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Rhodium(I)-Catalyzed Asymmetric Carbene Insertion into B–H Bonds: Highly Enantioselective Access to Functionalized Organoboranes

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Supporting Information

ABSTRACT: A unique rhodium(I)-catalyzed asymmetric B–H insertion of α-diazo carbonyl compounds with easily available amine–borane adducts was achieved using a newly developed C_1-symmetric chiral diene as ligand. This first Rh(I)–carbene-directed B–H insertion example represents an attractive and promising approach for synthesis of highly enantioenriched organoboron compounds, allowing for the efficient construction of α-boryl esters and ketones with excellent enantioselectivities (up to 99% ee) under exceptionally mild conditions.

Transition-metal-catalyzed C–H or X–H (X = O, N, S, Si) insertion of metal–carbene represents an excellent and powerful approach for the construction of C–C or C–X bonds.[1] Among them, catalytic asymmetric carbene insertion into C–H bonds has been well-defined,[1a−c] while asymmetric C–X bond formation via metal–carbene intermediate was established only recently.[1d−m] Rh(II),[1e] Cu(I),[1f−i] Cu(II),[1j,k] Ir(III),[1l] and Fe(II)[1m] with suitable chiral ligands are the most regularly used catalysts for these transformations.

It has been demonstrated that rhodium(I) complexes with diverse chiral ligands are efficient catalysts for various asymmetric reactions, such as addition of organoboron reagents to electron-deficient olefins, imines, and carbonyl compounds.[2] In contrast, the Rh(I)–carbene chemistry is far less studied. Although many examples of Rh(I) complexes with *N*-heterocyclic (NHC) carbene ligands have been known, their use as catalysts in asymmetric reactions is still an underexplored area of research.[3] On the other hand, Rh(I)–carbenes have proved to be useful intermediate species possessing novel and interesting reactivity in a few catalytic C–C bond-forming processes.[4,5] Nevertheless, asymmetric variants of related transformations are extremely rare. In 2010, Hayashi and co-workers succeeded in asymmetric cyclopropanation of alkenes with dimethyl diazomalonate using a cationic chiral diene–Rh(I) complex as catalyst.[5a] Very recently in 2014, Murakami reported enantioselective synthesis of cyclopentanols via Rh(I)–carbene insertion promoted by diphosphine ligands;[5b] Hu and co-workers achieved an enantioselective three-component reaction through trapping of Rh(I)-associated ammonium ylides generated from chiral Rh(I)–carbene.[5c] To the best of our knowledgement, the potential of Rh(I)–carbene intermediates to engage in C–H or X–H insertion reactions, even in non-asymmetric fashion, has not yet been disclosed.

Organoborons are among the most frequently used compounds in organometallic chemistry and organic synthesis. Typically, chiral boron compounds can be prepared by Brown's hydroboration using chiral borane reagents or transition-metal-catalyzed asymmetric hydroboration and boration of alkenes.[6] Although much progress has been made in recent years, the development of new strategies for efficient catalytic enantioselective synthesis of versatile organoboron compounds remains highly desirable. In fact, the carbene-directed B–H insertion approach could represent another ideal way for this purpose.[7] However, there have been no reports of catalytic variants of this type of process. A breakthrough has only recently been achieved by two research groups. Curran successfully demonstrated a rhodium(II)-catalyzed insertion reaction between NHC–borane and diazocarbonyl compounds, providing diverse α-NHC–boryl carbonyl compounds.[8a] Almost at the same time, Zhou and co-workers established a copper(I)-catalyzed carbene insertion into the B–H bonds of phosphine–borane adducts, and further achieved the first asymmetric B–H insertion using chiral spirobisoxazoline ligands (91–94% ee).[8b]

In recent years, we have been particularly interested in developing chiral olefin-based ligands for Rh(I)-catalyzed asymmetric reactions.[9] Intrigued by the fact that Rh(I)–carbenes can serve as reactive intermediate species for a series of C–C bond-forming transformations,[4,5] we envisaged the possibility of performing the asymmetric metal–carbene insertion into B–H bonds using Rh(I) complex with proper olefin-chelating ligand as catalyst. Herein, we describe our efforts toward the development of the first Rh(I)–carbene-mediated asymmetric B–H insertion reaction using unprecedented C_1-symmetric chiral diene ligands. This Rh(I)-catalyzed process allows practical construction of stereogenic C–B bonds in a highly enantioselective manner at room temperature, providing a promising new approach to the synthesis of enantiomerically enriched functionalized organoboranes.

Our initial experiments began with the reaction of methyl α-diazophenylacetate **1a** and easily available amine–borane adduct[10] **2a** in dichloromethane at room temperature. When

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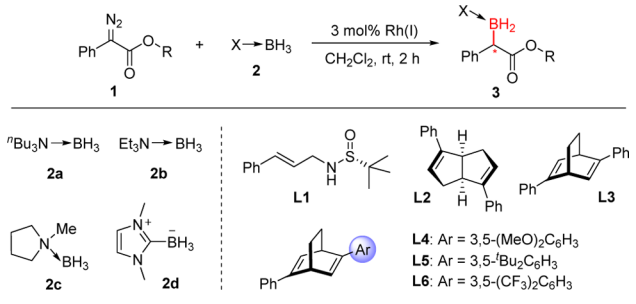
$Rh_2(OAc)_4$ was used as catalyst, the B–H insertion occurred smoothly to afford the corresponding borane product **3a** (Table 1, entry 1). Gratifyingly, we observed that, in the

Table 1. Optimization of Reaction Conditions[a]



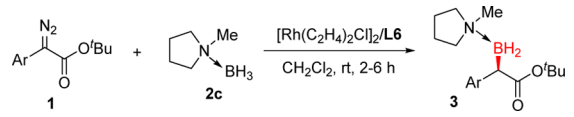
entry	R	adduct	ligand	3	yield (%)[b]	ee (%)[c]
1[d]	Me	**2a**		**3a**	70	
2[e]	Me	**2a**		**3a**	75	
3	Me	**2a**	**L1**	**3a**	6	−80
4	Me	**2a**	**L2**	**3a**	12	1
5	Me	**2a**	**L3**	**3a**	83	66
6	Me	**2b**	**L3**	**3b**	90	60
7	Me	**2c**	**L3**	**3c**	98	60
8	Me	**2d**	**L3**	**3d**	52	60
9	Me	**2c**	**L4**	**3c**	42	54
10	Me	**2c**	**L5**	**3c**	98	72
11	Me	**2c**	**L6**	**3c**	98	84
12	Ph	**2c**	**L6**	**3e**	94	95
13	^{t}Bu	**2c**	**L6**	**3f**	92	99
14[f]	^{t}Bu	**2c**	**L6**	**3f**	70	98

[a]The reaction was performed with **1** (0.1 mmol), **2** (0.15 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), and ligand (3.3 mol%) in 2 mL of CH_2Cl_2 at room temperature unless otherwise noted. [b]Isolated yield. [c]Determined by chiral HPLC. [d]2.5 mol% $Rh_2(OAc)_4$ was used. [e]2.5 mol% $[Rh(cod)Cl]_2$ was used. [f]0.8 mol% Rh(I) catalyst was used.

presence of 2.5 mol% $[Rh(cod)Cl]_2$, the reaction also worked well to give the expected borane **3a** in an even better yield (75%, entry 2), clearly indicating that Rh(I) could act as the center metal for this insertion reaction of metal–carbene. Next, several representative chiral olefin ligands were chosen to investigate the potential of asymmetric catalysis. Interestingly, our linear sulfur–olefin ligand **L1**[9c] showed good enantioselectivity but with very poor reactivity in this transformation (entry 3). While another previously developed bicyclo[3.3.0]-diene[9b] was not effective, promising results (83% yield, 66% ee) were obtained using Hayashi's bicyclo[2.2.2]octadiene **L3**[11] (entry 5). Examination of other amine–borane adducts and the NHC–borane adduct (entries 6–8) revealed that **2c** was the most reactive borane that maintained enantioselectivity (entry 7). To achieve better enantiocontrol, elaboration of chiral ligands for further screening was conducted. To our delight, the use of easily prepared C_1-symmetric dienes,[12] which are analogues of bicyclo[2.2.2]octadiene **L3**, gave the product in excellent yields with much improved enantioselectivities (entries 10 and 11). More interestingly, when phenyl α-diazophenylacetate was employed as substrate, it was quite encouraging that the use of **L6** furnished the insertion product **3e** in both excellent yield and ee (94% yield, 95% ee, entry 12). Changing the ester moiety of the diazoester to more sterically bulky *tert*-butyl further improved the enantioselectivity to an exciting 99% (entry 13). Notably, 0.8 mol% of catalyst (Rh(I)/**L6**) loading was found to be sufficient to achieve satisfactory results, albeit a decrease in yield (entry 14).

With the optimized reaction conditions established, we then investigated the substrate scope of this process. As summarized in Table 2, various *tert*-butyl α-diazoarylacetates with diverse

Table 2. Substrate Scope of Asymmetric B–H Insertion Reactions of α-Diazoesters[a]



entry	Ar	time (h)	3	yield (%)[b]	ee (%)[c]
1	Ph	3	**3f**	92	99
2	4-FC_6H_4	2	**3g**	86	99
3	4-ClC_6H_4	2	**3h**	87	99
4	4-MeC_6H_4	3	**3i**	96	98
5	2-naphthyl	6	**3j**	87	99
6	3-$CF_3C_6H_4$	2	**3k**	84	97
7	3,5-$Me_2C_6H_3$	4	**3l**	80	98
8	3-BrC_6H_4	3	**3m**	83	98
9	3-MeC_6H_4	3	**3n**	82	98
10	4-$MeOC_6H_4$	4	**3o**	82	97
11	2-MeC_6H_4	6	**3p**	75	97
12	2-FC_6H_4	6	**3q**	80	96

[a]The reaction was performed with **1** (0.1 mmol), **2c** (0.15 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), and **L6** (3.3 mol%) in 2 mL of CH_2Cl_2 at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC.

steric and electronic properties were examined in the Rh(I)/**L6**-catalyzed asymmetric B–H insertion reaction. In all cases, products **3** were obtained in good to excellent yields with uniformly high enantioselectivities (96–99%), regardless of the substitution pattern of the diazo substrates. In comparison with the only reported copper-catalyzed B–H insertion reaction,[8b] the enantioselectivities are generally superior. Moreover, the use of cheap and easily accessible amine–borane **2c** instead of a phosphine–borane adduct as boron reagent is also an advantage of our reaction.[13] The absolute configuration at the newly created stereocenter was determined to be *R* by X-ray crystallographic analysis of **3m** (Figure 1).

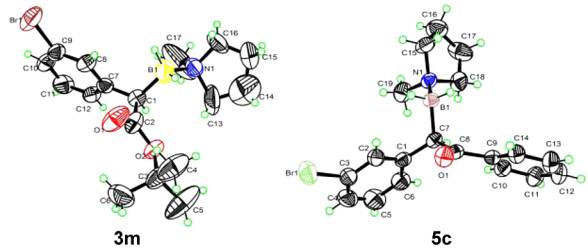


Figure 1. X-ray crystal structures of (*R*)-**3m** and (*R*)-**5c**.

Encouraged by success of the asymmetric B–H insertion of α-diazoesters, we turned our attention to the more challenging α-diazoketone substrates to explore the potential of generating chiral α-boryl ketones. Unlike α-diazoesters, the use of α-diazoketones as carbene precursors for the X–H insertion reaction is far less studied.[14] The asymmetric B–H insertion of α-diazoketone has not yet been reported. Under the same conditions, a structurally diverse set of α-diazoketones were subject to reaction with amine–borane adduct **2c** (Table 3).

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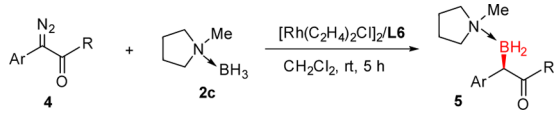
Table 3. Substrate Scope of Asymmetric B−H Insertion Reactions of α-Diazoketones[a,d]



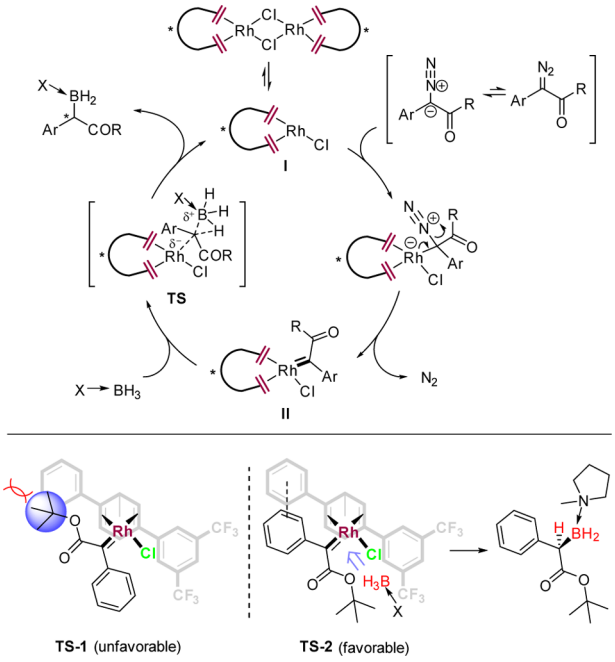
entry	4	Ar	R	5	yield (%)[b]	ee (%)[c]
1	**4a**	Ph	Ph	**5a**	76	96
2	**4b**	2-naphthyl	Ph	**5b**	67	96
3	**4c**	3-BrC_6H_4	Ph	**5c**	69	96
4	**4d**	4-ClC_6H_4	Ph	**5d**	64	96
5	**4e**	4-MeC_6H_4	Ph	**5e**	65	95
6	**4f**	Ph	4-FC_6H_4	**5f**	73	96
7	**4g**	Ph	4-MeC_6H_4	**5g**	75	97
8	**4h**	Ph	4-ClC_6H_4	**5h**	68	96
9	**4i**	Ph	4-$MeOC_6H_4$	**5i**	90	98
10	**4j**	Ph	2-MeC_6H_4	**5j**	48	95
11	**4k**	Ph	3-FC_6H_4	**5k**	71	96
12	**4l**	3-BrC_6H_4	4-MeC_6H_4	**5l**	70	98
13	**4m**	Ph	Et	**5m**	73	94
14	**4n**	Ph	Bu	**5n**	73	95
15	**4o**	Ph	*i*-Pr	**5o**	54	93

[a]The reaction was performed with **4** (0.1 mmol), **2c** (0.15 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), and **L6** (3.3 mol%) in 2 mL of CH_2Cl_2 at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The absolute configuration was determined by the X-ray crystallographic analysis of **5c**; see the Supporting Information for details.

Remarkably, all reactions of α-diazoketones **4a−l** bearing two aryl groups adjacent to diazo and carbonyl occurred in a highly enantioselective fashion (95−98% ee), providing the corresponding insertion products **5** in moderate to good yields (entries 1−12). It appeared that substitution on the either aryl ring did not affect the stereoselectivity of the reaction. Substrates **4m−o** that possess an alkyl group such as ethyl, butyl, and isopropyl at the ketone moiety also afforded the desired organoborane products **5m−o** with good yields and enantioselectivities (93−95% ee, entries 13−15). Thus, the scope of this new reaction is substantially expanded. The same reaction stereochemistry was confirmed by X-ray analysis of the product **5c** (Figure 1).

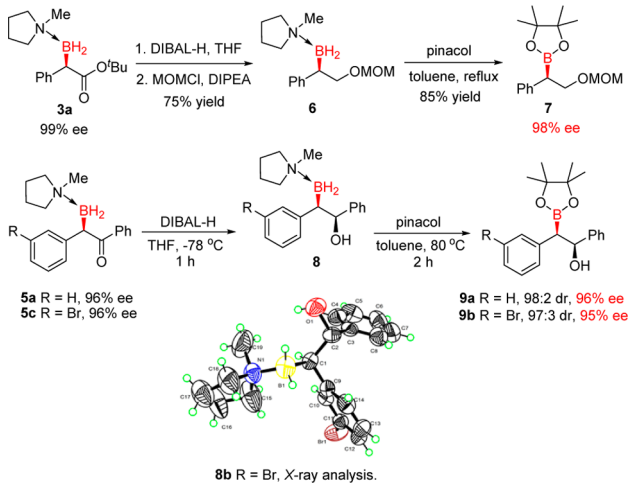
A plausible reaction mechanism is illustrated in Scheme 1. The bis(rhodium/diene) complex initially dissociates to give an active monorhodium catalyst **I**, which reacts with diazo compound to generate Rh(I)−carbene intermediate **II** having a square-planar coordination. Insertion of this highly reactive carbenoid species into the B−H bond of the amine−borane adduct probably via a concerted transition state[1a,c,8] then affords the corresponding organoborane product and regenerates the catalyst. To explain the observed stereochemical outcome, an empirical stereocontrol model is also proposed. We assume that the rhodium−carbene complex with unsymmetrically substituted diene ligand **L6** may take the conformation with Rh=C on the site *trans* to the more electron-deficient double bond,[15] where the carbenoid moiety is orthogonal to the coordination plane. To minimize the steric repulsion, the bulky ester orients away from the phenyl group of the ligand, and accordingly the two phenyl rings are likely to form a π−π stacking interaction (TS-1 and TS-2). Thus, the B−H insertion takes place preferentially from the unblocked carbene face at the site adjacent to Cl to provide the *R* product.

Scheme 1. Proposed B−H Insertion Mechanism



To highlight the versatility of this method, the insertion product **3f** was readily converted into the protected β-hydroxy pinacol borate ester in good yield with 98% ee (Scheme 2).

Scheme 2. Product Transformations



Furthermore, the reaction of chiral α-boryl ketones **5a** and **5c** with DIBAL-H followed by treatment with pinacol gave the valuable β-boryl alcohols **9a** and **9b** having two stereogenic centers. It should be noted that both excellent diastereoselectivity and enantioselectivity were observed. The *cis*-conformation was determined by the X-ray analysis of intermediate **8**.

In summary, we have achieved the first rhodium(I)−carbene-involved asymmetric insertion into B−H bonds for facile synthesis of a wide range of chiral α-carbonyl-containing organoboranes, which are versatile and potentially interesting intermediates in organic synthesis. The newly developed C_1-symmetric chiral bicyclo[2.2.2]octadiene ligand has demonstrated its remarkable efficiency in this Rh(I)-catalyzed C−B bond-forming reaction, enabling the achievement of exception-

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ally high enantioselectivities (93−99% ee). Moreover, the use of easily accessible and inexpensive amine−borane adduct as boron source makes the present protocol particularly attractive and practical. Studies to fully understand the reaction mechanism and further exploit the Rh(I)−carbene chemistry in asymmetric catalysis are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, including CIF data for **3m**, **5c**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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