Rhodium/diene-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides†

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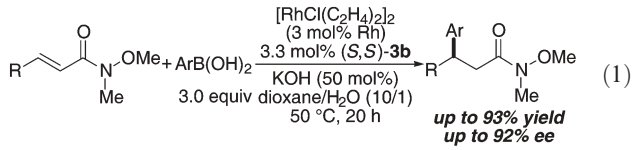
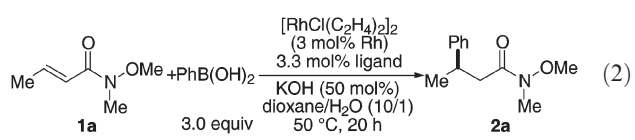
Rhodium/chiral diene (*S*,*S*)-3b complex has been found to effectively catalyze the 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides, furnishing useful β-chiral Weinreb amides in high enantioselectivity.

N-Methoxy-*N*-methylamides (also known as Weinreb amides) have shown their wide utility as effective acylating agents since their first introduction by Weinreb in 1981.[1] Due to the stability and versatility of these amides, it would be highly valuable if we could efficiently construct Weinreb amides bearing stereogenic centers in a highly enantio-enriched form. In this regard, we envisaged that an asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated Weinreb amides should be an efficient and straightforward method for the construction of such compounds enantioselectively.[2] Here we describe how a rhodium/chiral diene complex can effectively catalyze the 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides, furnishing β-chiral Weinreb amides with high enantioselectivity (eqn. 1).[3,4]



(1)

Initially, we employed compound **1a** (R = Me) as a model substrate and studied the effect of ligand in the presence of 3 mol% of rhodium at 50 °C (eqn. 2). Although (*S*)-binap is known to be the ligand of choice in the rhodium-catalyzed asymmetric 1,4-addition of arylboron nucleophiles to α,β-enamides,[5] the use of (*S*)-binap with this substrate led to a low yield of 1,4-adduct **2a** in moderate ee (32% yield, 77% ee). Changing the ligand from (*S*)-binap to chiral diene ligand (*R*,*R*)-**3a**[6] improved the yield, but the enantioselectivity stayed moderate (75% yield, 70% ee). Fortunately, however, benzyl substituted diene ligand (*S*,*S*)-**3b**[6] was found to be more effective, furnishing the desired 1,4-adduct in higher yield and ee (92% yield, 90% ee).[7]



(2)

† Electronic supplementary information (ESI) available: experimental procedures and compound characterization data. See http://www.rsc.org/suppdata/cc/b5/b502921j/

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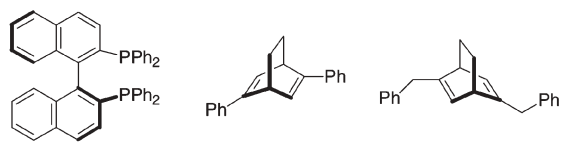
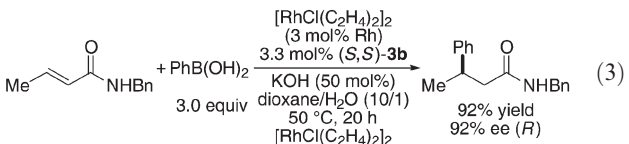
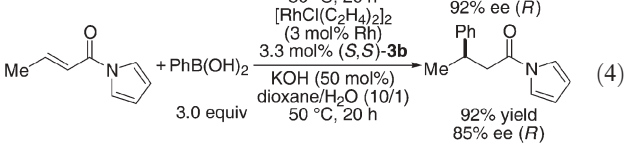


Under these conditions with (*S*,*S*)-**3b**, several other α,β-unsaturated Weinreb amides bearing a primary alkyl, a secondary alkyl, or an aryl group at the β-position can also be phenylated in good yield and enantioselectivity (74–92% yield, 80–90% ee; Table 1, entries 1–4). With respect to the nucleophilic component, various aromatic groups can be installed under the same conditions in high yield and ee as well (83–93% yield, 86–92% ee; entries 5–8).

These reaction conditions using a Rh/(*S*,*S*)-**3b** catalyst are not limited to α,β-unsaturated Weinreb amide substrates. Thus, other α,β-unsaturated amides, such as a benzylamide and an acyl pyrrole, are also suitable substrates for these 1,4-addition reactions, achieving high yield and ee (92% yield, 85–92% ee; eqns. 3 and 4).



(3)



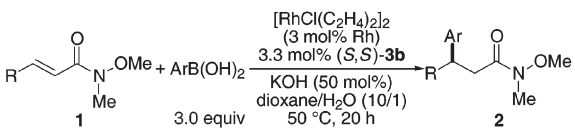
(4)

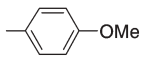
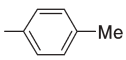
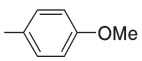
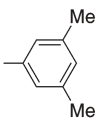
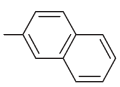
To show further the utility of this process, 1,4-adduct **2a** (90% ee) was converted to various β-chiral carbonyl compounds as shown in Scheme 1. Thus, the corresponding methyl ketone, aldehyde, and methyl ester can be obtained in high yield with no erosion of ee (75–94% yield).

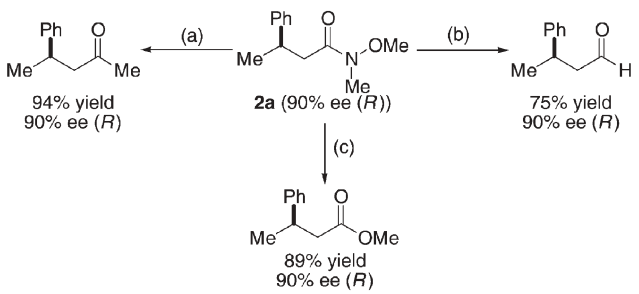
The stereochemical outcome of these 1,4-addition reactions using Rh/(*S*,*S*)-**3b** as a catalyst can be rationalized by the α*si* face approach of the substrate to avoid the steric hindrance created by the substituents on ligand (*S*,*S*)-**3b** (Fig. 1). This model is consistent with the observed stereoselectivity of the 1,4-addition products under these conditions.

In summary, we have developed a rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides. By employing chiral diene (*S*,*S*)-**3b** as a ligand, we have efficiently coupled a range of arylboronic acids with these substrates in good enantiomeric excess. The utility of this process has been further demonstrated by employing other α,β-unsaturated amides and by converting the 1,4-adducts to other useful carbonyl compounds. Future studies will explore further

Table 1 Rh/(*S*,*S*)-**3b**-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides: scope



Entry	–R	–Ar	Yield (%)	Ee (%)
1	–Me		92	90 (*R*)
2			86	87 (*R*)
3			74	86 (*S*)
4			91	80 (*R*)
5	–Me		83	89 (*R*)
6	–Me		93	87 (*R*)
7	–Me		84	92 (*R*)
8	–Me		90	86 (*R*)



Scheme 1 Conversion of Weinreb amide **2a** to various β-chiral carbonyl compounds. Conditions: (a) MeMgI, THF, r.t.; (b) DIBAL-H, THF, −78 °C; (c) H_2SO_4, MeOH, reflux.

development of chiral diene ligands and their application to various transition metal-catalyzed asymmetric processes.‡

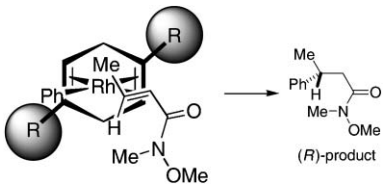


Fig. 1 Proposed stereochemical pathway for the asymmetric 1,4-addition to an α,β-unsaturated Weinreb amide.

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Notes and references

‡ General procedure for the 1,4-addition reaction: A solution of $[RhCl(C_2H_4)_2]_2$ (1.2 mg, 6.2 μmol Rh) and ligand (6.6 μmol) in 1,4-dioxane (0.5 mL) was stirred for 10 min at room temperature. KOH (0.1 mL, 0.10 mmol; 1.0 M aqueous) was then added to it, and the resulting solution was stirred for 5 min at room temperature. $ArB(OH)_2$ (0.60 mmol) and α,β-unsaturated Weinreb amide (0.20 mmol) were then added to this with additional 1,4-dioxane (0.5 mL). The resulting mixture was stirred for 20 h at 50 °C, and was then passed through a pad of silica gel with EtOAc. The solvent was removed under vacuum and the residue was purified by silica gel PTLC with Et_2O/hexane to afford the desired 1,4-adduct.

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