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Iridium/Chiral Diene-Catalyzed Asymmetric 1,6-Addition of Arylboroxines to α,β,γ,δ-Unsaturated Carbonyl Compounds

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Transition-metal-catalyzed asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds has been rapidly developed over the past decade.[1] On the contrary, progress in asymmetric addition to extended conjugated systems (e.g., 1,6-addition to α,β,γ,δ-unsaturated carbonyl compounds) has been modest to date because of the difficulty of controlling the regioselectivity as well as the enantioselectivity. Copper reagents and catalysts are often used for selective 1,6-addition reactions,[1−3] and reports of asymmetric 1,6-addition reactions catalyzed by rhodium[4] and copper have recently appeared.[5−7] Successful examples of asymmetric 1,6-addition to dienones and dienoates having β-substituents to suppress the competing 1,4-addition have been reported by us (Rh),[4] Fillion (Cu),[5] and Alexakis (Cu).[6] In 2008, Feringa succeeded in the highly enantioselective 1,6-addition of alkyl Grignard reagents to simple acyclic dienoates by use of a Cu/bisphosphine catalyst.[7] Here we report the enantioselective conjugate addition of arylboroxines to linear α,β,γ,δ-unsaturated carbonyl compounds with perfect 1,6-selectivity, which is realized by the use of a chiral iridium complex as a catalyst.[8−10]

We recently reported that perfect 1,6-selectivity is achieved in the addition of arylboroxines to α,β,γ,δ-unsaturated carbonyl compounds catalyzed by a hydroxoiridium complex coordinated with 1,5-cyclooctadiene (cod).[11] The findings prompted us to use chiral diene ligands[12] for the asymmetric variants of the iridium-catalyzed 1,6-addition. Of chiral diene ligands in our hands, C_2-symmetric tetrafluorobenzobarrelenes (tfb's)[13] were found to display high catalytic activity and enantioselectivity (Scheme 1 and entry 1 in Table 1). Thus, treatment of (3*E*,5*E*)-3,5-heptadien-2-one (**1a**) with phenylboroxine (**2m**) (3 equiv of B) in the presence of $[IrCl((S,S)\text{-Me-tfb*})]_2$[13b,14] (5 mol % Ir) and K_2CO_3 (5 mol %) in MeOH at 30 °C for 20 h gave a 90% yield of a mixture of 1,6-adducts consisting of (*Z*)-6-phenyl-4-hepten-2-one (**3am**) as the major isomer, its *E* isomer **4am**, and the conjugate enone **5am** (**3am**/**4am**/**5am** = 86/10/4).[15] The mixture was subjected to isomerization mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give conjugate enone **5am** as the major isomer (**5am**/**4am** = 94/6). Silica gel chromatography gave pure **5am** in 85% yield (based on **1a**), whose ee was 99% (*S*).[16] The use of phenyl- and benzyl-substituted tfb ligands (Ph-tfb* and Bn-tfb*)[13c] gave, after isomerization, **5am** with 97 and 99% ee, respectively (Table 1, entries 2 and 3). A chiral diene ligand having a bicyclo[2.2.2]octadiene framework (Bn-bod*)[17] displayed high enantioselectivity (99% ee), although the yield of **5am** was moderate (56%) because of incomplete conversion of starting enone **1a** (entry 4). The ligand (*R*)-**L1**,[18] which is readily derived from a natural product, gave **5am** in 97% ee (entry 5). The 1,6-addition was not observed at all in the presence of iridium catalysts with bisphosphine ligands (binap, segphos) or a phosphoramidite.[19]

The results obtained for the iridium-catalyzed 1,6-addition of arylboroxines to dienones are summarized in Table 2. Phenylation of dienones substituted with Et or ^{t}Bu at the carbonyl carbon and

Scheme 1

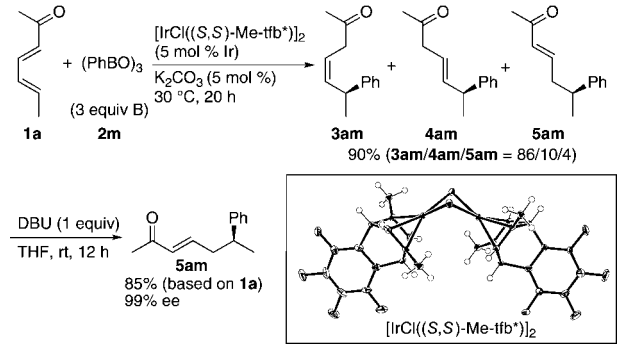
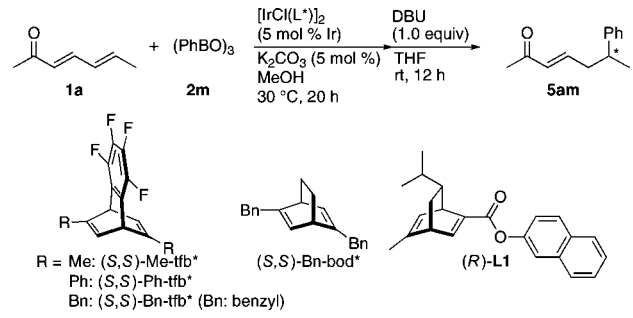


Table 1. Ligand Screening[a]



entry	ligand (L*)	isolated yield of **5am** (%)	ee (%)
1	(*S*,*S*)-Me-tfb*	85	99 (*S*)
2	(*S*,*S*)-Ph-tfb*	72	97 (*S*)
3	(*S*,*S*)-Bn-tfb*	73	99 (*S*)
4	(*S*,*S*)-Bn-bod*	56	99 (*S*)
5	(*R*)-**L1**	67	97 (*R*)

[a] Reaction conditions: dienone **1a** (0.30 mmol), phenylboroxine (**2m**) (0.30 mmol, 3 equiv of B), $[IrCl(L^*)]_2$ (5 mol % Ir), K_2CO_3 (5 mol %), MeOH (0.90 mL). See the Supporting Information for details.

Me or Pr at the δ-position gave, after isomerization, the corresponding conjugate enones **5bm**−**dm** in good yields with ≥90% ee (entries 2−4). Aryl groups having several substituents were successfully introduced in the reactions of **1a** or **1b** with **2n**−**r**, giving the corresponding 1,6-addition products (**5an**, **5bn**−**br**) in good yields with very high enantioselectivity (98−99% ee; entries 5−10).

This iridium-catalyzed reaction can also be applied to conjugate dienamides (**1e** and **1f**) and a dienoate **1g** to give, after hydrogenation of the initially formed 1,6-adducts, the corresponding δ-arylated amides and ester in high yields with high enantioselectivity (Table 3).

The present asymmetric 1,6-addition enables a short synthesis of a natural product, curcumene[20] (Scheme 2). Thus, rhodium-catalyzed 1,4-hydrosilylation[21] of conjugate enone **5an** obtained

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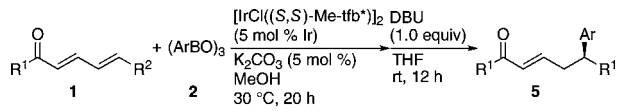
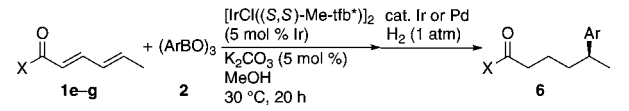
Table 2. 1,6-Addition to Dienones[a]



entry	R^1	R^2	Ar	yield (%)[b]	ee (%)
1	Me	Me (**1a**)	Ph (**2m**)	85 (**5am**)	99
2	Et	Me (**1b**)	Ph (**2m**)	84 (**5bm**)	98
3	^{t}Bu	Me (**1c**)	Ph (**2m**)	81 (**5cm**)	90
4	Et	Pr (**1d**)	Ph (**2m**)	57 (**5dm**)	97
5	Me	Me (**1a**)	4-MeC_6H_4 (**2n**)	76 (**5an**)	99
6	Et	Me (**1b**)	4-MeC_6H_4 (**2n**)	81 (**5bn**)	99
7	Et	Me (**1b**)	3-MeC_6H_4 (**2o**)	85 (**5bo**)	99
8[c]	Et	Me (**1b**)	4-ClC_6H_4 (**2p**)	83 (**5bp**)	99
9[c]	Et	Me (**1b**)	4-FC_6H_4 (**2q**)	82 (**5bq**)	99
10	Et	Me (**1b**)	2-naphthyl (**2r**)	76 (**5br**)	98

[a] See the Supporting Information for details. [b] Isolated yield. [c] Reaction for 48 h.

Table 3. 1,6-Addition to Dienamides and a Dienoate[a]



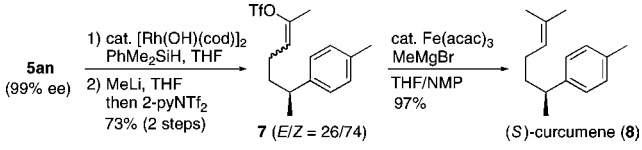
entry	X	Ar	yield (%)[b]	ee (%)
1	NPh_2 (**1e**)	Ph (**2m**)	99 (**6em**)	93
2	NPh_2 (**1e**)	4-MeC_6H_4 (**2n**)	95 (**6en**)	96
3	NPh_2 (**1e**)	4-$MeOC_6H_4$ (**2s**)	96 (**6es**)	93
4	NMe(OMe) (**1f**)	Ph (**2m**)	95 (**6fm**)	96
5[c]	O^{t}Bu (**1g**)	Ph (**2m**)	93 (**6gm**)	93

[a] Hydrogenation was carried out with $[Ir(cod)(PCy_3)(py)]PF_6$ (4 mol %) for entries 1−4 and Pd/C (4 mol %) for entry 5. See the Supporting Information for details. [b] Isolated yield of **6**. [c] Reaction at 50 °C for 12 h.

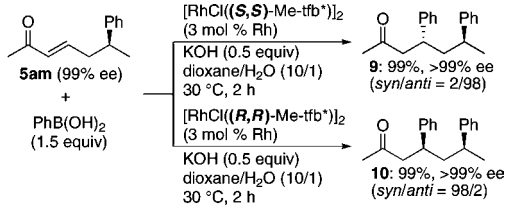
with 99% ee (Table 2, entry 5) followed by triflation via a lithium enolate gave alkenyl triflate **7**. Iron-catalyzed cross-coupling[22] with MeMgBr gave (*S*)-curcumene (**8**) {$[\alpha]_D^{20} = +48$ (*c* 1.19, $CHCl_3$); lit[20b] $[\alpha]_D^{20} = +43$ (*c* 2, $CHCl_3$) for (*S*)-curcumene}.

We also succeeded in the stereoselective synthesis of doubly phenylated ketones by using rhodium-catalyzed asymmetric 1,4-addition to conjugate enone **5am** (Scheme 3). The use of a rhodium complex coordinated with (*S*,*S*)-Me-tfb* in the asymmetric addition of phenylboronic acid to **5am** gave *anti*-diphenylated ketone **9**, while the use of (*R*,*R*)-Me-tfb* gave *syn*-adduct **10** with high stereoselectivity.

Scheme 2



Scheme 3



In summary, we have developed an iridium-catalyzed asymmetric 1,6-addition of arylboroxines to α,*β*,*γ*,*δ*-unsaturated carbonyl compounds that is realized by the use of an iridium/chiral diene complex and gives *δ*-arylated carbonyl compounds in high yields with high enantioselectivity.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystal data are reported in the Supporting Information.
(15) The reactions of **1a** with $PhBF_3K$, 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane, and $PhSnBu_4$ also gave the 1,6-addition products in 62, 84, and 58% yield, respectively.
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