low (<20%), albeit in excellent enantioselectivity (99% ee). With the use of alkylboronic acids, neither 1,4-addition nor 1,2-addition occurred.

To demonstrate the synthetic utility, we have applied this method for the synthesis of some structurally and biologically interesting compounds (Scheme 5). The ring-opening reaction

**Scheme 5. Synthetic Transformations of Addition Products**




of the 1,4-adduct **3a** was carried out by treatment with $NaBH_4$ and LAH at room temperature, and followed by the *N*-Boc-protection of amine, giving *gem*-diaryl substituted amino alcohol diastereomers **5a** and **5b** without loss of enantiopurity. Similarly, ring cleavage of the 1,2-adducts with LAH could also occur easily, leading to highly functional α,α-disubstituted chiral allylic amines bearing a quaternary stereocenter and β-amino alcohol framework, which are otherwise difficult to be prepared. Such compounds are extremely valuable synthetic building blocks. For example, exposure of the ring-opening product **6a** with BTC smoothly provided 4,4-disubstituted 2-oxazolidinone **7** in 80% yield. Through a three-step conversion involving Dess-Martin oxidation, Pinnick oxidation ($NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, $^tBuOH$, $H_2O$),[10] and esterification from the Boc-protected intermediate **6b**, challenging α,α-disubstituted-β,γ-unsaturated amino acid ester **8** could be readily obtained. On the other hand, upon treatment of appropriate nucleophiles, uniquely functionalized tetrasubstituted chiral allylic amines such as **9** and **10** could be successfully furnished.[11,12] It should be noted that no ee erosion was observed in all these transformations. Thus, we were able to flexibly construct diverse chiral amines bearing different substituent groups in a highly enantioenriched manner, which could be useful in medicinal chemistry.

Single-crystal X-ray analysis of the 1,4-adduct **3e** and compound **6b** (CCDC 1819866, 1819867) derived from the 1,2-adduct **4a** allowed us to determine the absolute configurations of the newly formed carbon stereocenters (Figure 1). To elucidate the stereocontrol of the 1,4-addition using the diene ligand and the 1,2-addition using sulfur-olefin ligand, two possible transition-state models were illustrated. Although the detailed reaction mechanism remains unclear, the switch in the reaction regioselectivity suggests two unique coordination modes of the rhodium and substrate in the presence of two different ligands. In both cases, the sulfonyl moiety of the imine substrates orients away from the substitution group attached to the double bond of the olefin ligands to minimize the steric interaction. Thus, the stereo-



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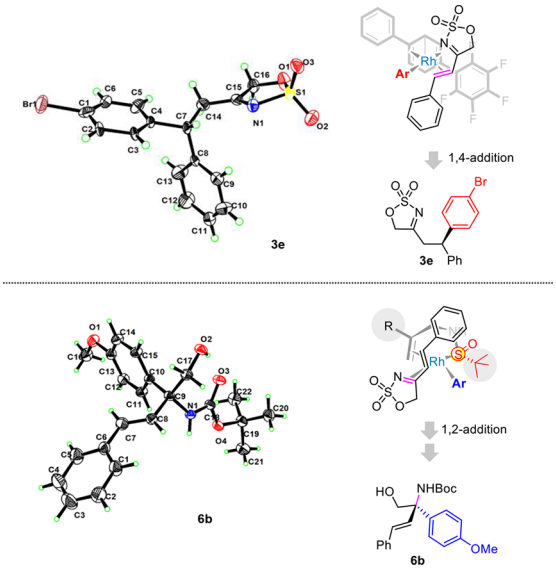


**Figure 1.** X-ray crystal structures of **3e** and **6b** and the proposed transition-state models.

chemical outcome of both addition reactions could be assigned by analogy assuming the same reaction pathway.

To summarize, we have developed a site-selective rhodium-catalyzed asymmetric 1,4-/1,2-addition of arylboronic acids to the challenging $\alpha,\beta$-unsaturated cyclic ketimines through a ligand-controlled strategy. $C_1$-symmetric chiral diene and branched chiral sulfur-olefin were utilized to afford stereospecific 1,4- and 1,2-adducts, respectively. This protocol enables efficient synthesis of various chiral $\beta$-gem-diaryl substituted ketimines and $\alpha,\alpha$-disubstituted chiral allylic amines bearing multifunctional groups in a highly regio- and enantioselective manner under mild conditions. Of particular note, this method provides the first achievement of rhodium-catalyzed regioselective asymmetric 1,2-addition to $\alpha,\beta$-unsaturated ketimines. Owing to the synthetic importance of the obtained products and the difficulty of their accessibility by other transformations, we believe that this work should be of great interest to both organic and medicinal chemists.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00289.

Experimental procedures and spectroscopic data of all new compounds (PDF)

### Accession Codes

CCDC 1819866−1819867 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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