JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Copper-Catalyzed B–H Bond Insertion Reaction: A Highly Efficient and Enantioselective C–B Bond-Forming Reaction with Amine–Borane and Phosphine–Borane Adducts

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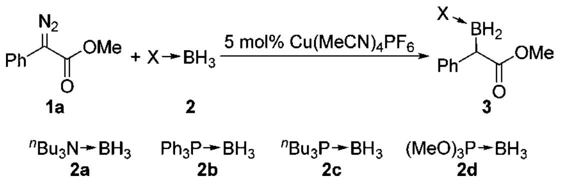
Supporting Information

ABSTRACT: A copper-catalyzed B–H bond insertion reaction with amine– and phosphine–borane adducts was realized with high yield and enantioselectivity under mild reaction conditions. The B–H bond insertion reaction provides a new C–B bond-forming methodology and an efficient approach to chiral organoboron compounds.

Organoboron compounds are widely used in modern organic synthesis, materials science, medicine, and other fields,[1] and the development of methodologies for the preparation of these compounds is an active, highly rewarding area of research. The most widely used method for constructing C–B bonds is Brown's hydroboration of olefins,[2] but several newer C–B bond-forming reactions have recently been developed. For example, the transition-metal-catalyzed hydroboration and boration of olefins using catecholborane, pinacolborane, and related biboranes are attractive routes for the formation of C–B bonds because the selectivity of these reactions can be controlled.[3] In addition, remarkable progress has been made in the direct construction of C–B bonds through C–H bond activation.[4]

Transition-metal-catalyzed insertion of carbenes into heteroatom–hydrogen (X–H) bonds is an efficient strategy for the formation of heteroatom–carbon (C–X) bonds, and various catalytic carbene insertions into X–H bonds, including N–H, O–H, Si–H, and S–H bonds, have been achieved.[5] However, the electron-deficient B–H bond does not readily undergo insertion with electron-deficient Fischer-type metal carbenes. Upon formation of an adduct with an amine or a phosphine, the B–H bond of borane becomes more electron-rich,[6] which provides an opportunity to achieve B–H bond insertion with electron-deficient metal carbenes. For example, insertion of samarium carbenes into the B–H bond of phosphine–borane has been described,[7] although a stoichiometric amount of samarium was needed. Here we report an efficient approach to organoborane compounds by means of copper-catalyzed carbene insertion into the B–H bonds of amine– and phosphine–borane adducts.[8] The asymmetric version of this B–H insertion reaction was also achieved with high enantioselectivity.[9]

Table 1. Catalytic B–H Bond Insertion Reactions: Optimization of Reaction Conditions[a]



entry	adduct	solvent	T (°C)	time (h)	product	yield (%)[b]
1	**2a**	DCE	25	24	**3aa**	83
2	**2b**	DCE	25	18	**3ab**	80
3	**2c**	DCE	25	14	**3ac**	87
4	**2d**	DCE	25	12	**3ad**	trace
5	**2c**	DCE	60	0.5	**3ac**	89
6[c]	**2c**	DCE	60	4	**3ac**	89
7	**2c**	$CHCl_3$	60	0.5	**3ac**	85
8	**2c**	toluene	60	4	**3ac**	85
9	**2c**	THF	60	12	**3ac**	73
10[d]	**2c**	DCE	60	0.5	**3ac**	81
11[e]	**2c**	DCE	60	2	**3ac**	81
12[f]	**2c**	DCE	60	0.5	**3ac**	82

[a] Reaction conditions: $Cu(MeCN)_4PF_6$/**1a**/**2** = 0.01:0.2:0.4 (mmol), in 2 mL of solvent at specified temperature. [b] Isolated yield. [c] Using 2 mol% catalyst. [d] Using $Cu(OTf)_2$ as catalyst. [e] Using $CuBr_2$ as catalyst. [f] Using $Rh_2(OAc)_4$ as catalyst.

In the initial study, we conducted the reaction of methyl α-diazophenylacetate **1a** with borane adducts in 1,2-dichloroethane (DCE) at 25 °C with $Cu(MeCN)_4PF_6$ as catalyst (Table 1). To our delight, easily accessible and highly stable amine–borane adduct **2a** and phosphine–borane adducts **2b** and **2c** smoothly underwent the B–H insertion reaction to afford the desired products in good yields (entries 1–3). In terms of the reaction rate and yield, tri-*n*-butylphosphine–borane adduct **2c**, bearing an electron-rich and less-hindered phosphine group, was the best choice (entry 3). In contrast, phosphite–borane adduct **2d** was less reactive (entry 4). $BH_3\cdot THF$, $BH_3\cdot SMe_2$, pinacolborane, and catecholborane afforded complicated product mixtures that did not contain any of the desired B–H insertion product (data not shown). Increasing the reaction temperature to 60 °C markedly shortened the reaction time (to 0.5 h) without compromising the yield (entry 5). Reducing the catalyst loading to 2 mol% gave the same yield, although a slightly longer reaction time was required (entry 6). Chloroform and toluene were also suitable solvents for this reaction, whereas THF lowered the reactivity (entries 7–9). Copper(II) salts, such as $Cu(OTf)_2$ and $CuBr_2$, gave

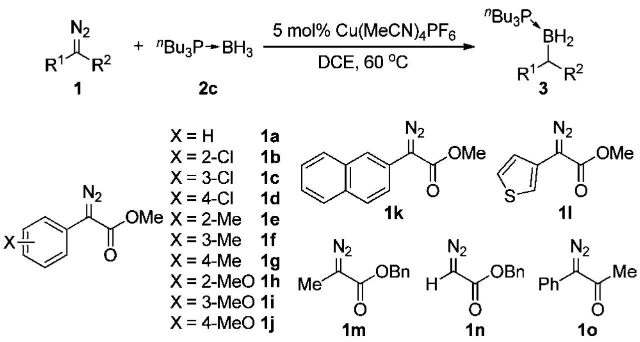
Received: August 10, 2013
Published: September 11, 2013

dx.doi.org/10.1021/ja408306a | *J. Am. Chem. Soc.* 2013, 135, 14094–14097

results similar to those obtained with $Cu(MeCN)_4PF_6$ (entries 10 and 11). A rhodium complex, $Rh_2(OAc)_4$, also efficiently catalyzed the insertion reaction in high yield (entry 12).

The copper-catalyzed B−H bond insertion reaction had a broad substrate scope (Table 2). All the tested α-aryl-α-diazoacetates **1a**−**1j** smoothly underwent reaction to afford the corresponding products in good to high yields (entries 1−10). Diazoesters **1e** and **1h**, which have 2-methyl and 2-methoxy substituents on their aryl rings, respectively, gave slightly lower yields (entries 5 and 8). α-Diazo-α-(2-naphthyl)acetate **1k** afforded the insertion product in 91% yield, although a longer reaction time was required (entry 11). Heterocyclic diazoester **1l** could also be used as the carbene precursor to afford the corresponding B−H insertion product in a reasonable yield (entry 12). α-Diazopropionate **1m**, which has an α-alkyl group, exhibited a reaction rate and yield similar to those of α-aryl-substituted diazoesters (entry 13). Benzyl α-diazoacetate **1n** underwent the B−H insertion reaction within 2 h to afford the desired product in 68% yield (entry 14). In addition to diazoesters, diazoketone **1o** also showed reasonable reactivity in the reaction (entry 15).

Table 2. Copper-Catalyzed B−H Bond Insertion Reactions: Substrate Scope[a]

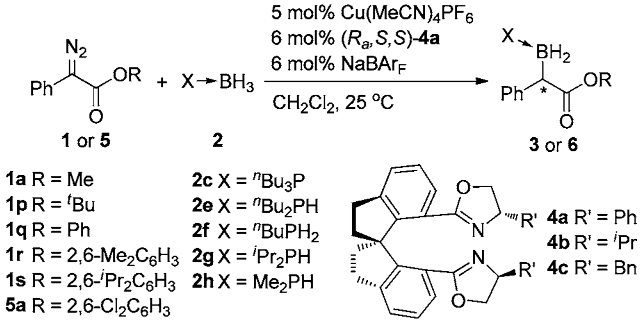


entry	substrate	time (h)	product	yield (%)
1	**1a**	0.5	**3ac**	89
2	**1b**	0.5	**3bc**	93
3	**1c**	0.5	**3cc**	86
4	**1d**	1.5	**3dc**	88
5	**1e**	0.5	**3ec**	78
6	**1f**	0.5	**3fc**	83
7	**1g**	0.5	**3gc**	83
8	**1h**	1	**3hc**	76
9	**1i**	1	**3ic**	81
10	**1j**	0.5	**3jc**	82
11	**1k**	5	**3kc**	91
12	**1l**	0.5	**3lc**	66
13	**1m**	0.5	**3mc**	80
14	**1n**	2	**3nc**	68
15	**1o**	2	**3oc**	71

[a] Reaction conditions and analysis were the same as those of Table 1, entry 5.

We next investigated the asymmetric version of the copper-catalyzed B−H bond insertion reaction by using chiral spirobisoxazoline ligand (R_a,S,S)-**4a** (Table 3).[10] The steric properties of the phosphine markedly affected the enantioselectivity of the reaction, with less-hindered Me_2PH (**2h**) giving the best combination of yield and enantioselectivity (entries 1−5). Although phosphine−boranes **2e**−**2h** have P−H bonds, no P−H bond insertion product was detected in the reaction. The steric and electronic properties of the ester moiety of the diazoester also strongly affected the enantioselectivity of the reaction (entries 5−10). When 2,6-dichlorophenyl α-diazophenylacetate **5a** was used instead of **1**, the reaction was complete within 4 h, and the enantioselectivity improved to 92% ee (entry 10). The absolute configuration of the B−H bond insertion product was confirmed to be *R* by means of X-ray diffraction analysis of a single crystal of **6ah** (Figure 1). Note that 1 mol% catalyst was sufficient to produce satisfactory results (entry 11).

Table 3. Enantioselective Copper-Catalyzed B−H Bond Insertion Reactions: Optimization of Reaction Conditions[a]



entry	diazoester	adduct	time (h)	product	yield (%)[b]	ee (%)[c]
1	**1a**	**2c**	5	**3ac**	84	16
2	**1a**	**2e**	5	**3ae**	89	57
3[d]	**1a**	**2f**	12	**3af**	nd	nd
4	**1a**	**2g**	6	**3ag**	90	45
5	**1a**	**2h**	5	**3ah**	87	61
6	**1p**	**2h**	12	**3ph**	79	77
7	**1q**	**2h**	12	**3qh**	88	72
8	**1r**	**2h**	20	**3rh**	86	88
9	**1s**	**2h**	72	**3sh**	81	68
10	**5a**	**2h**	4	**6ah**	96	92
11[e]	**5a**	**2h**	24	**6ah**	87	90
12[f]	**5a**	**2h**	48	**6ah**	82	4
13[g]	**5a**	**2h**	12	**6ah**	89	88
14[h]	**5a**	**2h**	5	**6ah**	86	64
15[i]	**5a**	**2h**	24	**6ah**	78	44
16[j]	**5a**	**2h**	20	**6ah**	75	5

[a] Reaction conditions: $Cu(MeCN)_4PF_6$/(R_a,S,S)-**4a**/$NaBAr_F$/diazoester/**2** = 0.01:0.012:0.012:0.2:0.2 (mmol), in 2 mL of CH_2Cl_2 at 25 °C. [b] Isolated yield. [c] Determined by supercritical fluid chromatography. [d] The reaction was complicated, and no desired product was determined. [e] Using 1 mol% catalyst. [f] Using (S_a,S,S)-**4a** as ligand. [g] Using (R_a,S,S)-**4b** as ligand. [h] Using (R_a,S,S)-**4c** as ligand. [i] Using (S,S)-Box as ligand. [j] Using (S,S)-Pybox as ligand.

Matching configurations of the spiro-bisoxazoline ligands was crucial for obtaining high enantioselectivity. In contrast to

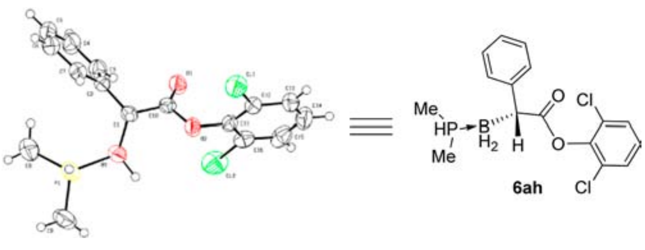
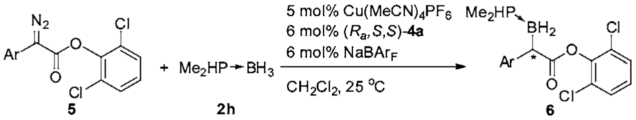


Figure 1. Single-crystal structure of (*R*)-**6ah**.

(R_a,S,S)-**4a**, (S_a,S,S)-**4a** afforded almost completely racemic product under identical reaction conditions (entry 12). The substituents on the oxazoline rings of ligand **4** also affected the reaction. (R_a,S,S)-**4b**, which has sterically hindered isopropyl groups, exhibited enantioselectivity similar to that of (R_a,S,S)-**4a**, but the reaction rate with the former was slightly lower than that with the latter (entry 13 vs entry 10). In contrast, benzyl-substituted bisoxazoline ligand (R_a,S,S)-**4c** exhibited markedly lower enantioselectivity (64% ee, entry 14). The structure of the spiro ligand backbone played an important role in the enantiocontrol of the reaction: bisoxazoline ligands 2,2′-(propane-2,2-diyl)bis(4-*tert*-butyl-4,5-dihydrooxazole) [(S,S)-Box] and 2,6-bis(4-phenyl-4,5-dihydrooxazol-2-yl)pyridine [(S,S)-Pybox] showed very low enantioselectivities (entries 15 and 16).

We next investigated various α-diazoesters with a 2,6-dichlorophenyl ester moiety in the copper-catalyzed asymmetric B−H insertion reaction (Table 4). The reactions of all the tested diazo compounds exhibited high yields (86−96%) and enantioselectivities (91−94% ee) under the standard reaction conditions. The electronic and steric properties of the aryl substituents of the diazo compounds had a negligible influence on the enantioselectivity, but substituents at the 2-position of the aryl group of the substrate slowed the reaction (entries 9 and 10).

Table 4. Enantioselective Copper-Catalyzed B−H Bond Insertion Reactions: Substrate Scopes[a]

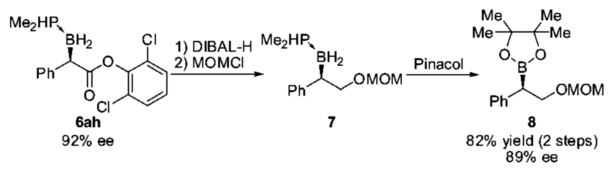


entry	Ar	time (h)	6	yield (%)	ee (%)
1	Ph (**5a**)	4	**6ah**	96	92
2	4-ClC$_6$H$_4$ (**5b**)	7	**6bh**	96	93
3	4-PhC$_6$H$_4$ (**5c**)	4	**6ch**	91	92
4	4-MeC$_6$H$_4$ (**5d**)	4	**6dh**	96	91
5	4-MeOC$_6$H$_4$ (**5e**)	4	**6eh**	92	91
6	3-ClC$_6$H$_4$ (**5f**)	7	**6fh**	96	94
7	3-MeC$_6$H$_4$ (**5g**)	4	**6gh**	96	93
8	3-MeOC$_6$H$_4$ (**5h**)	8	**6hh**	94	92
9	2-ClC$_6$H$_4$ (**5i**)	15	**6ih**	94	94
10[b]	2-MeC$_6$H$_4$ (**5j**)	20	**6jh**	92	94
11	3,4-O$_2$CH$_2$C$_6$H$_3$ (**5k**)	6	**6kh**	86	91
12	2-naphthyl (**5l**)	4	**6lh**	91	92

[a] Reaction conditions and analysis were the same as those of Table 3, entry 10. [b] Using 10 mol% catalyst.

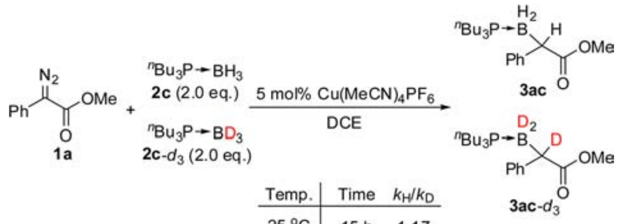
To demonstrate the synthetic utility of the B−H bond insertion reaction, we transformed **6ah** in high yield in two steps to protected β-hydroxy pinacolborane **8**, a β-functionalized borate that can be expected to find wide application in organic synthesis (Scheme 1).

Scheme 1. Product Transformations



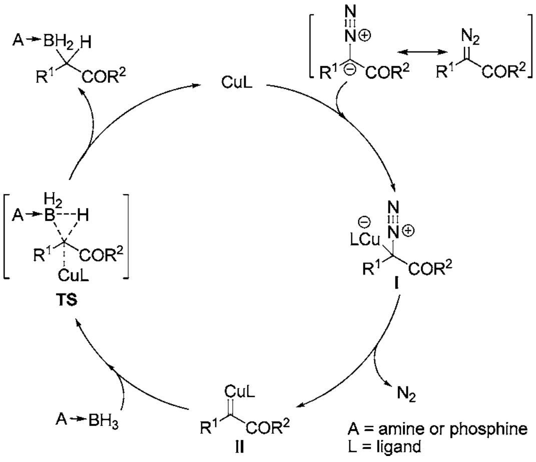
We performed an isotope effect experiment (Scheme 2). The small isotope effects (k_H/k_D = 1.17) that were observed both at room temperature and at 60 °C imply that neither B−H bond cleavage nor C−H bond formation was likely to have been involved in the rate-limiting step. By analogy with Si−H and C−H bond insertion reactions,[11] we propose a B−H bond insertion mechanism shown in Scheme 3. The diazo group generates the copper carbene **II**, which inserts into the B−H bond of the amine− or phosphine−borane adduct in a concerted manner via transition state **TS**. We are currently conducting a detailed study of the B−H insertion mechanism in our laboratory.

Scheme 2. Isotope Effect Experiments



Temp.	Time	k_H/k_D
25 °C	15 h	1.17
60 °C	0.5 h	1.17

Scheme 3. Proposed B−H Insertion Mechanism



In summary, we developed a copper-catalyzed B−H bond insertion reaction. This B−H activation strategy permitted the synthesis of organoboron compounds from easily accessible and highly stable amine− or phosphine−borane adducts under mild reaction conditions in high yields. This transition-metal-catalyzed C−B bond-forming reaction also allowed the efficient synthesis of chiral organoboranes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data, including CIF data for **6ah**. 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.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China and the National Basic Research Program of China (2012CB821600), the "111" project (B06005) of the Ministry of Education of China, and the Program for New Century Excellent Talents in University (NCET-10-0516) for financial support.

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