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Iridium/chiral phosphoramidite–olefin complex-catalysed enantioselective [3+2] annulation of *ortho*-ketoarylboron compounds with conjugated dienes†

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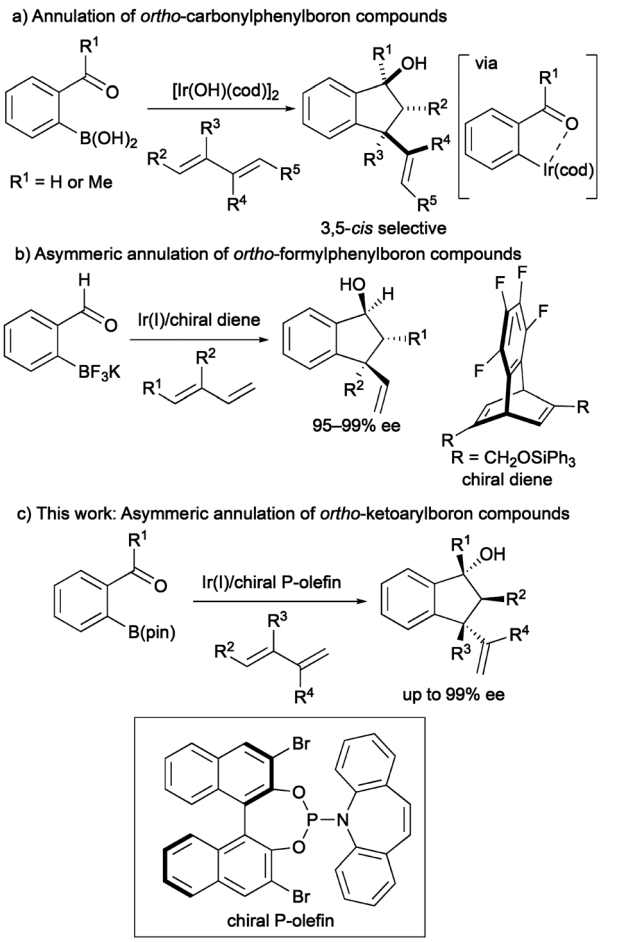
The iridium-catalysed enantioselective [3+2] annulation of *ortho*-ketoarylboron compounds with conjugated dienes proceeded to give chiral indanol derivatives bearing an all-carbon quaternary stereogenic center in high yields with high enantioselectivity. Chiral phosphoramidite–olefin ligands were effective for the high reactivity and enantioselectivity.

Indane derivatives, which have a fused structure of benzene ring and five-membered ring, are important structural motifs in several chiral drugs and natural products.[1] Transition-metal-catalysed stereoselective [3+2] annulation is one of the useful methods for the synthesis of indane derivatives, and *ortho*-functionalized arylboron reagents have often been used with unsaturated hydrocarbons such as allenes, alkynes and conjugated dienes for the [3+2] annulation.[2] In this respect, we reported iridium-catalyzed [3+2] annulation of *ortho*-carbonylated arylboronic acids with 1,3-dienes giving indanol derivatives with high regio- and diastereoselectivity (Scheme 1a).[3] The reaction proceeded *via* an *ortho*-carbonylaryliridium(I) species, which is generated from a hydroxoiridium complex and the corresponding arylboronic acids. The enantioselective annulation was also achieved by use of a chiral diene ligand (Scheme 1b).[4,5] However, the successful reaction was limited to *ortho*-formylarylboron compounds, and *ortho*-ketoarylboron reagents could not be applied to the annulation because of the low reactivity. In addition, high reaction temperature to promote the reaction can probably cause ligand exchange between the chiral diene ligand and the 1,3-diene, which exists in excess to the Ir catalyst. Unfortunately, the use of chiral diphosphine ligands, which strongly coordinate to the iridium, inhibited the reaction. It follows that new ligands bearing appropriate coordination ability are required for the realization of the iridium-catalyzed asymmetric annulation. In this context, we focused on chiral phosphine–olefin hybrid ligands,[6,7] which have stronger coordination ability than diene ligands, and are unique ligands that combine the coordination properties of both phosphines and olefins.[7,8] Here we report that iridium/chiral phosphine–olefin complexes are effective in catalysing asymmetric



Scheme 1 Ir-catalysed [3+2] annulation.

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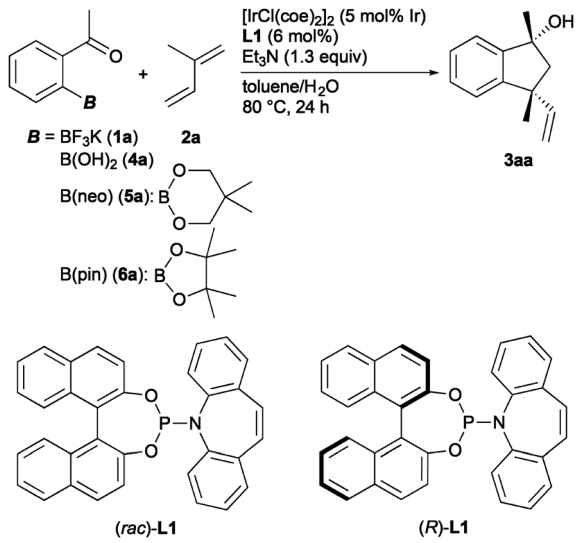
[3+2] annulation of *ortho*-keto arylboron compounds with 1,3-dienes.

In the first set of experiments, annulation of *ortho*-acetylphenylboron compound **1a** with isoprene (**2a**) was examined under several reaction conditions (Table 1). Treatment of **1a** with **2a** (3.0 equiv.) in toluene/H_2O (1 : 1) at 80 °C for 24 h in the presence of $[IrCl(coe)_2]_2$ (5 mol% of Ir, coe = cyclooctene), (*rac*)-**L1** (6 mol%), and Et_3N (1.3 equiv.) gave the corresponding product *cis*-**3aa** exclusively as a single isomer in 58% yield (entry 1).[9] The reaction in 1,4-dioxane or 1,2-dichloroethane instead of toluene decreased the yield of **3aa** (entries 2 and 3). The lower diastereoselectivity (*cis* : *trans* = 73 : 27) was observed in the reaction without triethylamine, which was added to inhibit the hydrolysis reaction of **1a** by the iridium catalysis (entry 4).[10] Water was necessary for the reaction (entry 5). The reaction without ligand (*rac*)-**L1**, where Ir(I)/isoprene complex is formed, did not procced (entry 6). Fortunately, the use of (*R*)-**L1**[7a] gave **3aa** with good enantioselectivity (85% ee, entry 7). It was found that a rhodium complex with (*rac*)-**L1** also promoted the present reaction albeit with low yield (20%, entry 8). Boron functional groups influenced the yield and enantioselectivity (entries 9–11). Commercially available *ortho*-acetylboronic acid (**4a**) showed slightly lower reactivity compared with potassium aryltrifluoroborate **1a** (entry 9). Boron esters can also be applied to the present reaction (entries 10 and 11), and, in particular, pinacol ester **6a** displayed excellent reactivity, thus giving **3aa** in 79% yield with 86% ee (entry 11). The absolute configuration of **3aa** obtained using (*R*)-**L1** was determined to be (1*R*,3*R*) by HPLC analysis of a separately synthesized (1*R*,3*R*)-**3aa** (see the ESI† for details).

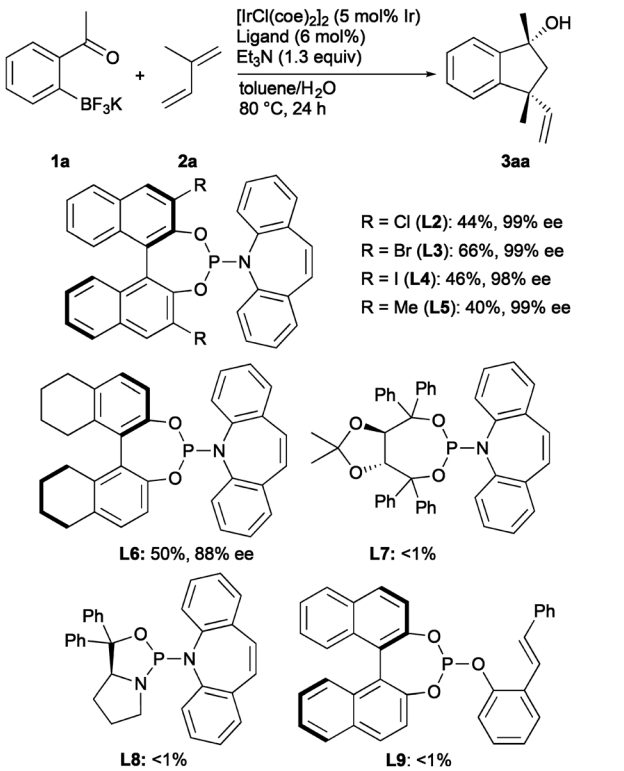
Screening results of chiral phosphoramidite–olefin ligands using **1a** as the substrate are shown in Scheme 2. We took an approach to revise the binaphthyl moiety due to easy synthesis and availability. The use of phosphoramidite–olefin ligands with a 3,3′-disubstituted binaphthyl moiety (**L2–L5**) gave **3aa** with excellent enantioselectivity (98–99% ee). In particular, **L3** substituted with a 3,3′-dibromo-substituted binaphthyl showed the best reactivity and enantioselectivity (66%, 99% ee). As the steric hindrance of the 3,3′-substituents further increased, the product yield decreased (**L4** and **L5**). H8-Binol backbone in **L6** did not improve the enantioselectivity. The phosphoramidite–olefin ligand derived from (*R*,*R*)-TADDOL (**L7**)[7b] or L-prolinol (**L8**)[7b] did not induce the catalytic activity. Phosphite–olefin

Table 1 Ir-catalyzed annulation of **1a** with isoprene (**2a**)[a]



Entry	Changes from standard conditions	Yield[b] (%)	ee[c] (%)
1	No changes	58	—
2	1,4-Dioxane instead of toluene	43	—
3	$ClCH_2CH_2Cl$ instead of toluene	31	—
4	Without Et_3N	43[d]	—
5	Without H_2O	15	—
6	Without (*rac*)-**L1**	<1	—
7	(*R*)-**L1** instead of (*rac*)-**L1**	66	85
8	$[RhCl(coe)_2]_2$ instead of $[IrCl(coe)_2]_2$	20	—
9	**4a** instead of **1a** with (*R*)-**L1**	55	87
10	**5a** instead of **1a** with (*R*)-**L1**	31	86
11	**6a** instead of **1a** with (*R*)-**L1**	79	86

[a] Reaction conditions: **1a** or **4a–6a** (0.20 mmol), **2a** (0.60 mmol, 3.0 equiv.), $[IrCl(coe)_2]_2$ (0.0050 mmol, 5 mol% of Ir), **L1** (0.012 mmol, 6 mol%) and Et_3N (0.26 mmol, 1.3 equiv.) in toluene (0.8 mL) and H_2O (0.8 mL) at 80 °C for 24 h under N_2 atmosphere. Unless otherwise stated, the ratio of diastereomers is >99 : 1. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC analysis. [d] The product was obtained as a mixture of diastereomers (*cis*/*trans* = 73 : 27).

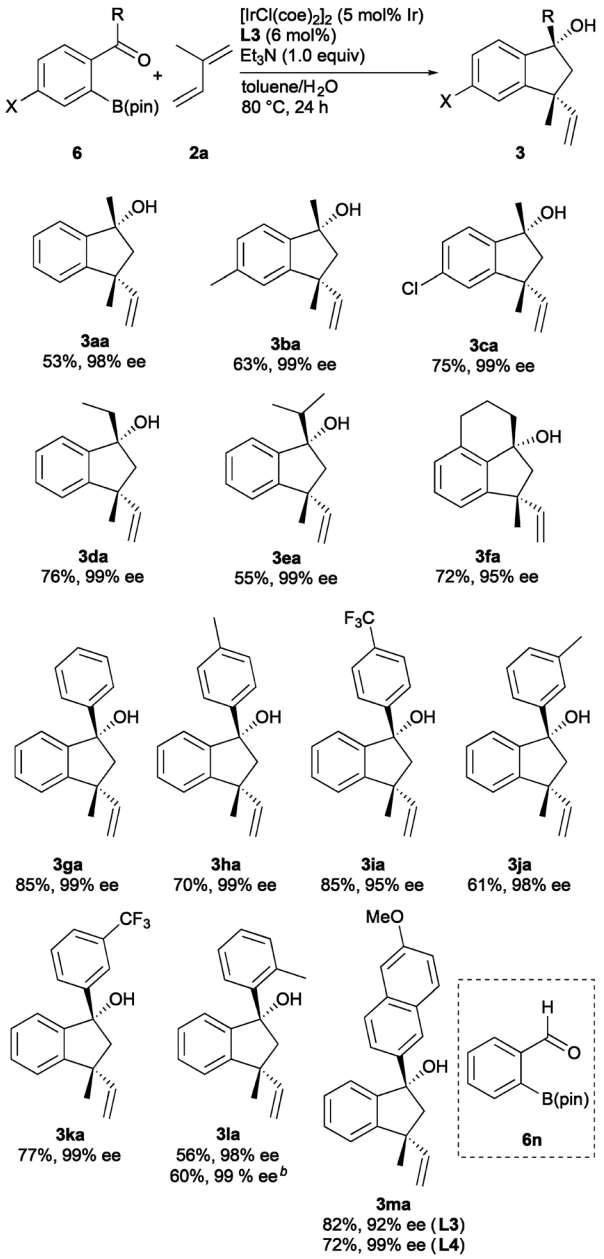


Scheme 2 Screening of chiral phosphoramidite–olefin ligands. [a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.60 mmol, 3.0 equiv.), $[IrCl(coe)_2]_2$ (0.0050 mmol, 5 mol% of Ir), ligand (0.012 mmol, 6 mol%) and Et_3N (0.26 mmol, 1.3 equiv.) in toluene (0.8 mL) and H_2O (0.8 mL) at 80 °C for 24 h under N_2 atmosphere. The ratio of diastereomers is >99 : 1. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC analysis.

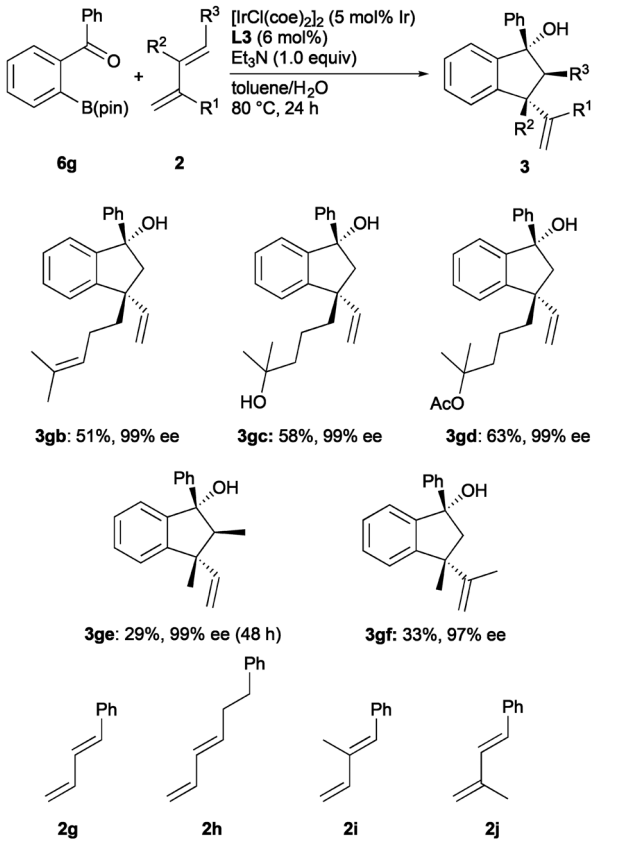
ligand **L9**,[8] which is used for Rh-catalyzed asymmetric 1,4-additions, could not be applied to the present annulation.

The scope of *ortho*-ketoarylboron esters **6**, some of which are readily available by C–H borylation,[11] is shown in Scheme 3.[12] The reaction of **6a** with isoprene (**2a**) gave **3aa** in 53% yield with 98% ee. *Para*-substituted acetophenone derivatives **6b** and **6c** underwent the annulation to give the corresponding products **3ba** and **3ca**, respectively, with high enantioselectivity (99% ee). Arylboron esters **6d** and **6e** substituted with ethyl and isopropyl groups reacted efficiently to give the corresponding products **3da** and **3ea** in 76 and 55% yields, respectively, with complete enantioselectivity. The reaction of α-tetralone derivative **6f** gave tricyclic product **3fa** in 72% yield with 95% ee. Boron ester **6g** bearing a benzoyl group is also a good substrate to give the corresponding indanol **3ga** in 85% yield with 99% ee. *Para*-, *meta*-, and *ortho*-substituted benzoylphenylboron esters **6h–6l** efficiently participated in the reaction to give the corresponding products **3ha–3la** in good yields (56–85%) with excellent selectivity (95–99% ee). The reaction using 1.0 mmol of **6l** gave **3la** in 60% yield with 99% ee. In the reaction of arylboron ester **6m**, which has a 6-methoxynaphthyl group, the use of **L4** was effective in displaying the high enantioselectivity (99% ee) of the product **3ma**. Unfortunately, the use of *o*-formylphenylboron ester **6n** resulted in the formation of unidentified complex mixtures.

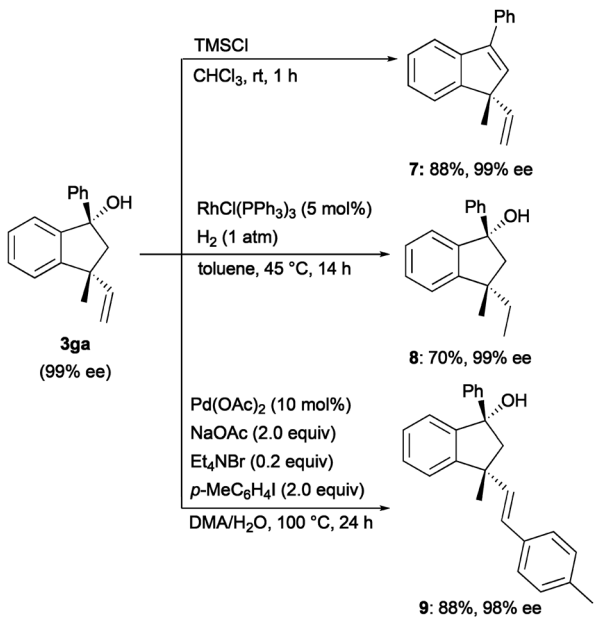
The results obtained for the reaction of several 1,3-dienes with **6g** are shown in Scheme 4. 2-Substituted 1,3-dienes such as myrcene (**2b**), myrcenol (**2c**), and acetylated myrcenol **2d** could be applied to the reaction of **6g** to give the corresponding products **3gb–3gd** with high enantioselectivity. The reactions of 3-methyl-1,3-pentadiene (**2e**) and 2,3-dimethyl-1,3-butadiene (**2f**) also displayed high enantioselectivity, albeit with the



Scheme 3 Ir-catalyzed asymmetric annulation of **6** with isoprene (**2a**).[a] [a] Reaction conditions: **6** (0.20 mmol), **2a** (0.60 mmol, 3.0 equiv.), $[IrCl(coe)_2]_2$ (0.0050 mmol, 5 mol% of Ir), **L3** (0.012 mmol, 6 mol%), and Et_3N (0.20 mmol, 1.0 equiv.) in toluene (0.8 mL) and H_2O (0.8 mL) at 80 °C for 24 h under N_2 atmosphere. The ratio of diastereomers is >99 : 1. [b] 1.0 mmol scale reaction.



Scheme 4 Ir-catalyzed asymmetric annulation of **6g** with dienes **2**.[a] [a] Reaction conditions: **6g** (0.20 mmol), **2** (0.60 mmol, 3.0 equiv.), $[IrCl(coe)_2]_2$ (0.0050 mmol, 5 mol% of Ir), **L3** or **L4** (0.012 mmol, 6 mol%) and Et_3N (0.20 mmol, 1.0 equiv.) in toluene (0.8 mL) and H_2O (0.8 mL) at 80 °C for 24 h under N_2 atmosphere. The ratio of diastereomers is >99 : 1.



Scheme 5 Transformation of **3ga**.

somewhat low yields. Unfortunately, however, dienes **2g–2j** were not applicable to the present reaction.

Indanol **3ga** was converted into several compounds while maintaining the stereochemistry (Scheme 5). Dehydration of **3ga** with trimethylsilyl chloride (TMSCl) in $CHCl_3$ gave indene **7** in 88% yield.[13] Rh(I)-catalysed hydrogenation of **3ga** gave indanol **8** in 70% yield.[14] Mizoroki–Heck reaction of indanol **3ga** with *p*-iodotoluene gave **9** in 80% yield.[15]

In summary, we have developed the asymmetric [3+2] annulation of *ortho*-ketoarylboron compounds with 1,3-dienes catalysed by the iridium/chiral phosphoramidite–olefin complex. The use of a new chiral phosphoramidite–olefin ligand with a 3,3′-bromo-substituted binaphthyl structure showed almost complete enantioselectivity of the annulation products bearing an all-carbon quaternary center.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

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