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Iridium-Catalyzed Enantioselective Allyl−Allyl Cross-Coupling of Racemic Allylic Alcohols with Allylboronates

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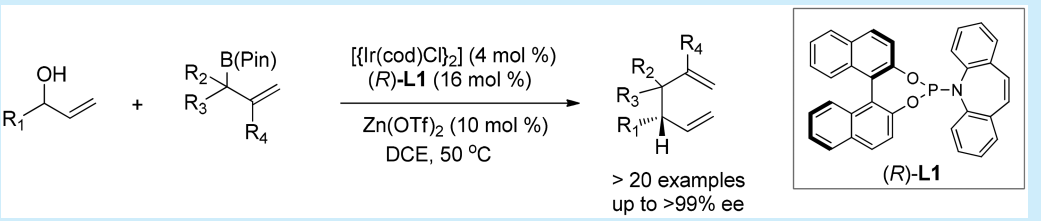
Supporting Information



ABSTRACT: Carreira's iridium-(P, olefin) phosphoramidite-based catalytic system that allows asymmetric allyl−allylboronate cross-coupling with high enantioselectivity is reported. This transformation tolerates a large variety of racemic branched allylic alcohols and allylboronate substrates. The utility of the coupling is demonstrated in a concise catalytic asymmetric synthesis of (−)-preclamol.

Catalytic asymmetric formation of carbon−carbon bonds is one of the most important challenges in modern organic synthesis.[1] Of a particular significance is the metal-catalyzed allyl−allyl cross-coupling between allylic electrophile and allylic nucleophile that provides enantioenriched chiral 1,5-diene structures.[2] Since chiral 1,5-dienes are abundant in naturally occurring terpenes and also serve as valuable intermediates and building blocks in organic synthesis, several methods of their preparation have been reported.[3] However, the formation of the linear, achiral dienes and poor enantioselectivity of the branched dienes render this allyl−allyl cross-coupling challenging. In 2010, Morken and co-workers made a breakthrough in this research and described the Pd-catalyzed regio- and enantioselective cross-coupling of allylic carbonates with allylboronates[4] (Scheme 1). Later, the Feringa group reported a Cu-catalyzed asymmetric allylation of allyl bromide with allyl Grignard reagents.[5] In 2014, Carreira and co-workers developed a direct Ir-catalyzed cross-coupling between branched, racemic allylic alcohols and simple olefins to provide 1,5-dienes.[6a] In the same year, they further reported an enantioselective allyl−allylsilane cross-coupling involving racemic branched allylic alcohols and allylsilanes, expanding the range of accessible chiral 1,5-dienes.[6b]

Although allylboronates as the nucleophiles have been utilized to the Pd-catalyzed asymmetric cross-coupling of allylic carbonate in the pioneering work from the Morken group, the similar Ir-catalyzed allylation of allylboronates has yet to be reported. To our knowledge, there is only one case in the literature reported by Jarvo and Barker, which documents the Ir-catalyzed allylation of ketones using allylboronic ester, leading to tertiary homoallylic alcohols.[7] In recent years, iridium-catalyzed allylations have emerged as a versatile tactic for the synthesis of chiral building blocks.[8,9] Inspired by the recent seminal and systematic studies by the Carreira group,[10] we proposed that the nucleophilic allylboronic ester would be coupled with an electrophilic, branched, racemic allylic alcohol under the conditions of Carreira's Ir-(P, olefin) catalyst system. This would offer an alternative to the known allyl−allyl cross-coupling reactions. Here we wish to report our results.

In the initial screening studies, we were pleased to find that allylboronates could be used as excellent nucleophiles. As shown in Table 1, with a catalyst system consisting of

Scheme 1. Catalytic Asymmetric Allyl−Allyl Cross-Coupling Methodologies

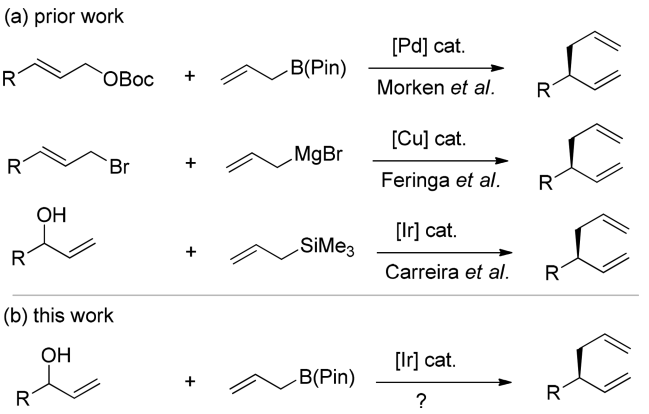


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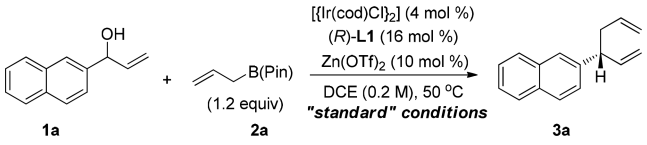
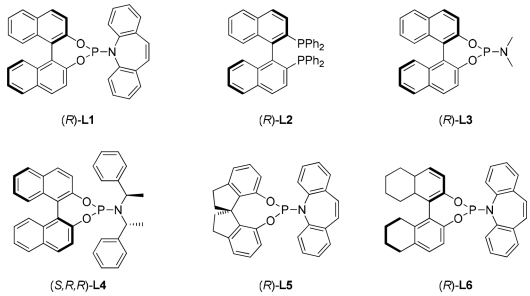
Table 1. Selected Optimization Studies for the Ir-Catalyzed Allyl−Allylboronate Cross-Coupling[a]



entry	variation from the "standard" conditions	yield (%)[b]	ee (%)[c]
1	none	82	>99
2	$Sc(OTf)_3$ instead of $Zn(OTf)_2$	23	98
3	TFA instead of $Zn(OTf)_2$	NR	–
4	1,4-dioxane instead of DCE	29	94
5	[Ir] (2 mol %), **L1** (8 mol %)	65	98
6	**L2** instead of **L1**	NR	–
7	**L3** instead of **L1**	decomp	–
8	**L4** instead of **L1**	decomp	–
9	**L5** instead of **L1**	decomp	–
10	**L6** instead of **L1**	51	98

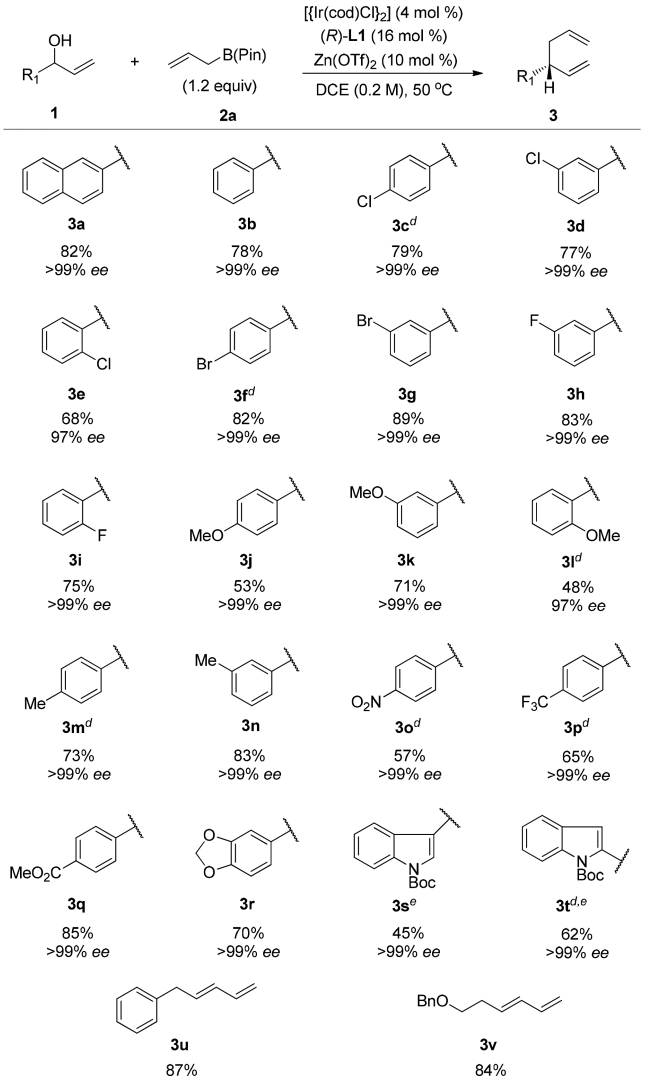


[a]Reactions were run on 0.1 mmol scale. [b]Isolated yields. [c]Determined by chiral HPLC analysis. – = not determined.

$[\{Ir(cod)Cl\}_2]$ (4 mol %) and Carreira's ligand (R)-**L1** (16 mol %) in the presence of $Zn(OTf)_2$ as the promoter and DCE as the solvent, the test substrate 2-naphthylvinyl carbinol **1a** underwent a smooth reaction with allylboronate **2a** to provide branched diene **3a** in 82% yield and >99% ee (Table 1, entry 1). It is noteworthy that in our hands the undesired, achiral linear diene was not observed. The use of other Lewis acid such as $Sc(OTf)_3$ as promoter led to low yield, albeit with high ee value (entry 2). A switch to protic acid TFA gave no reaction (entry 3). In 1,4-dioxane the reaction was performed with reduced efficiency, and **3a** could be obtained in a poor yield and slightly lowered enantioselectivity (entry 4). When the catalyst loading was decreased to 2 mol %, some reduction in yield (entry 5) was observed. Interestingly, when Carreira's ligand (*R*)-**L1** was replaced by other phosphoramidite ligands such as (*R*)-**L3**, (*S*,*R*,*R*)-**L4**, or SPINOL-derived (*R*)-**L5**, a complete decomposition of starting material occurred (entries 7−9).[11] Furthermore, when BINAP **L2** was used instead of (*R*)-**L1**, no reaction took place (entry 6), while octahydro-BINOL-derived (*R*)-**L6** took effect and led to a moderate yield (51%) with 98% ee (entry 10). Lastly, in accord with Carreira's recent mechanistic studies,[10q] we also found that better yields were obtained when the catalyst was prepared in the presence of allyl alcohol. For a detailed evaluation of the reaction parameters, see the Supporting Information.

Having established optimal conditions, we next set out to explore the substrate scope and generality of this allyl−allyl coupling reaction by using allylboronate **2a** as summarized in Scheme 2. 2-Naphthyl- (**3a**) and phenyl- (**3b**) vinyl carbinols underwent the reaction giving excellent isolated yields and enantioselectivity. Substrates with substituents on the aromatic ring all afforded the corresponding chiral 1,5-dienes. Several halogenated (**3c**−**3i**) substrates gave the products in good yields and >99% ee. Substrates with methoxyl group were also well tolerated (**3j**−**3l**). Interestingly, *o*- and *p*-OMe substitutions on the phenyl ring were less reactive than that of *m*-OMe. Other substitutes such as methyl (**3m** and **3n**) and ester (**3q**) could be employed. Although substrates possessing electron-withdrawing groups, such as nitro (**3o**) and trifluoromethyl (**3p**), were less reactive, reactions of these substrates still provide products in moderate yields with excellent enantioselectivity. In addition, the carbinols derived from heteroaromatic systems (**3r**−**3t**) could be employed as well. Currently, one limitation of the reaction is that aliphatic allylic alcohols did not undergo the described allyl−allylboronate cross-coupling, while 1,3-dienes (**3u** and **3v**) were obtained.

Scheme 2. Substrate Scope of the Enantioselective Allyl−Allylboronate Cross-Coupling[a,b,c]



[a]Unless otherwise noted, all reactions were performed on a 0.20 mmol scale under the standard conditions. [b]Isolated yields. [c]Enantiomeric excess values were determined by HPLC on a chiral stationary phase. [d]HPLC analysis performed after derivatization. [e]Reaction was run with 0.1 M reaction concentration.

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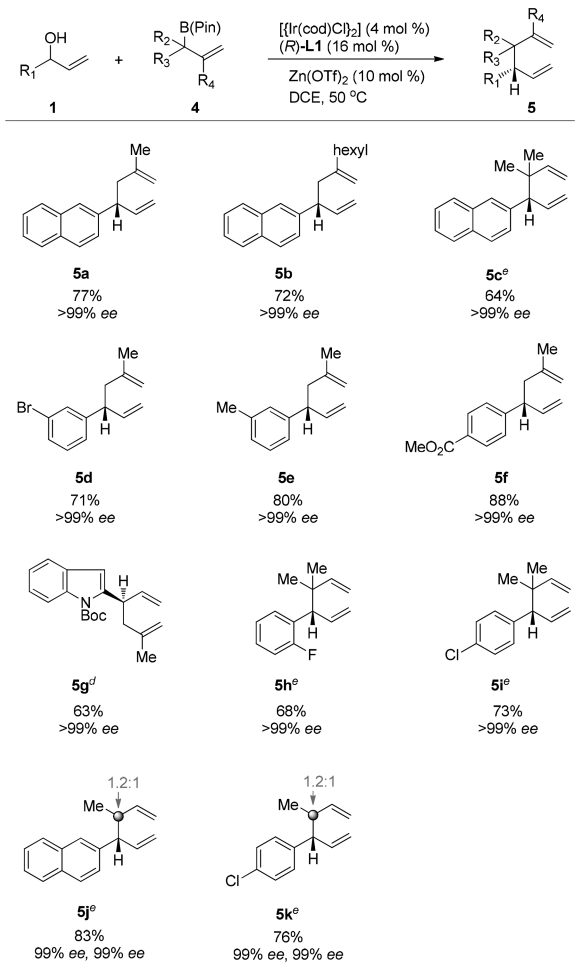
As illustrated in Scheme 3, we then surveyed a variety of allylboronates under the optimal reaction conditions. The

Scheme 3. Scope of the Enantioselective Allyl–Allylboronate Cross-Coupling with Respect to Allylboronates[a,b,c]

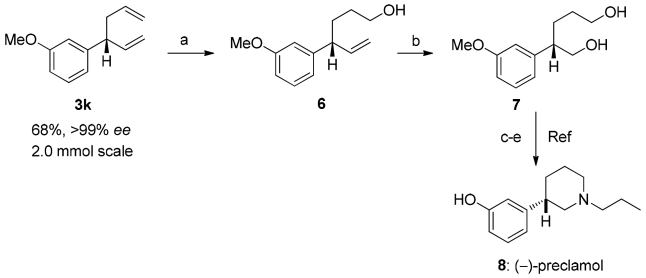


[a]Unless otherwise noted, all reactions were performed on a 0.20 mmol scale under the standard conditions. [b]Isolated yields. [c]Enantiomeric excess values were determined by HPLC on a chiral stationary phase. [d]Reaction was run with 0.1 M reaction concentration. [e]1.5 equiv of allylboronate.

substituted allylboronic esters **4** are readily prepared by Miyaura borylation of the corresponding allyl acetate and some known procedures.[4,12] Substitutions at the internal carbon atom of the allylboronate were well tolerated. Corresponding products using 2-methyl (**5a**), 2-hexyl (**5b**), and 3,3-dimethyl (**5c**) substitutes on the allylboronate were obtained in good yields and excellent enantioselectivity. Additionally, the substituted allylboronates could be coupled with many aromatic vinyl carbinols (**5d**–**5i**), giving the 1,5-dienes in respectful isolated yields and superb enantioselectivity. Notably, another limitation of the current method is that this reaction occurred with low diastereocontrol (dr 1.2:1, **5j** and **5k**) in contrast to the good levels of diastereoselectivity in the Morken[4c] and Carreira[6b] methods (dr ≥ 4:1), although the yields and ee values are still excellent.

The utility of this method is showcased through a concise enantioselective synthesis of (−)-preclamol,[10n,13] a potent dopaminergic drug candidate with antipsychotic therapeutic effects for the treatment of schizophrenia.[13,14] As shown in Scheme 4, when *m*-OMe-phenylvinyl carbinol **1k** was

Scheme 4. Enantioselective Synthesis of (−)-Preclamol[a]



[a]Reagents and conditions: (a) 9-BBN, THF, 0 °C, then $NaBO_3$, 0 °C, 73%; (b) O_3, CH_2Cl_2, −78 °C, then $NaBH_4$, −78 °C to rt; (c) MsCl, Et_3N, 25 °C; (d) propylamine, neat, 25 °C; (e) aqueous HBr, 120 °C.

subjected to the allyl–allylboronate cross-coupling conditions described in the study at 2 mmol scale, 1,5-diene **3k** was furnished in 68% yield and >99% ee. With exposure of the 1,5-diene **3k** to 9-BBN, the alkenes of **3k** could be effectively differentiated, leading to a primary alcohol **6** in 73% yield. Oxidative cleavage of **6** with ozone followed by the reductive workup gave the diol **7**, which could be further transformed into (−)-preclamol with a known 3-step sequence.[10n,13b]

In summary, we have disclosed an iridium-catalyzed asymmetric allyl–allylboronate cross-coupling reaction between unactivated racemic secondary allylic alcohols and allylboronic esters to provide chiral 1,5-dienes. The method affords the products with high regio- and stereoselectivity. The high functional group compatibility and operational convenience are also major features of the method, which offer an alternative to known allyl–allyl cross-coupling reactions. Finally, the utility of the coupling is demonstrated in a concise catalytic asymmetric synthesis of (−)-preclamol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03627.

Full characterization, analysis of enantioselectivity, spectral data, and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Ligand **L3** or **L4** could form an active iridacycle catalyst upon treatment with base as shown by Hartwig. As such, it is predictable that these ligands do not provide good reactivity with free alcohols and acidic promoters which would induce protodemetalation or preclude formation of active catalyst. For detailed discussion, see ref 8d. We thank the reviewer's comment on this point.

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