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Metal-Free Borylation

Transition-Metal-Free Synthesis of Pinacol Alkylboronates from Tosylhydrazones**

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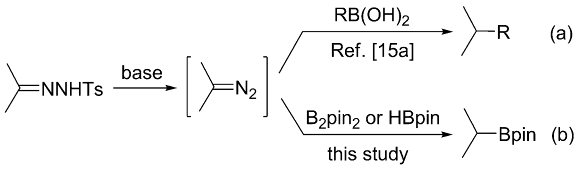
Organoboron compounds are highly important synthetic intermediates in transition-metal-catalyzed cross-coupling reactions[1] and other functional-group transformations.[2] In this context, arylboron compounds have been extensively used in organic synthesis, and the corresponding alkylboron compounds are also useful building blocks. In recent years great progress has been made in the Suzuki–Miyaura cross-coupling reactions involving alkylboron compounds.[1b,h,3,4]

In general, alkylboron compounds can be accessed by four different methods: 1) nucleophilic reaction by Grignard[5] or organolithium reagents[6] with suitable boron compounds, such as BX_3 (X = Cl, F) or $B(OR)_3$; 2) hydroboration of alkenes;[3,7,8] 3) Miyaura borylation;[9–11] 4) transition-metal-catalyzed borylation of alkanes by C–H bond activation.[12,13] These powerful methods for the preparation of alkylboron compounds have been widely practiced in modern organic synthesis. However, a common requirement is that metals, either as catalysts or in stoichiometric amounts, have to be used. This can make these preparative methods environmentally unfriendly and less cost effective. Moreover, heavy metals may contaminate the final boron products, a problem which is frequently encountered in the manufacturing process.[14]

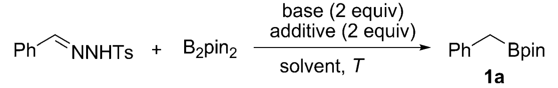
Recently, significant progress has been made in the development of metal-free transformations to form C–C,[15] C–O,[16] C–N,[17] C–S,[18] and C–B[19] bonds. Among the various metal-free transformations that have appeared in the recent literature, we were particularly attracted by the metal-free carbon–carbon bond formation between boronic acids and tosylhydrazones reported by Barluenga and coworkers (Scheme 1 a).[15a] This remarkable transformation successfully utilizes the combination of three consecutive steps: the in situ generation a of nonstabilized diazo compound, the coordination of the diazo compound to a boronic acid, and the 1,2-migration of the aryl or alkyl substituent from boron to carbon. We have also previously reported the metal-free arylation of α-diazocarbonyl compounds with boroxins.[15b] Encouraged by these transformations, we conceived that a transition-metal-free carbon–boron bond-forming reaction may be possible with a similar reaction system. Research along this line led to the development of a highly efficient transition-metal-free borylation of tosylhydrazones, a method which represents novel access to alkylboron compounds (Scheme 1 b).



Scheme 1. Metal-free C–C bond and C–B bond formations. pin = pinacolato, Ts = *p*-toluenesulfonyl.

At the outset, bis(pinacolato)diboron (B_2pin_2) was used as a borylating agent and to our delight, the reaction with the tosylhydrazone derived from benzaldehyde in the presence of LiO*t*Bu in toluene afforded the expected borylation product **1a** in 21 % yield (Table 1, entry 1). We then optimized the reaction conditions by examining the effect of the base and

Table 1: Optimization of the reaction of tosylhydrazone with B_2pin_2.[a]



1a

Entry	Base	Additive	Solvent	*T* [°C]	Yield [%][b]
1	LiO*t*Bu	–	Toluene	90	21
2	NaO*t*Bu	–	Toluene	90	16
3	NaOEt	–	Toluene	90	48
4	NaOMe	–	Toluene	90	43
5	NaOH	–	Dioxane	90	46
6	K_2CO_3	–	Dioxane	90	16
7	CsF	–	Dioxane	90	30
8	NaOEt	EtOH	Toluene	90	54
9	NaOH	H_2O	Dioxane	90	49
10	NaOMe	MeOH	Toluene	90	63
11	NaOMe	MeOH	Dioxane	90	56
12	NaOMe	MeOH	DCE	90	54
13	NaOMe	MeOH	THF	70	39
14	NaOMe	MeOH	MeCN	90	20

[a] Reaction conditions: tosylhydrazone (0.5 mmol), B_2pin_2 (0.6 mmol), base (1 mmol), additive (1 mmol), solvent (2 mL), 1–12 h. [b] Determined by GC with dodecane as internal standard. DCE = 1,2-dichloroethane.

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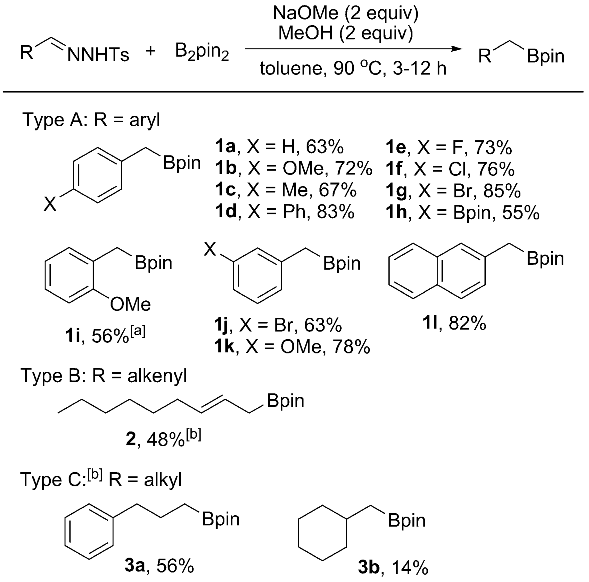
found that EtONa, NaOMe, and NaOH could give better results than other bases (Table 1, entries 1–7). In view that the protonation process is essential for the reaction, we then introduced two equivalents of an alcohol or H_2O, as a proton source, to the reaction (Table 1, entries 8–11). The yield of **2a** was indeed slightly improved, with MeOH affording the optimal result. The solvent also affects the reaction and toluene was found to give the best yield.

With the optimized reaction conditions (Table 1, entry 10) in hand, the substrate scope was investigated (Scheme 2). A series of tosylhydrazones conjugated with aromatic systems could be converted into the corresponding benzylboronates (Scheme 2, type A). As expected, halides are compatible with the transition-metal-free reactions (**1e–g, j**). It is noteworthy that a boron group is also compatible with the reaction conditions (**1h**). With a tosylhydrazone derived from a α,β-unsaturated aldehyde, the reaction afforded moderate yield (Scheme 2, type B). For the alkyl-substituted tosylhydrazones, the reaction needed a higher temperature and only gave low to moderate yields (Scheme 2, type C).

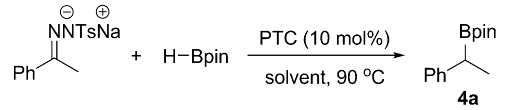


Scheme 2. Reaction of tosylhydrazone with B_2pin_2. Reaction conditions: tosylhydrazone (0.5 mmol), B_2pin_2 (0.6 mmol), NaOMe (1 mmol), MeOH (1 mmol), toluene (2 mL), 90 °C, 3–12 h. Yields were determined by GC with dodecane as internal standard. [a] Yields were determined by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as internal standard. [b] The reactions were carried out at 110 °C.

However, when tosylhydrazones derived from ketones were used as reactants, only a trace amount of the desired borylation products could be detected, even with an elevated reaction temperature or prolonged reaction time. Moreover, it was noticed that for the tosylhydrazone with a secondary alkyl substituent the corresponding borylation only afforded a very low yield (Scheme 2, **3b**). These observations led us to hypothesize that the diminished reactivity might be due to steric hindrance between the tosylhydrazone substrate and the diboron reagent. To circumvent such a problem, we conceived that pinacolborane (HBpin) might be a suitable borylating agent, as it is less sterically demanding. HBpin is also a commonly used borylation reagent and it is much cheaper than B_2pin_2.

After some initial experiments, we concluded that a sodium tosylhydrazone salt was better suited for the borylation with HBpin (Table 2). When a mixture of the tosylhydrazone salt and HBpin was heated at 90 °C for 48 hours, 36 % yield of the borylation product **4a** was obtained (Table 2, entry 1). In view of the fact that phase-transfer catalysts (PTC) can facilitate the dissolution and subsequent conversion of the tosylhydrazone salt into the corresponding diazo compound,[20] several typical PTC were tested in the reaction. Benzyltrimethyl ammonium chloride (BTMAC), a commercially available and cheap PTC, was found to be the best one for the reaction (Table 2, entry 6).

Table 2: Optimization of the reaction of tosylhydrazone salt with HBpin.[a]



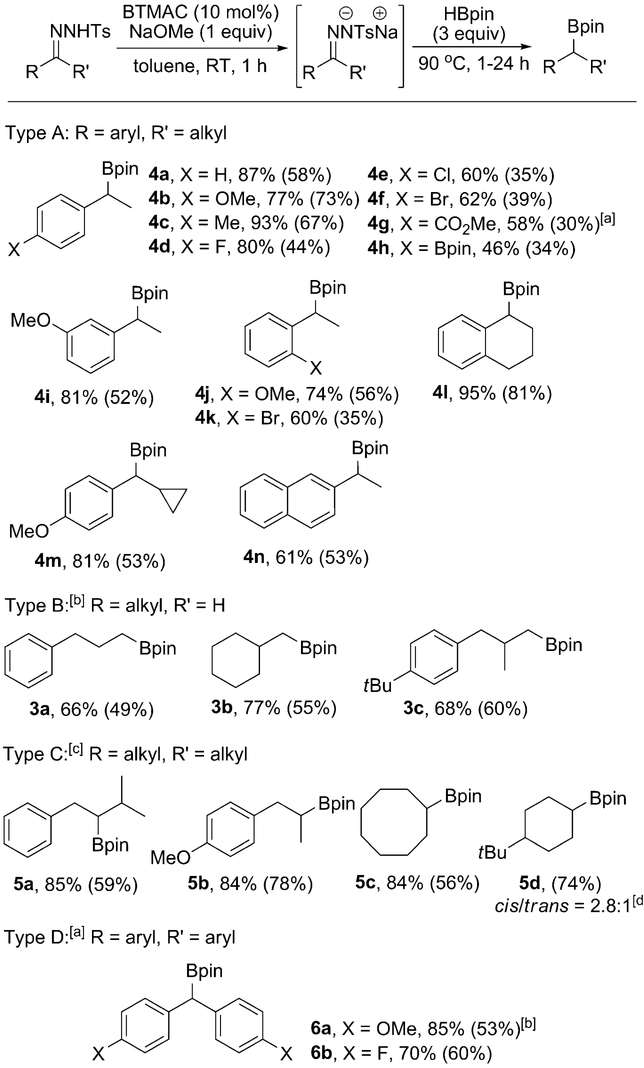
Entry	Solvent	PTC	*t* [h]	Yield [%][b]
1	Toluene	–	48	36
2	Toluene	TBAB	6	60
3	Toluene	TBAC	16	53
4	Toluene	15-crown-5	3	50
5	Toluene	BTEAC	2	63
6	Toluene	BTMAC	3	74

[a] Reaction conditions: tosylhydrazone salt (0.5 mmol), HBpin (0.75 mmol), PTC (0.05 mmol), toluene (1 mL), 90 °C. [b] Determined by GC with dodecane as internal standard. TBAB = tetrabutylammonium bromide, TBAC = tetrabutylammonium chloride, BTEAC = benzyltriethylammonium chloride.

The optimized reaction conditions (Table 2, entry 6) could be further simplified by generating the tosylhydrazone salts in situ. To our delight, in the case of **4a**, a slightly higher yield could be obtained with the in situ tosylhydrazone salt preparation procedure.

A series of tosylhydrazones were then examined under the optimized reaction conditions (Scheme 3). This borylation procedure worked well with a variety of tosylhydrazones derived from ketones and aldehydes (Scheme 3, types A–D).

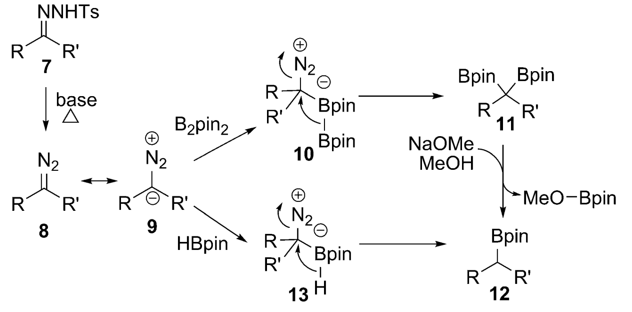
For the type A substrates, moderate to high yields of borylation products could be obtained, no matter whether the substituents on the aromatic ring are electron-donating groups (Scheme 3, **4b, c, j, l**) or electron-withdrawing groups (Scheme 3, **4d–h, i, k**). It is noteworthy that the cyclopropyl group remains intact in the reaction (Scheme 3, **4m**). This fact suggests that a free carbene species is not involved in the reaction mechanism, because a carbene adjacent to a cyclopropyl group would undergo a ring-expansion rearrangement or the carbene may be protonated.[21] For type B substrates, the borylation with tosylhydrazones derived from aliphatic aldehydes proceeded well. Compared with the reaction shown in Scheme 2 (type C), the yield for **3b** is now significantly improved. The borylation



Scheme 3. Reaction of tosylhydrazone salt with HBpin. Reaction conditions: tosylhydrazone (1 mmol), NaOMe (1 mmol), BTMAC (0.1 mmol), HBpin (3 mmol), toluene (8 mL), 90 °C, 1–24 h. The yields were determined by GC with dodecane as internal standard, and those in the brackets are yields of the isolated products, purified by silica gel column chromatography. [a] No BTMAC was added. [b] The reactions were carried out at 110 °C for 12 h. [c] The reactions were carried out at 110 °C for 24 h. [d] Isolated as the corresponding alcohol and the ratio of *cis* to *trans* was based on the analysis of the crude product by ^{1}H NMR spectroscopy (400 MHz).

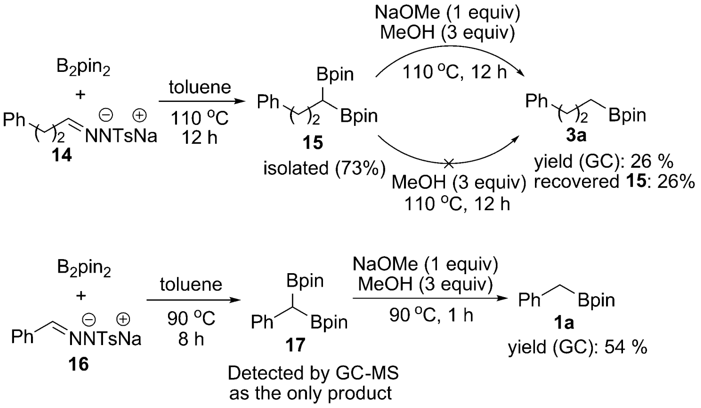
also works well with tosylhydrazones derived from aliphatic ketones (Scheme 3, type C) and those derived from aromatic ketones (Scheme 3, type D).

The proposed reaction mechanism for this borylation reaction is shown in Scheme 4. First, diazo compound **8** is generated in situ from tosylhydrazone in the presence of base. The nucleophilic diazo carbon then coordinates to the B_2pin_2 or HBpin to form boronate intermediate **10** or **13**. From intermediate **10**, 1,2-boron migration occurs to form 1,1-diboron intermediate **11**,[22,23] which is further converted into product **12** after protodeboronation of one boronate group. From intermediate **13**, 1,2-H migration occurs to give the borylation product **12** directly.



Scheme 4. Mechanistic rationale.

To verify the mechanistic hypothesis, we carried out an experiment to isolate the 1,1-diboron intermediate (Scheme 5). Thus, tosylhydrazone salt **14** was prepared separately, and was then reacted with B_2pin_2 at 110 °C. The 1,1-diboron compound **15** was detected as the only product by GC-MS, and it was isolated in 73 % yield. A parallel reaction, in which NaOMe and MeOH were added after **15** was formed, was then carried out. The corresponding product **3a** was obtained in 26 % yield, together with recovery of 26 % of **15**. A control experiment showed that the base was essential for the protodeboronation step, because **3a** was not formed when only MeOH was added. The same experiment was carried out with tosylhydrazone salt **16** and similar results were obtained.



Scheme 5. Isolation and reaction of 1,1-diboron intermediates.

It is noteworthy that in Scheme 3, the thermodynamically less-favorable *cis* isomer **5d** is formed as the major borylation product. The stereoselectivity of boron product **5d** can be interpreted according to the proposed reaction mechanism.[24]

In summary, we have developed a metal-free reaction to convert tosylhydrazones into pinacol boronates. Both B_2pin_2 and HBpin can be used as the borylation reagents. The reaction has wide substrate scope and can be applied to the synthesis of benzyl-, alkyl-, and allylboronates. Since tosylhydrazones can be easily prepared from aldehydes or ketones, this novel approach is expected to find wide applications for the synthesis of boron compounds. Finally, this reaction represents another important synthetic application of tosylhydrazones, which have recently attracted great attention in transition-metal-catalyzed cross-coupling and metal-free reactions.[25]

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