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COMMUNICATION

Rhenium-Catalysed Dehydrogenative Borylation of Primary and Secondary C(sp³)-H Bonds Adjacent to a Nitrogen Atom

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Rhenium-catalysed C(sp³)-H bond borylation in the absence of any oxidant, hydrogen acceptor, or external ligand, with the generation of H₂ as the sole byproduct is described. The transformation, which represents a rare example of rhenium-catalysed C(sp³)-H bond functionalisation, features high atom efficiency and simple reaction conditions.

Catalytic dehydrogenative functionalisation has emerged as a powerful and elegant tool for the construction of complicated molecules without preactivation of starting compounds.¹ Because the only byproduct is hydrogen, this method represents an ideal synthetic procedure in terms of atom economy. A wide variety of catalytic functionalisations of C(sp²)-H bonds have already been developed, and there have had a significant impact in the field of organic chemistry. Much attention is currently focused on direct functionalisation of relatively unreactive C(sp³)-H bonds through dehydrogenation. Although catalytic dehydrogenative carbon-carbon and carbon-heteroatom bond formation have been much examined using copper, iron, and palladium complexes, these methods usually require an excess amount of oxidant as a hydrogen acceptor in order to overcome the unfavourable thermodynamic conditions. We report herein rhenium-catalysed dehydrogenative borylation of *primary and secondary* C(sp³)-H bonds with the aid of a nitrogen directing group under *oxidant- and hydrogen-acceptor-free* conditions (Figure 1).²

Transition metal-catalysed C(sp³)-H borylation is an important transformation, because it provides straightforward access for the

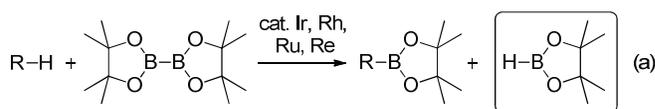
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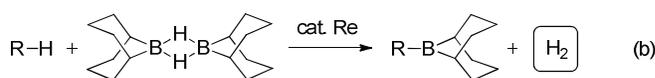
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† Electronic Supplementary Information (ESI) is available: Experimental details and analytical data are provided. See DOI: 10.1039/b000000x/

Previous Work



This Work (Catalytic dehydrogenative borylation of primary and secondary C(sp³)-H bonds)



High atom economy. No oxidants, external ligands or additives.

Figure 1. Transition metal-catalysed borylation of C(sp³)-H bonds

introduction of various functional groups to simple alkyl chains.³⁻⁵ Since the seminal work reported by Hartwig and co-workers, a variety of catalytic borylation reactions of C(sp³)-H bonds, using bis(pinacolato)diboron (B₂pin₂) as a boron source, have been developed.^{2,4} While these methods are very useful, their major drawback is low atom efficiency due to the generation of pinacolborane (HBpin), whose reactivity is reported to be low, as a byproduct (Figure 1(a)).^{4a,6} Indeed, catalytic dehydrogenative borylation reactions of C(sp³)-H bonds with HBpin have been mostly limited to the primary methyl groups of aliphatic hydrocarbons and benzylic methyl groups, and reactions of secondary C(sp³)-H bonds have been found not to proceed efficiently.^{4b-d,i,m} Moreover, most of them require a large excess of substrate as a solvent. One exception is found in Sawamura's recent work on the borylation of secondary C(sp³)-H bonds using an immobilized-rhodium catalyst, in which it is suggested that HBpin, potentially generated from B₂pin₂, also acts as a boron source.^{4i,m} Although non-catalytic-dehydrogenative borylations of primary C(sp³)-H bonds with borane (B₂H₆) have been reported in the literature, they have not been widely applied to organic synthesis due to the requirement for a large amount of substrate with highly reactive promoters under relatively harsh reaction conditions.⁷

In our study aimed at the development of a new and efficient reaction system utilizing rhenium-catalysed $C(sp^3)$ -H bond activation,² the reaction of 2-(*N,N*-dimethylamino)pyridine **1a** with 9-BBN in the presence of $[ReBr(CO)_3(thf)]_2$ as a catalyst in toluene at 125 °C was found to give the borylated compound **2a** in 95% yield (eq 1). The efficiency of the reaction was significantly affected by the choice of solvent, with toluene found to be optimal.⁸ Although several rhenium complexes, including $ReBr(CO)_5$, $ReCl(CO)_5$, $Re_2(CO)_{10}$, and $[HRe(CO)_4]_n$, exhibited catalytic activity, none of them is superior to $[ReBr(CO)_3(thf)]_2$.⁹ Other metal complexes, such as $Mn_2(CO)_{10}$, $MnBr(CO)_5$, $Ru_3(CO)_{12}$, $RhCl(PPh_3)_3$, $Ni(cod)_2$, and $AuCl(PPh_3)$, were totally ineffective, with **1a** recovered intact.¹⁰ Surprisingly, $Pd(OAc)_2$ and $Pd_2(dba)_3$, which were two of the most effective catalysts for our previous dehydrogenative borylation of $C(sp^2)$ -H bonds with 9-BBN, did not give **2a** at all, even when heated up to 200 °C.¹¹ This might be due to the formation of palladium black in the presence of 9-BBN at high temperatures.^{4c} In sharp contrast to the previous $C(sp^3)$ -H borylation with $(Bpin)_2$ or $HBpin$, an iridium-based catalyst system derived from a combination of $[Ir(OMe)(cod)]_2$ and bipyridine or phenanthroline ligands was found to be totally ineffective.⁴ The reaction proceeded efficiently even in the absence of any hydrogen acceptor or oxidant such as norbornene or 3,3-dimethyl-1-butene.¹² The reaction took place efficiently even on a gram scale (1.09 g of **1a** with 1.54 g of 9-BBN) in a 200 mL round-bottom flask under the reaction conditions described.¹³

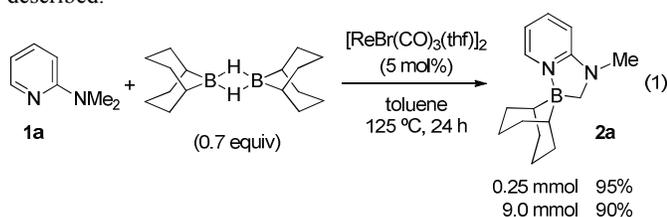


Table 1 shows the scope of substrates for dehydrogenative borylation of primary $C(sp^3)$ -H bonds adjacent to a nitrogen atom under the standard reaction conditions.¹⁴ As expected, higher reactivity of primary over secondary $C(sp^3)$ -H bonds was observed for the reaction of 2-(*N*-hexyl-*N*-methylamino)pyridine **1b** to afford **2b** in 89% yield (entry 1). 2-(*N,N*-Dimethylamino)-4-picoline **1c** reacted with 9-BBN at 150 °C to yield the corresponding borylated compound **2c** in 63% yield, along with recovery of **1c** in 27% yield (entry 2). In contrast, the reaction of **1d**, possessing a fluoride group on the pyridine ring, proceeded smoothly to furnish **2d** in good yield (entry 3). The structure of **2d** was unambiguously determined by single-crystal X-ray structure analysis (Figure S1 in ESI).¹⁵ The electronic nature of directing groups had a significant effect on the efficiency of the reaction. When substrate **1e**, containing a pyrimidyl group in place of a pyridyl group, was used, the yield of the borylated compound **2e** decreased (entry 4). This result may indicate that electron deficiency in the pyrimidyl directing group means that it cannot facilitate the approach of 9-BBN, thus destabilizing the borylated product. Borylation with 1-(*N,N*-dimethylamino)isoquinoline **1f** took place to afford the corresponding product **2f** in moderate yield (entry 5). The current reaction system could also work for 2-isopropylpyridine to afford the corresponding borylated compound albeit in low (< 5%) yield. Dehydrogenative borylation through the activation of $C(sp^3)$ -H

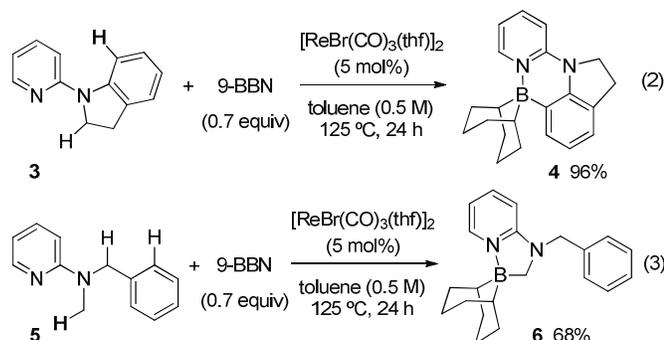
bonds in the substrates shown in Figure S2 in ESI, including 2-methoxypyridine and 8-methylquinoline, did not take place. However, dehydrogenative borylation of secondary $C(sp^3)$ -H bonds proceeded under the current reaction conditions.^{4b-d,i} The reaction of 2-(1-pyrrolidinyl)pyridine **1g** with 9-BBN gave the borylated compound **2g** in 74% yield (entry 6). In contrast, the corresponding borylated piperidine **2h** was not formed, probably due to the slightly lower acidity of the $C(sp^3)$ -H bond derived from lower *s*-character in the larger ring (entry 7).^{4m,h} This hypothesis was supported by the observation that borylation of the benzylic proton adjacent to nitrogen in the six-membered ring took place to afford **2i** in 72% yield (entry 8).

Table 1. Re-catalysed dehydrogenative borylation of the $C(sp^3)$ -H bond of **1**

entry	1	2	recov. of 1 ^a / % yield of 2 ^b / %
1			0 89 (96)
2 ^c			27 63 (67)
3			0 72 (83)
4			73 9 (16)
5			23 51 (62)
6 ^c			0 74 (83)
7 ^c			92 0
8 ^c			4 72 (78)

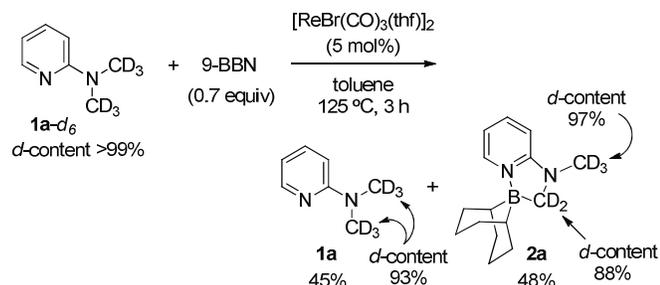
^aDetermined by ¹H NMR. ^bIsolated yields after the purification by silica gel chromatography. Yields in the parentheses are determined by ¹H NMR analysis of the crude product. ^cAt 150 °C.

In a previous study, we reported dehydrogenative borylation of $C(sp^2)$ -H bonds to form N-B coordinated azaboroles, containing a five-membered ring.¹¹ When a reaction of 2,3-dihydro-1H-indole **3** with 9-BBN was carried out, borylation occurred selectively at the sp^2 carbon to form the N-B coordinated compound **4**, containing a six-membered ring, in 96% yield (eq 2).¹⁶ This result clearly reveals the order of reactivity for borylation as $C(sp^2)$ -H > $C(sp^3)$ -H, even for the formation of six-membered rings. Moreover, selective borylation of primary over secondary $C(sp^3)$ -H bonds occurred for 2-(*N*-benzyl-*N*-methyl)pyridine **5** to afford **6** in 68% yield (eq 3). Note that the benzyl group, which is a common protecting group for amines, was tolerated under these reduction conditions.



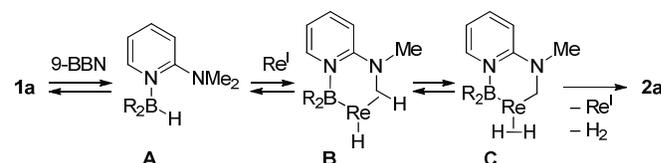
For a preliminary mechanistic study, deuterium-labelling experiments were carried out on the reaction of **1a-d₆** and 9-BBN for 3 h under the standard reaction conditions (Scheme 1). In the presence of 9-BBN, a decrease in D content was observed in both the recovered **1a** and the borylated compound **2a**. This result suggests that the cleavage of C-H bonds occurred competitively and reversibly before C-B bond formation with 9-BBN. Since no hydrogen-deuterium exchange occurred in the absence of 9-BBN, it was concluded that the presence of 9-BBN was required for cleavage of the $C(sp^3)$ -H bonds to take place, and the formation of a rhenacycle intermediate *via* concerted metallation-deprotonation of the $C(sp^3)$ -H bond with Re(I) can be ruled out.^{17,18} Although the correct values for the kinetic isotope effect could not be calculated due to the competitive hydrogen-deuterium scrambling, these results indicate that (1) C-H bond cleavage in **1a** took place reversibly, and (2) the formation of C-B bonds by reductive elimination of Re(I) proceeded slowly compared with C-H bond cleavage in **1a**.

Scheme 1. Deuterium labelling experiment



Based on these results, the reaction mechanism is tentatively proposed as shown in Scheme 2. Lewis acid-base interaction to form **A** may be the key step because the use of other boron reagents with weak Lewis acidity or steric repulsion, including pinacolborane (HBpin), bis(pinacolato)diboron (B_2pin_2), thexylborane, and catecholborane, resulted in no reaction.^{19,20} Oxidative addition of Re^I to the B-H bond followed by the $C(sp^3)$ -H bond cleavage *via* σ -complex-assisted metathesis (σ -CAM) afforded intermediate **C**,²¹ and the subsequent reductive elimination furnished **2a** along with regeneration of the Re^I complex. Although the reaction sequence of oxidative addition of the $C(sp^3)$ -H bond to Re^{III} in intermediate **B** followed by its reductive elimination cannot be ruled out, the energy barrier of this redox process is thought to be higher than that through the σ -CAM pathway.^{22,23}

Scheme 2. Proposed reaction mechanism



In conclusion, rhenium-catalysed dehydrogenative borylation of primary as well as secondary $C(sp^3)$ -H bonds directed by a pyridyl group has been developed. It is noted that the present work constitutes a rare example of rhenium-catalysed transformation of $C(sp^3)$ -H bonds and an example of dehydrogenative borylation of secondary C-H bonds.^{2, 4b-d,i,m} A deuterium-labelling study revealed the reversible nature of C-H activation under the present catalytic cycle. Further investigation to develop the asymmetric version of the reaction is currently in progress.

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- 15 See electronic supplementary information for the detail of X-ray crystal analysis data. CCDC-1035997 contains the supplementary crystallographic data for **2d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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