Communication

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Rhodium-Catalyzed B–H Bond Insertion Reactions of Unstabilized Diazo Compounds Generated *in situ* from Tosylhydrazones

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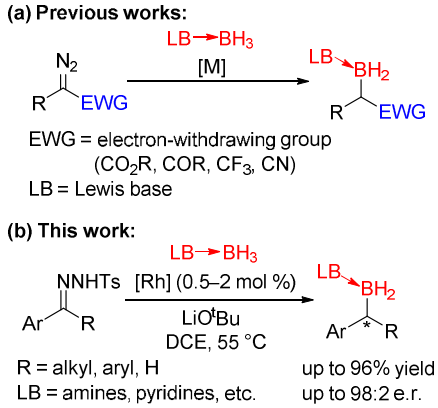
Supporting Information Placeholder

ABSTRACT: Although transition-metal-catalyzed B–H bond insertion of carbenes into stable borane adducts has emerged as a promising method for organoborane synthesis, all the diazo compounds used to date as carbene precursors have had an electron-withdrawing group to stabilize them. Herein, we report a protocol for rhodium-catalyzed B–H bond insertion reactions of unstabilized diazo compounds generated *in situ* from tosylhydrazones. In addition, by using chiral dirhodium catalysts, we also achieved an asymmetric version of the reaction with good to excellent enantioselectivities (up to 98:2 e.r.). This is the first enantioselective heteroatom–hydrogen bond insertion reaction to use unstabilized diazo compounds as carbene precursors. The protocol exhibited good functional group tolerance and could be carried out on a gram scale. It also enabled one-pot transformation of a carbonyl group to a boryl group enantioselectively. The B–H bond insertion products could be easily transformed into chiral alcohols and other widely used organoboron reagents with enantiomeric fidelity.

Because organoboron compounds have a wide variety of applications, the development of efficient methods for their synthesis has drawn considerable attention from synthetic chemists.[1] Recently, transition-metal-catalyzed B–H bond insertion reactions of carbenes with stable borane adducts, first developed by Curran's group[2] and independently by our group,[3] emerged as a promising method for organoborane synthesis.[4] Various diazo compounds have been used as carbene precursors, and enantioselective transformations have been achieved (Scheme 1a). However, all the diazo compounds used to date have contained an electron-withdrawing group that is directly connected to the diazo carbon and that stabilizes the diazo compound by increasing the number of resonance forms.[4a] The need for an electron-withdrawing group greatly limits the diversity of the B–H bond insertion products, as well as their synthetic applications. Herein, we report a protocol for rhodium-catalyzed B–H bond insertion reactions of unstabilized diazo compounds generated *in situ* from tosylhydrazones (Scheme 1b). In addition, by using chiral dirhodium catalysts we also achieved an asymmetric version of the reaction with good to excellent enantioselectivities (up to 98:2 enantiomeric ratio, e.r.). To the best of our knowledge, this is the first enantioselective heteroatom–hydrogen bond insertion reaction that uses unstabilized diazo compounds as carbene precursors.[5] Unlike the known catalytic methods for constructing C–B bonds,[1] our method directly connects carbonyl groups to boryl groups, avoids the regioselectivity problem often encountered in olefin hydroboration, and can be performed enantioselectively.

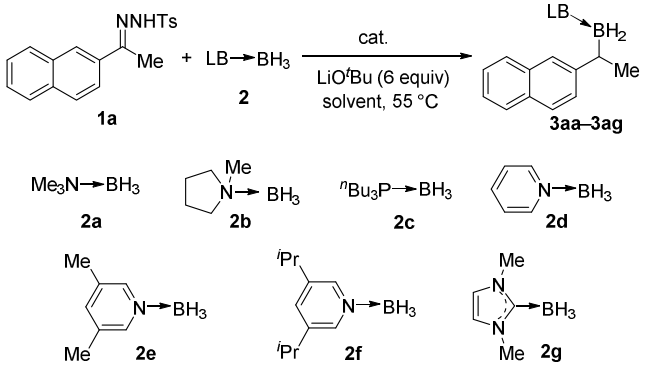
Scheme 1. Transition-Metal-Catalyzed B–H Bond Insertion Reactions



Our study began with the reaction of tosylhydrazone **1a** and readily accessible trimethylamine-borane adduct **2a** (2 equiv) in 1,2-dichloroethane (DCE) at 55 °C (Table 1). Although unstabilized diazo compounds can be easily generated *in situ* from tosylhydrazones by means of the Bamford–Stevens process in the presence of base at high temperature (generally over 80 °C),[6] this method is problematic for B–H bond insertion reactions because borane adducts are generally thermally labile. To solve this problem, we used a large amount of base (Li^{t}OBu, 6.0 equiv) to facilitate *in situ* generation of the diazo compounds at a relatively low temperature (55 °C). First, we evaluated various transition-metal catalysts that have been used in other carbene-transfer reactions (entries 1–10).[5c] To our delight, we found that in the presence of a copper, palladium, or rhodium complex, the reaction smoothly afforded desired B–H bond insertion product (1-(naphthalen-2-yl)ethyl)borane (**3aa**) in moderate to good yield (entries 1–3 and 6–10). CuI, Rh_2(TPA)$_4$, and Rh_2(piv)$_4$ gave yields over 70%, with Rh_2(piv)$_4$ giving the highest yield (92%, entry 10).[7] The amount of Rh_2(piv)$_4$ could be reduced to as low as 1 mol

% without substantially compromising the yield (entries 10–12). Fortunately, $Rh_2(piv)_4$ could be easily recovered in 83% by means of flash chromatography after the reaction and could be reused without any loss in activity (see Table S2 for details). Evaluation of various solvents showed that chlorobenzene was also suitable, whereas coordinating and protic solvents were deleterious (entries 13–15). In addition to trimethylamine-borane adduct **2a**, borane adducts stabilized by different Lewis bases, such as *N*-methylpyrrolidine (**2b**), tributylphosphine (**2c**), pyridine and pyridine derivatives (**2d**–**2f**), and an *N*-heterocyclic carbene (**2g**), also underwent B–H bond insertion reactions smoothly and afforded the desired products in good to excellent yields (entries 16–21).

Table 1. Transition-Metal-Catalyzed B–H Bond Insertion of Tosylhydrazone 1a with Borane Adducts 2: Optimization of the Reaction Conditions. [a]

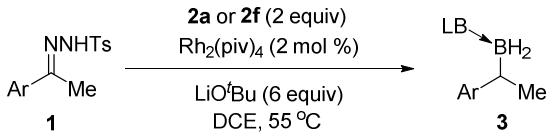


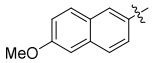
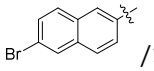
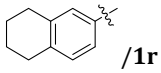
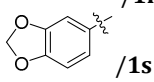
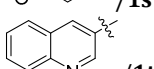
entry	cat. (mol %)	**2**	time (h)	conv. (%)[b]	yield (%)[c]
1	$Cu(MeCN)_4PF_6$ (10)	**2a**	4	80	26
2	CuI (10)	**2a**	4	99	74
3	$CuBr_2$ (10)	**2a**	4	89	45
4	$FeCl_2$ (10)	**2a**	23	80	trace
5	AuCl (10)	**2a**	23	trace	trace
6	$Pd(dba)_2$ (10)	**2a**	4	60	43
7	$[Rh(cod)Cl]_2$ (10)	**2a**	2	35	24
8	$Rh_2(TFA)_4$ (5)	**2a**	6	20	10
9	$Rh_2(TPA)_4$ (5)	**2a**	4	100	79
10	$Rh_2(piv)_4$ (5)	**2a**	4	100	92
11	$Rh_2(piv)_4$ (2)	**2a**	4	100	89
12	$Rh_2(piv)_4$ (1)	**2a**	5	95	80
13[d]	$Rh_2(piv)_4$ (2)	**2a**	7	100	79
14[e]	$Rh_2(piv)_4$ (2)	**2a**	12	trace	33
15[f]	$Rh_2(piv)_4$ (2)	**2a**	4	0	trace
16	$Rh_2(piv)_4$ (2)	**2b**	11	100	93
17	$Rh_2(piv)_4$ (2)	**2c**	4	100	66
18	$Rh_2(piv)_4$ (2)	**2d**	11	100	75
19	$Rh_2(piv)_4$ (2)	**2e**	4	100	91
20	$Rh_2(piv)_4$ (2)	**2f**	4	100	81
21	$Rh_2(piv)_4$ (2)	**2g**	11	100	65

[a]Reaction conditions: **1a**/**2**/LiO^{t}Bu = 0.2:0.4:1.2 (mmol), in 3 mL of DCE, 4 h. cod = 1,5-cyclooctadiene. dba = dibenzylideneacetone. TFA = trifluoroacetate. TPA = triphenylacetate. piv = pivalate. [b] Based on the recovery of **1a**. [c] Isolated yield. [d] Used C_6H_5Cl as solvent. [e] Used 1,4-dioxane as solvent. [f] Used MeOH as solvent

Next, we investigated B–H bond insertion reactions of aryl methyl tosylhydrazones with borane adducts **2a** or **2f** under the optimal reaction conditions (Table 2). The reactions gave the desired B–H bond insertion products in satisfactory yields (generally around 80%). A variety of functional groups, including methoxy (**1b**, **1e**; entries 2 and 5), halogen (**1c**, **1h**, **1n**–**1p**; entries 3, 8, and 14–16), ester (**1i**; entry 9), nitrile (**1j**; entry 10), nitro (**1k**; entry 11), and trifluoromethyl (**1l**; entry 12) were tolerated. Phenyl-substituted compounds with an electron-withdrawing group on the phenyl ring (entries 8–12) gave higher yields than compounds with an electron-donating group (entries 2 and 5). The catalytic system was sensitive to the steric bulk of the substrates; specifically, compound **1q**, which has an *ortho*-methyl group, gave a dramatically lower yield (entry 17). Tosylhydrazone **1t**, which contains a coordinating quinoline moiety, afforded desired B–H bond insertion product **3tf** in 75% yield when the borane adduct **2f** was used (entry 20). Dialkyl tosylhydrazones were unreactive under the standard reaction conditions.

Table 2. Rhodium-Catalyzed B–H Bond Insertion of Aryl Methyl Substituted Tosylhydrazones. [a]

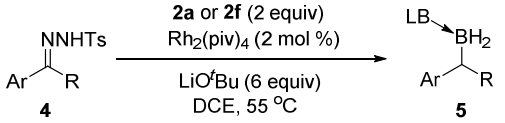


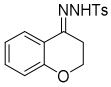
entry	Ar/**1**	**2**	**3**	yield (%)
1	2-naphtyl/**1a**	**2a**	**3aa**	89
2	 /**1b**	**2a**	**3ba**	55
3	 /**1c**	**2a**	**3ca**	84
4	Ph/**1d**	**2a**	**3da**	80
5	4-$MeOC_6H_4$/**1e**	**2a**	**3ea**	60
6	4-MeC_6H_4/**1f**	**2a**	**3fa**	70
7	4-PhC_6H_4/**1g**	**2a**	**3ga**	80
8	4-IC_6H_4/**1h**	**2a**	**3ha**	85
9	4-$(CO_2Me)C_6H_4$/**1i**	**2a**	**3ia**	86
10	4-CNC_6H_4/**1j**	**2a**	**3ja**	83
11	4-$NO_2C_6H_4$/**1k**	**2a**	**3ka**	86
12	4-$CF_3C_6H_4$/**1l**	**2a**	**3la**	92
13	3-MeC_6H_4/**1m**	**2a**	**3ma**	84
14	3-FC_6H_4/**1n**	**2a**	**3na**	80
15	3-ClC_6H_4/**1o**	**2a**	**3oa**	88
16	3-BrC_6H_4/**1p**	**2a**	**3pa**	90
17	2-MeC_6H_4/**1q**	**2a**	**3qa**	22
18	 /**1r**	**2a**	**3ra**	79
19	 /**1s**	**2a**	**3sa**	60
20	 /**1t**	**2f**	**3tf**	75

[a]Reaction conditions: $Rh_2(piv)_4$/**1**/**2a** or **2f**/LiO^{t}Bu = 0.004:0.2:0.4:1.2 (mmol), in 3 mL of DCE at 55 ℃, 4 h.

We next evaluated B–H bond insertion reactions of tosylhydrazones **4** derived from various other carbonyl compounds as carbene precursors (Table 3). Tosylhydrazones derived from aromatic aldehydes (**4a** and **4l**; entries 1 and 12), aryl alkyl ketones with linear or branched R groups

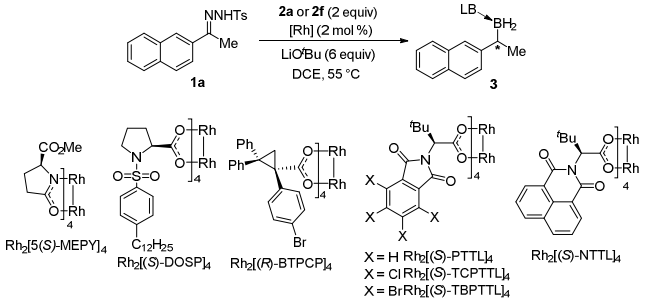
Table 3. Rhodium-Catalyzed B–H Bond Insertion of Other Tosylhydrazones with Borane Adduct 2a or 2f. [a]



entry	Ar/R	4	2	5	yield (%)[b]
1	Ph/H	**4a**	**2a**	**5aa**	75
2	Ph/Et	**4b**	**2a**	**5ba**	75
3	Ph/^{n}Bu	**4c**	**2a**	**5ca**	70
4[c]	Ph/cyclopropyl	**4d**	**2a**	**5da**	71
5	Ph/Ph	**4e**	**2a**	**5ea**	94
6	Ph/4-MeOC$_6$H$_4$	**4f**	**2a**	**5fa**	85
7	Ph/2-ClC$_6$H$_4$	**4g**	**2a**	**5ga**	88
8	Ph/2-naphtyl	**4h**	**2a**	**5ha**	93
9	Ph/C$_6$F$_5$	**4i**	**2a**	**5ia**	87
10	4-ClC$_6$H$_4$/Bn	**4j**	**2f**	**5jf**	72
11		**4k**	**2a**	**5ka**	75
12	ferrocenyl/H	**4l**	**2a**	**5la**	60

[a]Reaction conditions: Rh$_2$(piv)$_4$/**4**/**2a** or **2f** /LiO^{t}Bu = 0.004:0.2:0.4:1.2 (mmol), in 3 mL of DCE at 55 ℃, 4 h. [b] Isolated yield. [c] Used 10 mol % CuI as catalyst.

Table 4. Enantioselective Rhodium-Catalyzed B–H Bond Insertion of Tosylhydrazone 1a and Borane Adducts 2: Optimization of the Reaction Conditions. [a]

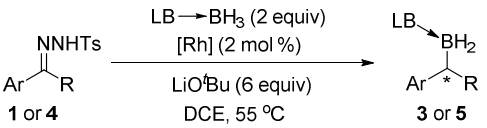


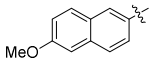
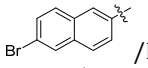
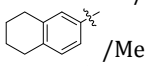
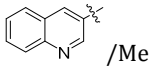
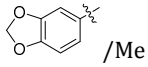
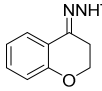
entry	[Rh]	2	3	yield (%)[b]	e.r.[c]
1	Rh$_2$[5(*S*)-MEPY]$_4$	**2a**	**3aa**	5	51:49
2	Rh$_2$[(*S*)-DOSP]$_4$	**2a**	**3aa**	36	54:46
3	Rh$_2$[(*R*)-BTPCP]$_4$	**2a**	**3aa**	91	56:44
4	Rh$_2$[(*S*)-PTTL]$_4$	**2a**	**3aa**	71	80:20
5	Rh$_2$[(*S*)-TCPTTL]$_4$	**2a**	**3aa**	96	89:11
6	Rh$_2$[(*S*)-TBPTTL]$_4$	**2a**	**3aa**	94	88:12
7	Rh$_2$[(*S*)-NTTL]$_4$	**2a**	**3aa**	94	73:27
8	Rh$_2$[(*R*)-BTPCP]$_4$	**2f**	**3af**	78	96:4

[a] Reaction conditions: [Rh]/**1a**/**2**/LiO^{t}Bu = 0.004:0.2:0.4:1.2 (mmol), in 3 mL of DCE at 55 ℃, 4 h. [b] Isolated yield. [c] Determined by HPLC.

(**4b**, **4c**, and **4j**; entries 2, 3, and 10), and diaryl ketones (**4e**–**4i**; entries 5–9) were all suitable carbene precursors for B–H bond insertion reactions with borane adduct **2a** or **2f**.[7,8] Reaction of an aryl alkyl ketone with a sterically hindered R group (**4d**) was achieved with CuI as a catalyst (entry 4). Moreover, the tosylhydrazone derived from cyclic ketone **4k** reacted smoothly with **2a** to afford the desired product **5ka** in good yield (entry 11). It is worth mentioning that the carbene transfer reactions with α-alkyl diazo compounds easily undergo β-hydride elimination,[9] but give B–H bond insertion products with satisfactory yields in this study.

Table 5. Enantioselective Rhodium-Catalyzed B–H Bond Insertion Reactions: Substrate Scope. [a]



entry	Ar/R (**1** or **4**)	2	3	yield (%)[b]	e.r.[c]
Condition A					
1	2-naphtyl/Me (**1a**)	**2f**	**3af**	78	96:4
2	 /Me (**1b**)	**2f**	**3bf**	49	95:5
3	 /Me (**1c**)	**2f**	**3cf**	82	91:9
4	 /Me (**1r**)	**2f**	**3rf**	65	95:5
5	 /Me (**1t**)	**2f**	**3tf**	74	93:7
6	Ph/Et (**4b**)	**2e**	**5be**	63	88:12
7	Ph/^{n}Bu (**4c**)	**2e**	**5ce**	63	88:12
Condition B					
8	Ph/Me (**1d**)	**2a**	**3da**	70	93:7
9	4-MeOC$_6$H$_4$/Me (**1e**)	**2a**	**3ea**	50	93:7
10	4-MeC$_6$H$_4$/Me (**1f**)	**2a**	**3fa**	62	92:8
11	3-MeC$_6$H$_4$/Me (**1m**)	**2a**	**3ma**	68	92:8
12	3-FC$_6$H$_4$/Me (**1n**)	**2a**	**3na**	76	91:9
13	3-ClC$_6$H$_4$/Me (**1o**)	**2a**	**3oa**	70	92:8
14	 /Me (**1s**)	**2a**	**3sa**	50	98:2
15	 (**4k**)	**2a**	**5ka**	72	95:5

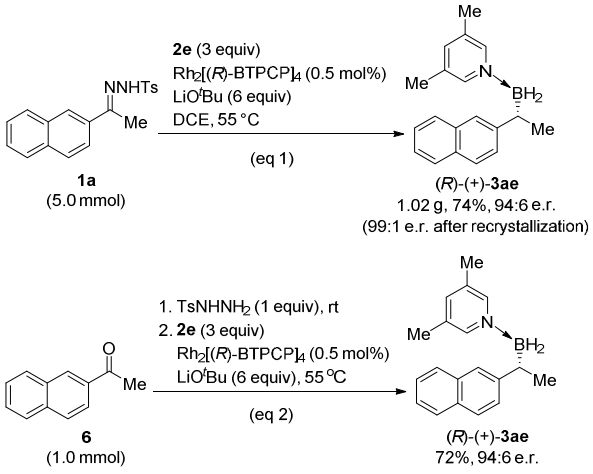
[a]**Condition A**: Rh$_2$[(*R*)-BTPCP]$_4$/**1** or **4**/**2f** or **2e**/LiO^{t}Bu = 0.004:0.2:0.4:1.2 (mmol), in 3 mL of DCE at 55 ℃, 4 h. **Condition B**: Rh$_2$[(*S*)-TBPTTL]$_4$/**1** or **4**/**2a**/LiO^{t}Bu = 0.004:0.2:0.4:1.2 (mmol), in 3 mL of DCE at 55 ℃, 4 h. [b] Isolated yield. [c] Determined by HPLC.

We then investigated the asymmetric version of the B–H bond insertion reaction (Table 4). First, several commercially available chiral dirhodium catalysts were tested in the reaction of tosylhydrazone **1a** and borane adduct **2a** (entries 1–7). Although Rh$_2$[5(*S*)-MEPY]$_4$,[10] Rh$_2$[(*S*)-DOSP]$_4$,[11] and Rh$_2$[(*R*)-

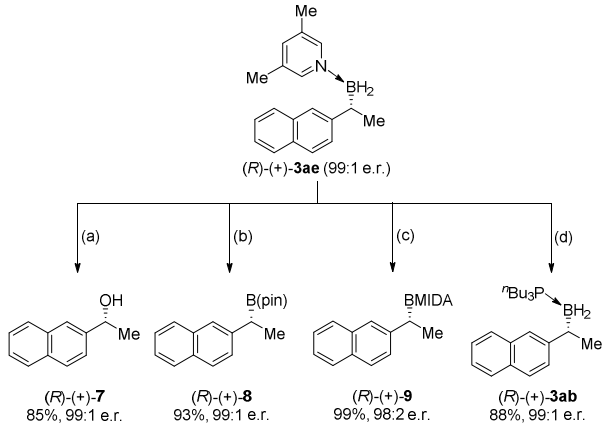
BTPCP]$_4$[12] gave very poor enantioselectivities, dirhodium complexes modified with α-imido acids (Rh$_2$[(*S*)-PTTL]$_4$,[13] Rh$_2$[(*S*)-TCPTTL]$_4$, Rh$_2$[(*S*)-TBPTTL]$_4$[14] and Rh$_2$[(*S*)-NTTL]$_4$[15]) gave good enantioselectivities (73:27–89:11 e.r.; entries 4–7). A careful investigation of other chiral dirhodium catalysts and orthogonal test of borane adducts and catalysts (see Table S1 for details) showed that the combination of Rh$_2$[(*R*)-BTPCP]$_4$ and 3,5-diisopropylpyridine-borane adduct (**2f**) gave the highest enantioselectivity (96:4 e.r.; Table 4, entry 7).

Under the optimal reaction conditions, asymmetric B–H bond insertion reactions with various tosylhydrazones were then performed (Table 5). The enantioselectivity of the reaction was highly sensitive to the combination of catalysts and substrates, so we developed two different catalytic systems. The combination of Rh$_2$[(*R*)-BTPCP]$_4$ and pyridine-borane adduct **2f** or **2e** (condition A) exhibited good enantioselectivity for tosylhydrazones with shapes similar to that of 1-(naphthalen-2-yl)ethan-1-ones (**1a**–**1c**, **1r**, and **1t**; entries 1–5) and with tosylhydrazones of aryl alkyl ketones (R = Et or ^{n}Bu, **4b** and **4c**, entries 6 and 7). In contrast, the combination of Rh$_2$[(*S*)-TBPTTL]$_4$ and trimethylamine-borane adduct (**2a**, condition B) gave better enantioselectivity for the tosylhydrazones of acetophenone and its derivatives (**1d**–**1f**, **1m**–**1o**, and **1s**; entries 8–14) or cyclic ketone **4k** (entry 15). Notably, the highest e.r. (98:2) was obtained in the reaction of tosylhydrazone **1s** and borane adduct **2a** under condition B (entry 14).

Scheme 2. Gram-scale and One-pot Preparation of 3ae



Scheme 3. Transformations of (*R*)-(+)-3ae

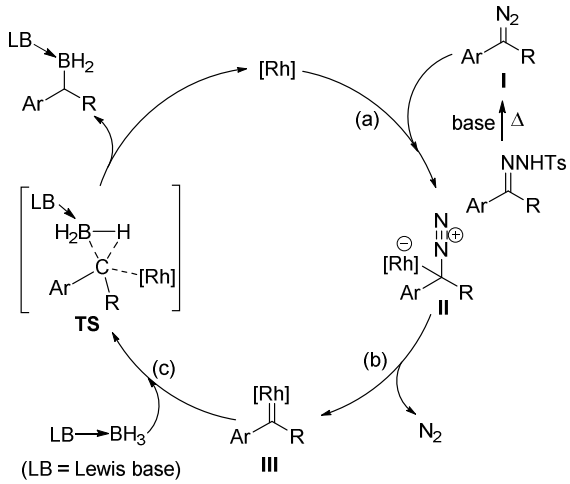


Reaction conditions: (a) H_2O_2, MeOH, 80 °C, 2 h. (b) pinacol, toluene, reflux, 2 h. (c) *N*-methyl imidodiacetic acid (MIDA), toluene/DMSO (5:1, *v*/*v*), reflux, 12 h. (d) ^{n}Bu$_3$P, toluene, 85 °C, 7 h.

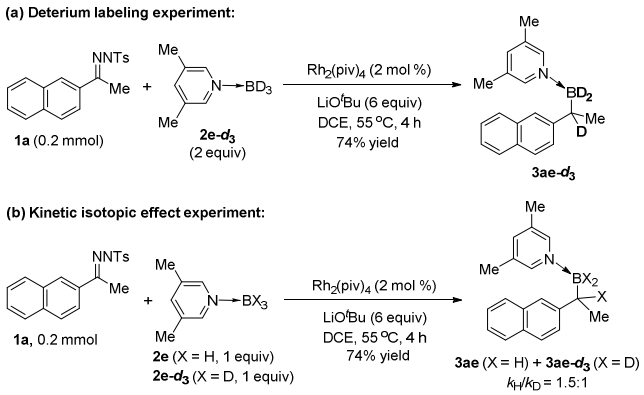
The B–H bond insertion reaction of tosylhydrazone **1a** and borane adduct **2e** could be performed on a gram scale with satisfactory yield and e.r. by using 0.5 mol % Rh$_2$[(*R*)-BTPCP]$_4$ as the catalyst (Scheme 2, eq 1). The B–H bond insertion product, (*R*)-(+)-**3ae**, was readily crystallized, and its optical purity could be enhanced to 99:1 e.r. by means of recrystallization. The Rh$_2$[(*R*)-BTPCP]$_4$ catalyst could be recovered by flash chromatography (80% yield, see Table S3 for details) and reused without substantial loss of catalytic activity. Moreover, we successfully converted ketone **6** into the corresponding organoborane in one pot by means of a condensation and B–H bond insertion sequence with high overall yield and retained e.r. (Scheme 2, eq 2).

Organoboranes obtained from the B–H bond insertion reaction were relatively stable during subsequent transformations and during storage. However, they could also undergo diverse transformations under mild conditions (Scheme 3). For instance, (*R*)-(+)-**3ae** was easily converted to corresponding alcohol (*R*)-(+)-**7** by oxidation (Scheme 3a), and to widely used boron reagents (*R*)-(+)-**8** (Scheme 3b) and (*R*)-(+)-**9** (Scheme 3c) by condensation with pinacol and MIDA. Moreover, (*R*)-(+)-**3ae** could be directly transformed to (*R*)-(+)-**3ab** by means of a Lewis base exchange reaction under heating (Scheme 3d). In all cases, the stereochemistry was retained and the yield was high. The results shown in Schemes 2 and 3 clearly demonstrate the high potential utility of this protocol.

Scheme 4. Proposed Mechanism



Scheme 5. Control Experiments



We proposed a mechanism of the rhodium-catalyzed B–H bond insertion reaction by analogy with the other rhodium-catalyzed carbene transfer reactions (Scheme 4).[7] The reaction starts with the generation of diazo compound **I** from a tosylhydrazone through Bamford-Stevens process.[6] Rhodium catalyst then coordinates with the electron-rich diazo connected carbon (step a, **II**), extrudes nitrogen gas, and generates highly active rhodium carbene **III** (step b). The rhodium carbene **III** finally inserts into a B–H bond of the borane adduct to give the insertion product (step c). A deuterium labeling experiment (Scheme 5a) showed that all the deuterium atoms located either at boron or at α-carbon of the insertion product **3ae-*d*$_3$**, while a kinetic isotopic effect experiment (Scheme 5b) exhibited a minor k_H/k_D (1.5:1). These experiments indicate a concerted and fast B–H bond insertion process (**TS**).[3] The studies towards detailed mechanism understanding of the enantioselectivity are undergoing in our laboratory.

In summary, we have described a protocol for rhodium-catalyzed B–H bond insertion reactions of borane adducts and unstabilized diazo compounds generated *in situ* from tosylhydrazones at low temperature. This protocol constitutes a new method for preparation of organoboranes starting from readily available aldehydes or ketones in reasonable yields and with high enantioselectivity and good functional group tolerance. Investigation of the mechanism and additional synthetic applications of this reaction is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and computational study results. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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Graphic for TOC