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# Electronic tuning of chiral diene ligands in iridium-catalyzed asymmetric 1,6-addition of arylboroxines to δ-aryl-α,β,γ,δ-unsaturated ketones†

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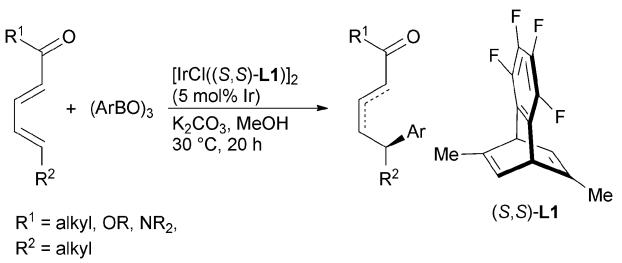
**Asymmetric addition of arylboroxines to δ-aryl-α,β,γ,δ-unsaturated ketones proceeded in the presence of an iridium catalyst coordinated with a chiral diene ligand to give high yields of δ-diaryl ketones with very high enantioselectivity.**

The transition metal-catalyzed asymmetric addition of organometallic reagents to α,β-unsaturated carbonyl compounds offers a practical access to a variety of chiral carbonyl compounds, where diverse aryl, alkenyl, and alkyl groups are introduced with high regioselectivity and enantioselectivity.[1] On the other hand, the addition to extended conjugated systems such as α,β,γ,δ-unsaturated ketones has been a challenging objective in organic synthesis because of the difficulty of controlling the regioselectivity (*e.g.*, 1,2-, 1,4-, and 1,6-addition).[2] Copper reagents and catalysts have been reported to display high 1,6-selectivity[3,4] and, recently, successful examples of copper-catalyzed enantioselective 1,6-addition to dienones and dienoates have been reported by Feringa,[5] Alexakis,[6] and Fillion[7] *et al.* Asymmetric rhodium catalysis has also been reported in the 1,6-addition of arylzinc reagents to dienones having β-substituents to suppress the competing 1,4-addition.[8] Iron-catalyzed diastereoselective addition of arylmagnesium reagents to dienoates having a chiral auxiliary has been reported by Urabe *et al.*[9–11] In this context, we recently reported that the enantioselective conjugate addition of arylboroxines to linear α,β,γ,δ-unsaturated carbonyl compounds with perfect 1,6-selectivity is realized by the use of a chiral iridium complex as a catalyst (Scheme 1).[12] The iridium complex coordinated with the chiral tetrafluorobenzobarrelene (tfb) ligand **L1**,[13] which is substituted with methyl groups, displayed a high catalytic activity and enantioselectivity in the addition of arylboroxines to dienyl ketones that have alkyl groups at the δ-position. Unfortunately, however, the catalyst displayed no catalytic activity toward the reaction of δ-aryl dienyl ketones, which would provide diarylmethine stereogenic centers. Here we report that the electronic tuning of chiral diene ligands develops a catalytic activity of the iridium complex in the asymmetric 1,6-addition of arylboroxines to δ-aryl dienyl ketones giving the 1,6-addition products in high yields with high enantioselectivity.




**Scheme 1** Iridium-catalyzed enantioselective 1,6-addition to α,β,γ,δ-unsaturated carbonyl compounds.

We found that the electronic nature of the diene ligands has a significant influence on the catalytic activity of the iridium complexes in the reaction of δ-aryl dienyl ketones (Table 1). Treatment of (2*E*,4*E*)-1,5-diphenyl-2,4-pentadien-1-one (**1a**) with *p*-tolylboroxine (**2s**) (1.5 equiv. of B) in the presence of $[IrCl((S,S)\text{-}\mathbf{L1})]_2$ (2 mol% of Ir) and $K_2CO_3$ (5 mol%) in $MeOH/CH_2Cl_2$ (4 : 1) at 30 °C for 24 h, which is one of the best catalytic conditions for the asymmetric addition to δ-alkyl-substituted dienyl carbonyl compounds, did not give any of the addition products (entry 1). The reaction using ligand **L2** substituted with benzyl groups also resulted in no formation of the 1,6-adducts (entry 2). On the other hand, the use of ligand **L3** substituted with phenyl groups gave 1,6-addition products as a mixture of non-conjugated (*Z*)-enone **3as** and its (*E*)-isomer **4as** in 21% yield (entry 3). The enantioselectivity was determined to be 99.5% ee by HPLC analysis of conjugated enone **5as** formed by isomerization with DBU. The catalytic activity was greatly improved by the use of ligand **L4**, which is substituted with 4-(trifluoromethyl)phenyl groups, giving the addition products in 64% yield (entry 4). Electron-deficient chiral dienes **L5** and **L6** bearing ester groups at the alkene moieties, which are prepared from ditriflate **L0**[13b] as shown in Scheme 2, also displayed high performance in the present reaction (entries 5 and 6), and the reaction using 2-naphthyl ester **L6** gave 93% yield of the addition products, which were transformed into conjugated enone **5as** in 81% yield (entry 6). The ee of **5as** was over 99.5% ee.[14] The tetrafluorobenzo (tfb) moiety of the diene ligands is important for the catalytic activity of the iridium complex. Thus, the ligand

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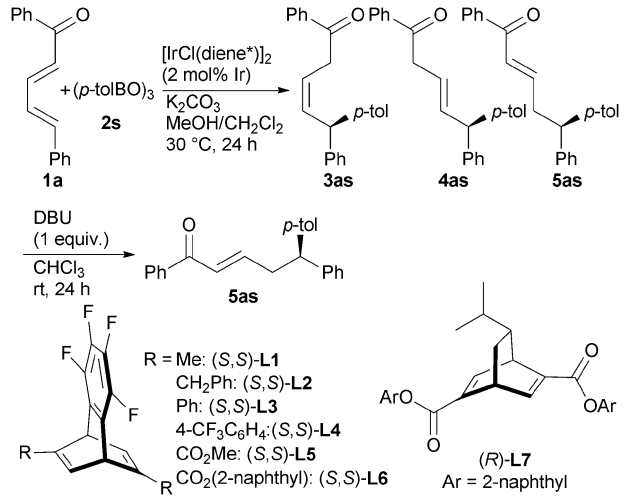
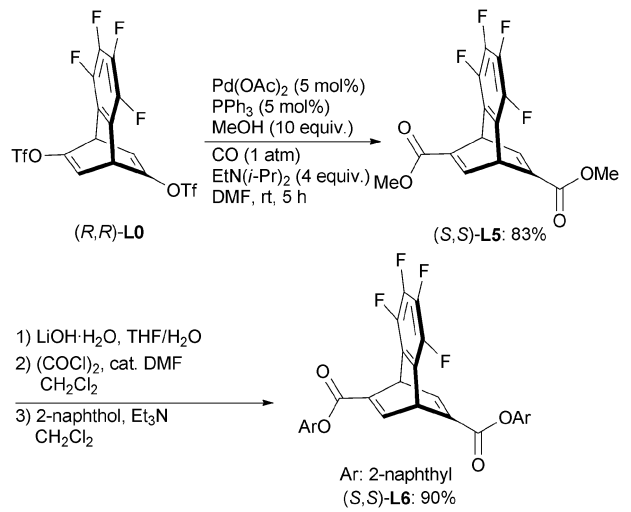
**Table 1** Iridium-catalyzed 1,6-addition of **2s** to dienone **1a**[a]




| Entry | Ligand | Yield[b] (%) | Yield of **5as**[c] (%) | ee[d] (%) |
|---|---|---|---|---|
| 1 | **L1** | 0 | — | — |
| 2 | **L2** | 0 | — | — |
| 3 | **L3** | 21 (71 : 29 : 0) | 14 | 99.5 |
| 4 | **L4** | 64 (39 : 58 : 3) | 49 | > 99.5 |
| 5 | **L5** | 62 (30 : 65 : 5) | 46 | > 99.5 |
| 6 | **L6** | 93 (33 : 64 : 3) | 81[e] | > 99.5 |
| 7 | **L7** | 6 (50 : 50 : 0) | —[f] | —[f] |

[a] Reaction conditions: **1a** (0.20 mmol), *p*-tolylboroxine (**2s**) (0.10 mmol, 1.5 equiv. of B), $[IrCl(diene*)]_2$ (2 mol% of Ir), $K_2CO_3$ (5 mol%), $MeOH/CH_2Cl_2$ (4 : 1, 1.0 mL) at 30 °C for 24 h. [b] Combined yield of **3as–5as** determined by $^1H$ NMR. The values in parenthesis are the ratios of **3as**, **4as**, and **5as**. [c] Yield of **5as** determined by $^1H$ NMR after treatment with DBU. [d] Determined by chiral HPLC analysis. [e] Isolated yield. [f] Not determined. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

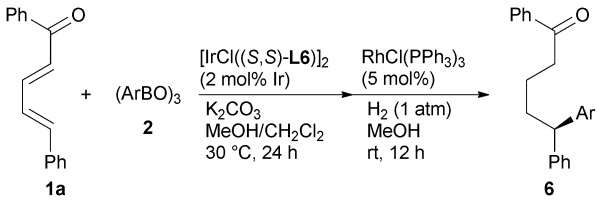



**Scheme 2** Preparation of ligands **L5** and **L6**.

**L7**, which lacks the tfb moiety but has a bicyclo[2.2.2]octadiene skeleton and 2-naphthyl ester groups at the diene moieties, gave only 6% yield of the addition products (entry 7) in contrast to the high catalytic activity of **L6** based on the tfb moiety (entry 6).

The present catalytic system can be applied to the asymmetric addition of several arylboroxines **2** to dienone **1a** to give, after hydrogenation of the initially formed 1,6-adducts,

**Table 2** Scope of arylboroxines **2**[a]

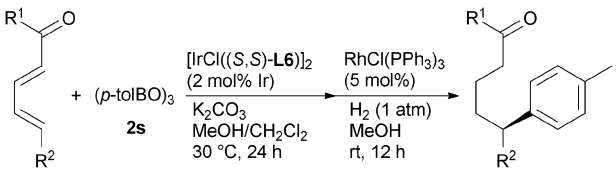



| Entry | Ar | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | 4-$MeC_6H_4$ (**2s**) | 93 (**6as**) | > 99.5 |
| 2 | 3-$MeC_6H_4$ (**2t**) | 90 (**6at**) | 99.5 |
| 3[d] | 4-$MeOC_6H_4$ (**2u**) | 87 (**6au**) | 99.0 |
| 4[d] | 3,4-$(OCH_2O)C_6H_3$ (**2v**) | 86 (**6av**) | 99.4 |
| 5 | 4-$ClC_6H_4$ (**2w**) | 82 (**6aw**) | 99.3 |
| 6[d,e] | 3,4-$Cl_2C_6H_3$ (**2x**) | 79 (**6ax**) | > 99.5 |
| 7 | 4-$FC_6H_4$ (**2y**) | 91 (**6ay**) | > 99.5 |

[a] Reaction conditions: **1a** (0.20 mmol), arylboroxine **2** (0.10 mmol, 1.5 equiv. of B), $[IrCl((S,S)\text{-}\mathbf{L5})]_2$ (2 mol% of Ir), $K_2CO_3$ (5 mol%), $MeOH/CH_2Cl_2$ (4 : 1, 1.0 mL) at 30 °C. Hydrogenation was carried out in the presence of $RhCl(PPh_3)_3$ (5 mol%) in MeOH under $H_2$ (1 atm). [b] Isolated yield of **6**. [c] Determined by chiral HPLC analysis. [d] Performed with 0.20 mmol of arylboroxine **2**. [e] For 48 h.

the corresponding δ-diaryl ketones in high yields with over 99.0% ee (Table 2). Aryl groups having a variety of substituents at the *meta* and *para* position of phenyl (**2s–2y**) were successfully introduced into the δ-position of the dienone **1a** with high enantioselectivity (entries 1–7), but the reaction with *o*-tolylboroxine

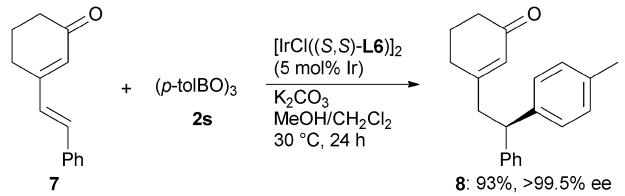
**Table 3** Iridium-catalyzed 1,6-addition of **2s** to dienone **1**[a]




| Entry | $R^1$ | $R^2$ | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | Ph | Ph (**1a**) | 93 (**6as**) | > 99.5 |
| 2 | 4-$CF_3C_6H_4$ | Ph (**1b**) | 93 (**6bs**) | > 99.5 |
| 3 | 4-$FC_6H_4$ | Ph (**1c**) | 84 (**6cs**) | > 99.5 |
| 4 | 4-$ClC_6H_4$ | Ph (**1d**) | 96 (**6ds**) | > 99.5 |
| 5 | 3-$ClC_6H_4$ | Ph (**1e**) | 95 (**6es**) | > 99.5 |
| 6[d] | 4-$MeC_6H_4$ | Ph (**1f**) | 91 (**6fs**) | 99.0 |
| 7[d] | 4-$MeOC_6H_4$ | Ph (**1g**) | 91 (**6gs**) | > 99.5 |
| 8[d] | 2-$MeOC_6H_4$ | Ph (**1h**) | 91 (**6hs**) | > 99.5 |
| 9[d] | 2-Furyl | Ph (**1i**) | 95 (**6is**) | > 99.5 |
| 10[d] | 2-Thienyl | Ph (**1j**) | 95 (**6js**) | 99.0 |
| 11 | Ph | 2-$BrC_6H_4$ (**1k**) | 92 (**6ks**) | > 99.5 |
| 12 | Ph | 2-$MeOC_6H_4$ (**1l**) | 90 (**6ls**) | 99.1 |
| 13[d] | Me | Ph (**1m**) | 79 (**6ms**) | > 99.5 |
| 14[d] | Et | Ph (**1n**) | 76 (**6ns**) | 99.5 |
| 15[d] | Bu | Ph (**1o**) | 82 (**6os**) | 98 |
| 16 | Ph | Me (**1p**) | 96 (**6ps**) | 98 |
| 17 | Ph | Pr (**1q**) | 87 (**6qs**) | 99.0 |
| 18 | Ph | *i*-Pr (**1r**) | 93 (**6rs**) | > 99.5 |

[a] Reaction conditions: **1a** (0.20 mmol), arylboroxine **2** (0.10 mmol, 1.5 equiv. of B), $[IrCl((S,S)\text{-}\mathbf{L6})]_2$ (2 mol% of Ir), $K_2CO_3$ (5 mol%), $MeOH/CH_2Cl_2$ (4 : 1, 1.0 mL) at 30 °C. Hydrogenation was carried out in the presence of $RhCl(PPh_3)_3$ (5 mol%) in MeOH under $H_2$ (1 atm). [b] Isolated yield of **6**. [c] Determined by chiral HPLC analysis. [d] Performed with $[IrCl((S,S)\text{-}\mathbf{L6})]_2$ (5 mol% of Ir).




**Scheme 3** Iridium-catalyzed asymmetric 1,6-addition to dienone **7**.

gave only 3% yield of the addition products (the result is not shown).

The results obtained for the 1,6-addition of *p*-tolylboroxine (**2s**) to several dienones are summarized in Table 3, where the initial 1,6-adducts were subjected to hydrogenation. The addition of the *p*-tolyl group to dienones having substituted phenyls (**1b–1h**) and heteroaromatic groups (2-furyl (**1i**) and 2-thienyl (**1j**)) at carbonyl ($R^1$) gave after hydrogenation the corresponding ketones **6bs–6js** in high yields with over 99.0% ee (entries 2–10). The addition to dienones **1k** and **1l** substituted with *o*-bromo- and *o*-methoxyphenyl at δ-position ($R^2$) gave high yields of the corresponding 1,6-adducts **6ks** and **6ls** (entries 11 and 12). Dienones substituted with alkyl groups at carbonyl (**1m–1o**, entries 13–15) or at δ-position (**1p–1r**, entries 16–18) are also good substrates to give the corresponding ketones **6ms–6rs** in high yields with high enantioselectivity.

The reaction of non-linear dienone (*E*)-3-styryl-2-cyclohexenone (**7**) with *p*-tolylboroxine (**2s**) in the presence of the Ir/(*S*,*S*)-**L6** (5 mol% of Ir) catalytic system also proceeded with perfect 1,6-selectivity and enantioselectivity to give the conjugated enone **8** in 93% yield (Scheme 3).

In summary, we have developed an iridium-catalyzed asymmetric 1,6-addition of arylboroxines to dienones bearing an aryl group at the δ-position, which was realized by the use of an iridium/electron-deficient chiral diene catalyst. The reaction gave 1,6-adducts, which have a diarylmethine stereogenic center, in high yields with very high enantioselectivity.

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14 The absolute configuration of **5as** was determined to be *R* by analogy with (*R*)-**5au**. See ESI† for details.