

α,β -Divinyl Tetrahydropyrroles as Chiral Chain Diene Ligands in Rhodium(I)-Catalyzed Enantioselective Conjugated Additions

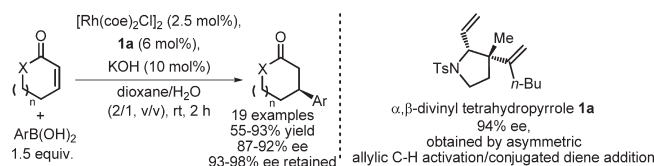
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ABSTRACT



A series of α,β -divinyl tetrahydropyrroles, synthesized by asymmetric allylic C–H bond activation/conjugated diene addition reaction of en-2-dienes, were found to be very efficient chiral chain diene ligands in the rhodium-catalyzed conjugated addition of organoboronic acids to various α,β -unsaturated compounds, achieving the desired chiral adducts with good to excellent yields and ee values.

Since the pioneering studies by the groups of Hayashi and Carreira, chiral cyclic dienes have now emerged as a novel class of highly effective steering ligands in transition metal-catalyzed enantioselective synthesis (Figure 1).^{1–5} Accordingly, ever increasing enantioselective reactions can be catalyzed by transition metal–diene complexes.^{6,7} Particularly noteworthy is that in some cases chiral dienes are

even more advantageous than other types of ligands in achieving challenging asymmetric reactions. To increase the practicability and versatility of these novel ligands, easy and straightforward synthetic accesses to these dienes are of prime importance and continuous endeavors in this line are ongoing in many research groups.

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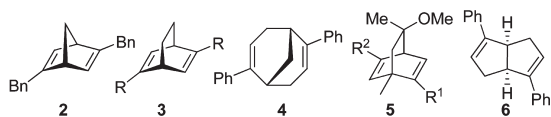
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Representative chiral bicyclic diene ligands



Du's chiral chain diene ligands

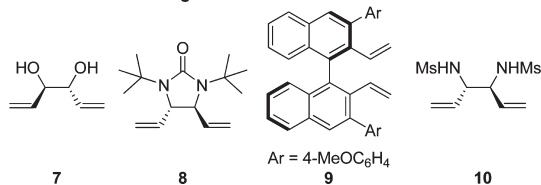


Figure 1. Examples of chiral diene ligands.

In addition to trying to design novel routes to easy synthesis of chiral cyclic dienes, which are the first generation of the widely used chiral diene ligands, scientists also tested whether acyclic dienes, which are usually much easier to access, can also function as efficient diene ligands for the asymmetric catalysis. Du and co-workers have found a family of flexible chiral chain dienes (**7**, **8**, and **9**, see Figure 1) that can achieve up to 85% ee in Rh-catalyzed conjugated addition reactions.⁸ This demonstrated the possibility of using flexible chiral chain dienes in the asymmetric catalysis. The low asymmetric induction in Du's ligands could be due to the facts that acyclic dienes are very flexible in geometry and have many orientations in coordination to the metal center in catalysis. Continuous efforts are required to develop other chiral acyclic diene ligands that can achieve high asymmetric inductions as chiral cyclic dienes do.

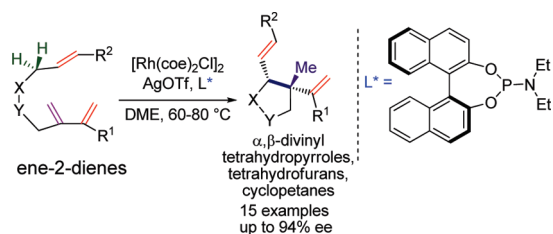
Recently, we reported a highly enantioselective Rh-catalyzed allylic C–H activation/addition to conjugated dienes using ene-2-dienes as substrates to synthesize multifunctional

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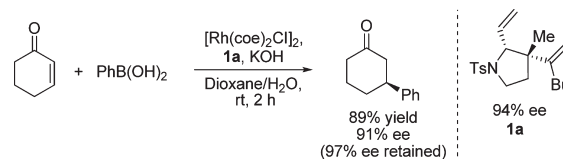
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Scheme 1. Rhodium-Catalyzed Allylic C–H Activation/Addition to Conjugated Diene



Scheme 2. Conjugated Addition of Phenylboronic Acid to 2-Cyclohexenone, Using **1a**



α,β -divinyl tetrahydropyrroles, tetrahydrofurans, and cyclopentanes (Scheme 1).^{9a,b} Asymmetric synthesis of two adjacent sp^3 carbon centers with one quaternary carbon in a series of α,β -divinyl tetrahydropyrrole, tetrahydrofuran, and cyclopentane structures was also achieved by us (Scheme 1).^{9c} We are currently trying to apply this reaction and its products to synthesis. Inspired by the chemistry of diene ligands, we decided to test whether these α,β -divinyl tetrahydropyrroles could also act as chiral chain diene ligands for transition metal-catalyzed enantioselective reactions.

Our first attempt was to test whether α,β -divinyl tetrahydropyrroles can act as chiral chain dienes in Rh-catalyzed conjugated addition of organoboronic acids to 2-cyclohexenone (Scheme 2).¹⁰ To our delight, our chiral chain diene ligand **1a** (which was directly obtained by the reaction shown in Scheme 1 and was 94% in ee) can give 89% yield and 91% ee (this equals a retained 97% ee, if a pure chiral ligand could be used)¹¹ in the conjugated addition of phenyl boronic acid to 2-cyclohexenone at room temperature in 2 h. During the course of our work, Du and co-workers realized up to 96% ee in similar reactions using diene **10** (Figure 1).^{8c} Therefore, our and Du's results clearly show that chiral chain dienes are competitive with chiral cyclic dienes as ligands in rhodium-catalyzed conjugated additions of organoboronic acids to the α,β -unsaturated compounds.

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(11) As one referee required that at least one reaction should be tested using the enantiomeric pure diene ligand, we carried out a standard reaction shown in Table 1 using diene ligand **1a** in 100% ee, which was obtained by preparative HPLC (Chiralpak OD column). In this case, 97% ee was obtained (see entry 9, Table 1, and the study of nonlinear effect part of the Supporting Information).

A great advantage of our allylic C–H activation/diene addition is that a series of acyclic dienes can be readily synthesized with very good enantioselectivity so that they can be tested as chiral chain diene ligands in transition metal-catalyzed conjugated addition. Therefore, besides chiral diene **1a**, we also tested other chiral dienes to see if better results could be achieved in the present Rh-catalyzed conjugated addition of organoboronic acid to 2-cyclohexenone (Scheme 3). It was found that different alkyl substituents at the internal position of the alkene of the ligands (**1b**, **1c**, and **1d**) did not influence the ee obviously. When a terminal substituent was introduced to the alkene of the ligands (**1e** and **1g**), only a trace amount of product could be obtained in these reactions, presumably due to the steric hindrance in the ligands that prevents the effective coordina-

tion of the diene to the rhodium center. Besides, the scaffold of these ligands is also important for achieving high ee, as the ligand **1f** with the diene motif one more carbon away from the N atom than that in **1d** gave a sharply decreased ee.

Diene **1a** is not a good solid and it is difficult for us to further improve its enantiopurity by recrystallization. Therefore, optimizing other reaction conditions was carried out to achieve higher ee of the target reaction by using **1a** (94% in enantiomeric excess).¹¹ We found that lowering the reaction temperature resulted in a decreased reaction yield, although the ee was slightly improved by 1% (Table 1, entry 2). We also tested the catalytic reaction using different rhodium loadings. The reaction yields were decreased without erosion of ee when less than 2.5 mol % of [Rh(coe)₂Cl]₂ was used (entries 3 and 4). However, further increasing the rhodium loading gave no better yield and ee (entry 5). Besides, the ratio of water is important to achieve high yield and ee (entries 1, 6, and 7). When the ratio of water was decreased, a low yield and lower ee were obtained. This indicates that water is responsible for the acceleration of this catalytic reaction. When the ratio of water was increased, the yield was improved with a slightly decreased ee. We also tested the solvent effect by using methanol instead of water (entry 8). It was shown that water is especially vital to obtain a high ee in this reaction. Finally, we chose 2.5 mol % of [Rh(coe)₂Cl]₂, 6.0 mol % of **1a** (with 94 ee%),¹¹ dioxane/H₂O (v/v, 2/1), and room temperature as the optimal reaction conditions to further study the scope of this asymmetric reaction.

We were pleased to find that the rhodium-catalyzed conjugated addition under the optimal reaction conditions proceeded smoothly in 2 h to give a variety of chiral adducts in 55–93% yields, and 85–91% ee's (90–98% ee's were retained). Various para- and meta-substituted aryl boronic acids afforded the corresponding chiral adducts in good to excellent yields and ee values (Table 2). In this transformation, ester and ketone, as well as hydroxyl groups can be tolerated without any erosion in ee (entries 6–8). Notably,

Scheme 3. Screening of the Chiral Chain Dienes (the addition products ee values in parentheses are the retained ee values)

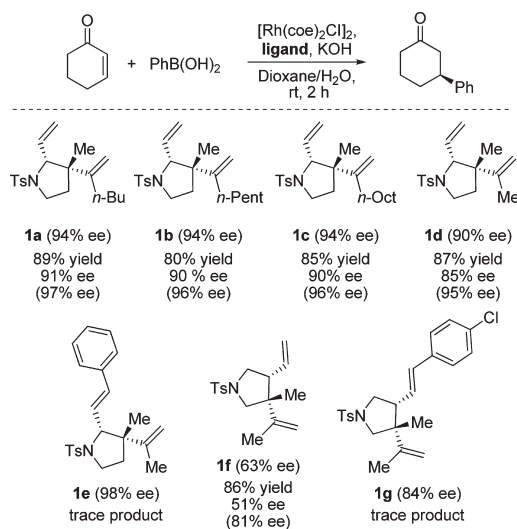


Table 1. Optimization of Reaction Conditions^a

entry	[Rh(coe) ₂ Cl] ₂ (mol %)	solvent	temp	yield ^b (%)	ee ^c (%)	ee retained (%)
1	2.5	dioxane/H ₂ O (v/v, 2/1)	rt	89	91	97
2	2.5	dioxane/H ₂ O (v/v, 2/1)	0 °C	61	92	98
3	1.0	dioxane/H ₂ O (v/v, 2/1)	rt	70	90	96
4	1.5	dioxane/H ₂ O (v/v, 2/1)	rt	79	91	97
5	3.5	dioxane/H ₂ O (v/v, 2/1)	rt	90	90	96
6	2.5	dioxane/H ₂ O (v/v, 10/1)	rt	42	89	95
7	2.5	dioxane/H ₂ O (v/v, 1/3)	rt	95	88	94
8	2.5	dioxane/MeOH (v/v, 2/1)	rt	91	88	94
9 ^d	2.5	dioxane/H ₂ O (v/v, 2/1)	rt	89	97	

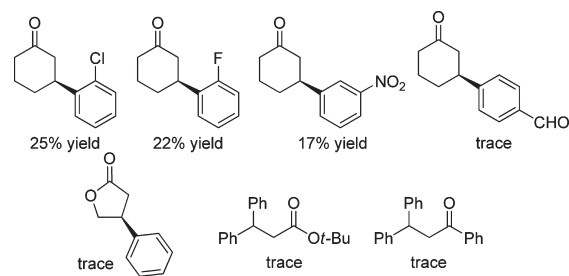
^a 10 mol % of KOH was used, which was added to the reaction system as a 0.075 M solution. ^b Isolated yield. ^c Ee was determined by HPLC (Chiralpak AD-H column). ^d The enantiomerically pure diene ligand obtained by preparative HPLC (Chiralpak OD column) was used (see ref 11).

Table 2. Scope of the Asymmetric Conjugated Additions

entries ^a	boronic acid	product ^b	yield (%) ^c	ee, ee retained (%) ^d
1	R = H		89	91, 97
2	R = Me		91	88, 94
3	R = OMe		82	89, 95
4	R = F		72	90, 96
5	R = CF3		69	91, 97
6	R = CH2OH		89	92, 98
7	R = CO2Me		55	87, 93
8	R = COMe		88	87, 93
9	R = Me		93	90, 96
10	R = Cl		90	88, 94
11			77	89, 95
12			70	88, 94
13			96	88, 94
14			81	91, 97
15			72	89, 95
16			60	87, 93
17			85	88, 94
18			83	85, 90
19			75	92, 98

^aThe diene ligand **1a** used in these reactions is in 94% ee. ^bThe absolute configuration was determined by comparing the optical rotation with the reported one or by analogy. ^cIsolated yield. ^dThe ee was determined by chiral HPLC (Chiralpak AD-H, AS-H, OB-H, OD-H, OJ-H columns were used as indicated in the Supporting Information).

when the arylboronic acid bearing a hydroxymethyl group at the para-position was used, the highest ee in this catalytic reaction was obtained (entry 6). The catalytic conjugated addition reaction is not sensitive to the steric effects using

Scheme 4. Unsuccessful Reactions


our ligands. The ortho-substituted arylboronic acid (entry 11) and naphthalen-1-ylboronic acid (entry 12) can participate in this reaction and gave the desired products in excellent ee values, which were superior to the results obtained by Du's chiral chain ligands. Besides 2-cyclohexenone, the conjugated additions to 2-cyclopentenone, 2-cycloheptenone, and 5,6-dihydro-2H-pyran-2-one (entries 17–19) were also tested, showing that the ee values of these reactions were 88%, 85%, and 92% (94%, 90%, and 98% retained), respectively. We also studied the nonlinear effect of the conjugated addition of phenylboronic acid to 2-cyclohexenone. It turned out that there is no nonlinear effect in this reaction, suggesting that there is one chiral diene ligand coordinated to the rhodium center in the stereo-determining step (see the Supporting Information for details).

Unfortunately, for some of the electron-deficient aryl boronic acids, our ligand cannot give reasonable yields (Scheme 4). Besides, the addition of phenylboronic acids to furan-2(5H)-one, the acyclic α,β -unsaturated ester, and ketone only yield trace products, respectively (Scheme 4).

In summary, we have reported a new family of chiral chain dienes, synthesized by asymmetric allylic C–H activation/addition reaction, as effective steering ligands for the conjugated addition of organoboronic acids to α,β -unsaturated compounds. These results highlight the synthetic utility of products obtained by the asymmetric C–H activation methodology. These substituted tetrahydropyrroles are not only useful structural motifs in organic synthesis, but are also applicable to the transition metal-catalyzed asymmetric reactions as a new class of diene ligands. Further application of these chiral chain diene ligands in other asymmetric reactions and understanding the coordination mode as well as the origin of the chiral induction are under investigation in our group.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.