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Boron

A Clear-Cut Example of Selective Bpin–Bdan Activation and Precise Bdan Transfer on Boron Conjugate Addition**

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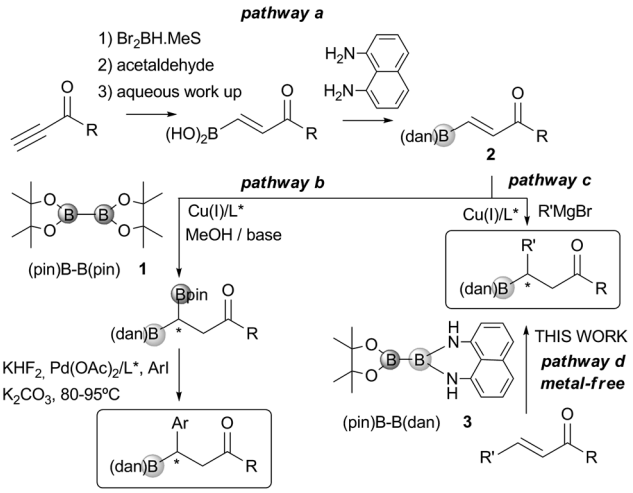
Abstract: Activating the non-symmetrical Bpin–Bdan diboron reagent with alkoxide leads to the formation of two possible adducts: $MeO^- \rightarrow$Bpin–Bdan or $MeO^- \rightarrow$Bdan–Bpin. Experimental and theoretical investigation confirms that the $MeO^- \rightarrow$Bpin interaction is preferred and thus selective formation of a C–Bdan bond upon reaction with an activated C=C bond.

The Lewis acidity of the boron atom is the key factor governing the reactivity of organoboron compounds. The vacant p orbital of the boron atom can be partially filled with the electron lone pair of adjacent atoms, tuning the Lewis acid property. Nitrogen atoms donate their lone pair of electrons, thus lowering the acidity significantly in comparison with that of the corresponding oxygen atoms of boronic acids and their esters.[1] Diamines, which form cyclic diaminoboranes, increase the overall stability of the boryl species, thus reducing the reactivity.[2] Interestingly, organoboranes with C–Bdan moieties (dan = 1,8-diaminonaphthalene) are particularly easy to handle because the dan moiety act as a masking group on the boron atom.[3–5] So far, Bpin moieties have been exclusively transferred from symmetric reagent, B_2pin_2 (**1**), to unsaturated substrates, but the pinacol substituent on the boron center does not mask the boron atom towards further interactions. In that context, the interest of generating C_β–Bdan enoates **2** was justified because they have served as intermediates towards the copper-mediated asymmetric conjugate borylation (Scheme 1, pathway b)[6] or alkylation (Scheme 1, pathway c)[7] with total efficiency. However, nowadays, the synthesis of C_β–Bdan enoates requires a multistep synthetic methodology (Scheme 1, pathway a).[8] We became interested in developing a method to access directly chiral alkylboronate derivatives containing the Bdan moiety from commercially accessible α,β-unsaturated esters and ketones, following a catalytic β-boration reaction (Scheme 1, pathway d).[9] Towards this new strategy, we envisaged the activation of the mixed diboron reagent, Bpin–Bdan (**3**), with an alkoxide.[10] To the best of our knowledge, there is only one example in the literature in which Bpin–Bdan has been used to diborate alkynes in a regioselective manner, and the activation of the diboron by transition-metal complexes was required.[11]



Scheme 1. Synthesis of C_β–Bdan carbonyl compounds.

Initially, we computationally explored the potential reactivity of the Bpin–Bdan reagent. Previous DFT studies by Bo et al. have already demonstrated the nucleophilic character of the B(sp^2) moiety of $MeO^- \rightarrow$Bpin–Bpin adducts.[10b,12] Subsequently, a tendency map was constructed based on DFT calculations and NBO analysis of ground-state structures in order to establish a gradient in the nucleophilic character of trivalent boron moieties.[13a] An approach based on structure–activity relationships (SAR) can be used to screen a large and varied dataset of compounds for homogeneous catalysis.[14] The boron p/s ratio in the M–B σ bond was considered an indicator of the intrinsic nucleophilicity of the boryl fragment, based on a previous work of Lin and Marder.[13b] For diboron reagents that are activated with Lewis bases, the p/s ratio of the B(sp^2) atom is relatively low with respect to the corresponding fragment bonded to Pt (Figure 1). This indicated the greater polarizability of the B(sp^2) moiety in the B–B bond, and consequently, its propensity to react with soft electrophiles. Moreover, the MeO^- ion induced greater polarization of the B–B bond than the nitrogen- and carbon-donor Lewis bases.[13a] Thus, we initially calculated the p/s ratio of the boron atom, from the Bdan(sp^2) moiety, in the $MeO^- \rightarrow$Bpin-Bdan adduct in other to evaluate the potential of Bdan as a nucleophilic boryl moiety.[15] The computed

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[**] pin = Pinacol; dan = 1,8-diaminonaphthalene.

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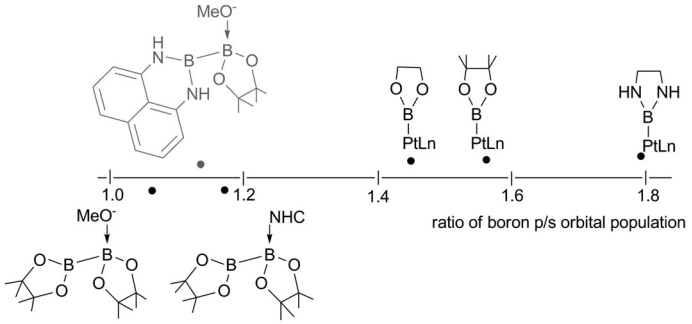


Figure 1. Relative distribution of p/s ratio of the orbital population of the boron atom in B-Pt(PMe_3)$_2$Cl moieties and Lewis acid–base adducts.

p/s value, 1.15, is within the range (1.03–1.19) of other tested diboron compounds activated with Lewis bases (Figure 1).[13a]

Although the tendency map identifies Bdan as a potential nucleophilic boryl moiety,[13a] its semi-quantitative nature does not allow discerning whether the Bdan moiety is more or less reactive than the Bpin moiety. Therefore, we performed a more detailed DFT study in order to compare the reactivity of both adducts (Figure 2).[15] Using the CH_2CHCHO substrate as the simplest model of α,β-unsaturated carbonyl compound, we located the transition states (TSs) corresponding to the nucleophilic attack of the Bpin(sp^2) and Bdan(sp^2) moieties at the β-carbon atom of the olefinic group. The computed energy barrier for the Bdan group (+12.0 kcal mol^{-1}) is higher than that for the Bpin moiety, +4.2 kcal mol^{-1}, indicating that the Bdan(sp^2) has a lower nucleophilic character than Bpin(sp^2). However, owing to the π donation from nitrogen lone pair to boron empty orbital, the acidity of the boron unit is weakened and has less tendency to add the alkoxide. The MeO^-→Bpin–Bdan adduct is 7.4 kcal mol^{-1} lower in energy than MeO^-→Bdan–Bpin. In this scenario, the 1,8-diaminonaphtalene group might protect the boron atom from alkoxide attack, forming preferentially the MeO^-→Bpin–Bdan reagent, which only needs to overcome a modest energy barrier to release Bdan as a nucleophile.[16]

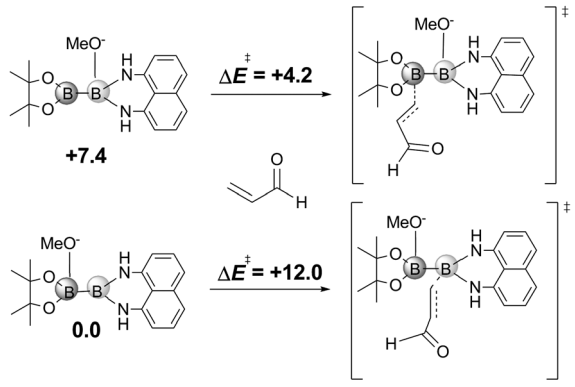
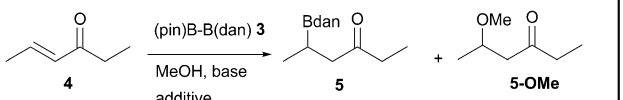


Figure 2. Relative MeO^-→Bpin–Bdan and MeO^-→Bdan–Bpin adduct formation and relative reactivity with CH_2CHCHO. Electronic energies in kcal mol^{-1}.

These results prompted us to use the Bpin–Bdan reagent in the organocatalyic β-boration reation of α,β-unsaturated carbonyl compounds. We adapted the synthetic protocol from Suginome's method,[11] by mixing tetrakis(dimethylamino)diboron, $B_2(NMe_2)_4$,[17] with 1,8-diaminonaphthalene and pinacol in a 1:1:1 ratio. In the presence of a base and MeOH, some spectroscopic evidences demonstrated the formation of the Lewis acid–base adduct [RO^-→Bpin–Bdan]. The original ^{11}B NMR spectra of the mixed diboron reagent Bpin–Bdan, in MeOH as solvent, shows signals at 28.5 and 25.2 ppm owing to the sp^2 Bpin and sp^2 Bdan fragments, respectively. After the addition of 1 equiv of NaO*t*Bu, one of the signals completely shifted to higher fields (1.59 ppm), with one signal remaining at low field (33.2 ppm). The new signal might correspond to the sp^3 Bpin moiety of the adduct [RO^-→Bpin–Bdan] in agreement with previous spectroscopic evidences of [RO^-→Bpin–Bpin].[10] This finding is also in agreement with the DFT calculations that suggested the preferred formation of the Lewis acid–base adduct [MeO^-→Bpin-Bdan].

With the aim of activating organocatalytically Bpin–Bdan (**3**) and selectively transfer the Bdan moiety to activated olefins, we first attempted to find the optimal conditions for the β-boration of 4-hexen-3-one with Bpin–Bdan (Table 1). When the reaction was carried out in MeOH as solvent at 70 °C, no β-borated product was observed. The sole addition of 9 mol% of NaO*t*Bu favored the formation of 5-methoxy-hexan-3-one (**5-OMe**) as the only product, with a conversion of 72% (Table 1, entry 1). It seemed that the MeOH–base interaction provided the methoxy group that directly attacked the substrate instead of activating Bpin–Bdan. However, when no base was present in the reaction media and PCy_3 was added as additive (6 mol%), the substrate was totally transformed into the β-borated product **5** with exclusive formation of the C_β–Bdan bond, (Table 1, entry 2).

Table 1. Optimization of reaction conditions for the organocatalytic β-boration of 4-hexen-3-one (**4**) with Bpin–Bdan (**3**).[a]



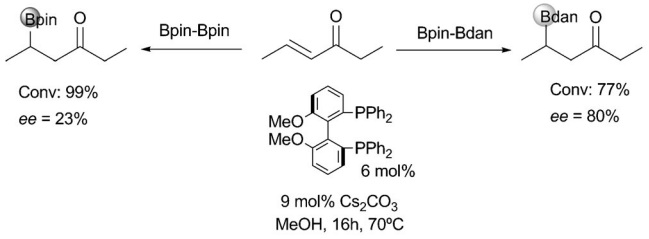
Entry	Additive	Base	Conv [%][b]	C_β–B(dan) (**5**) [%][c]	C_β–OMe (**5-OMe**) [%][c]
1	—	NaO*t*Bu	72	—	99
2	PCy_3	—	99	99	—
3	PCy_3	NaO*t*Bu	99	99	—
4[d]	PCy_3	NaO*t*Bu	23	99	—
5	PPh_3	NaO*t*Bu	99	60	40
6	PPh_3	—	70	99	—

[a] Reaction conditions: substrate (0.25 mmol), Bpin–Bdan (0.275 mmol), base (9 mol%), PR_3 (6 mol%), MeOH (2 mL), 70 °C, 16 h. [b] Conversion calculated by averaging GC-MS data from two reactions. [c] Selectivity calculated by 1H NMR analysis. [d] 25 °C.

The use of phosphines to assist the organocatalytic β-boration reaction of α,β-unsaturated carbonyl compounds was already demonstrated.[18] The presence of base and the use of phosphine as an additive was beneficial (Table 1, entry 3), and the reaction was observed even at 25 °C (Table 1, entry 4). The nature of the phosphine is also important. When PPh_3 was used together with NaO*t*Bu as base, selectivity towards the β-borated product decreased to 60% with the generation of 5-methoxy-hexan-3-one (**5-OMe**) as byproduct (Table 1, entry 5). But once again, when no base was present and PPh_3 assisted the reaction, the β-borated product was exclusively formed, but with lower conversion (Table 1, entry 6). Importantly, the activation of Bpin–Bdan (**3**) with the alkoxide exclusively renders C_β–Bdan formation as no C_β–Bpin product has been detected. The scope of substrates was also a subject of study. Under optimized reaction conditions, we were able to generalize the selective transfer of the Bdan moiety to a variety of α,β-unsaturated ketones and esters (Figure 3).

We recently pointed out that chiral phosphines can assist the asymmetric organocatalytic β-boration of α,β-unsaturated carbonyl compounds with B_2pin_2.[10a] In the present study, we explored this possibility and conducted a parallel β-boration of model substrate **4**, with B_2pin_2 and Bpin–Bdan in the presence of (*R*)-(+)-MeO-BIPHEP diphosphine, (*R*)-(+)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine). Scheme 2 shows that the asymmetric induction in the organocatalytic C_β–Bdan formation is much higher (*ee* = 80%) than that observed in the formation of the C_β–Bpin bond (*ee* = 23%). Other chiral phosphines such as Josiphos-type ligands provided similar results to the β-boration with B_2pin_2.

To get more insight into the selective addition of Bdan moiety in the presence of phosphines as additive, we performed a systematic DFT study using PMe_3 and CH_2CHCHO as model phosphine and substrate, respectively. First of all, DFT studies related to the plausible interaction of PMe_3 with Bpin–Bdan demonstrated the lack of stability of the corresponding



Scheme 2. Comparative asymmetric β-boration of **4** with B_2pin_2 and Bpin–Bdan assisted by (*R*)-(+)-MeO-BIPHEP diphosphine.

[PMe_3→Bpin–Bdan] adduct. Similar conclusion was made from the spectroscopic studies carried out in ^{11}B NMR and ^{31}P NMR by mixing Bpin–Bdan and PMe_3. Recently, Bo et al. computationally characterized the role of the phosphine in the organocatalytic β-boration of α,β-unsaturated ketones and esters with the Bpin–Bpin reagent.[18] In that previous study, the role of the phosphine was associated with the preactivation of the substrate, by forming a phosphonium salt. Following previous proposal,[18] we suggest a catalytic cycle that starts with the plausible phosphine attack on the electrophilic carbon atom of the α,β-unsaturated carbonyl compound, yielding the zwitterionic phosphonium enolate, species **B** in Figure 4. In the presence of an excess of methanol, a MeOH molecule might be hydrogen bonded to the α-carbon atom of intermediate **B**, species **C** in Figure 4. This species may act as a Brönsted base, deprotonating directly the MeOH molecule; however, the process is computed to be thermodynamically disfavored by 5.1 kcal mol^{-1}. From **C**, two ion pairs can be also formed by the interaction with Bpin–Bdan: the [α-H,β-PMe_3-propionaldehyde]$^+$[MeO^-→Bdan–Bpin], **Da**, (Figure 4, mechanism a) and the [α-H,β-PMe_3-propionaldehyde]$^+$[MeO^-→Bpin–Bdan], **Db**, (Figure 4, mechanism b). The corresponding energies associated to the formation of ion pair **Da** (+5.6 kcal mol^{-1}) and **Db** (−7.5 kcal mol^{-1}), clearly shows the favored formation of ion pair **Db**, in which the Bpin moiety acts as the preferred Lewis acid. Moreover, the energy barrier to reach ion pair **Db** is significantly lower than that calculated to reach ion pair **Da**, 4.0 and 13.9 kcal mol^{-1}, respectively. These results are coherent with previous experimental findings in which quantitative formation of the phosphonium species required the presence of the diboron reagent,[18] and indicate that the Bdan moiety is not as good a Lewis acid as the Bpin moiety.

In the next step, it has been suggested that the enhanced nucleophilic sp^2 boryl unit in ion pairs **Da** and **Db** might trans-

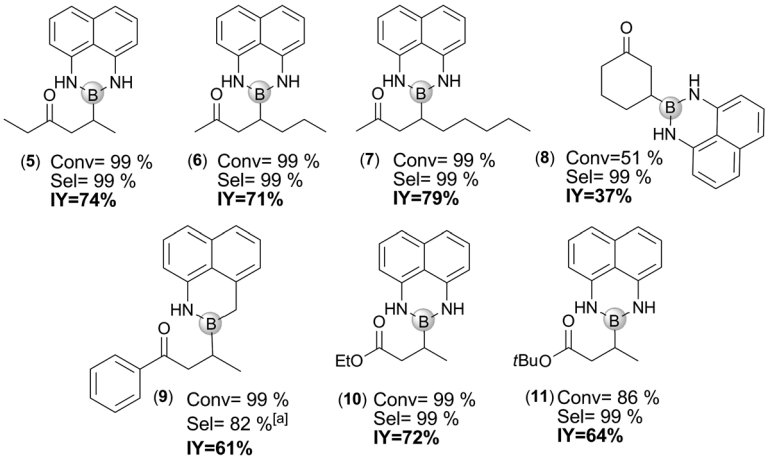


Figure 3. Substrate scope of selective organocatalytic β-boration of α,β-unsaturated carbonyl compounds with Bpin–Bdan under the conditions listed in Table 1 and PCy_3 as additive. IY = isolated yield. [a] 18% of β-methoxy byproduct was observed.

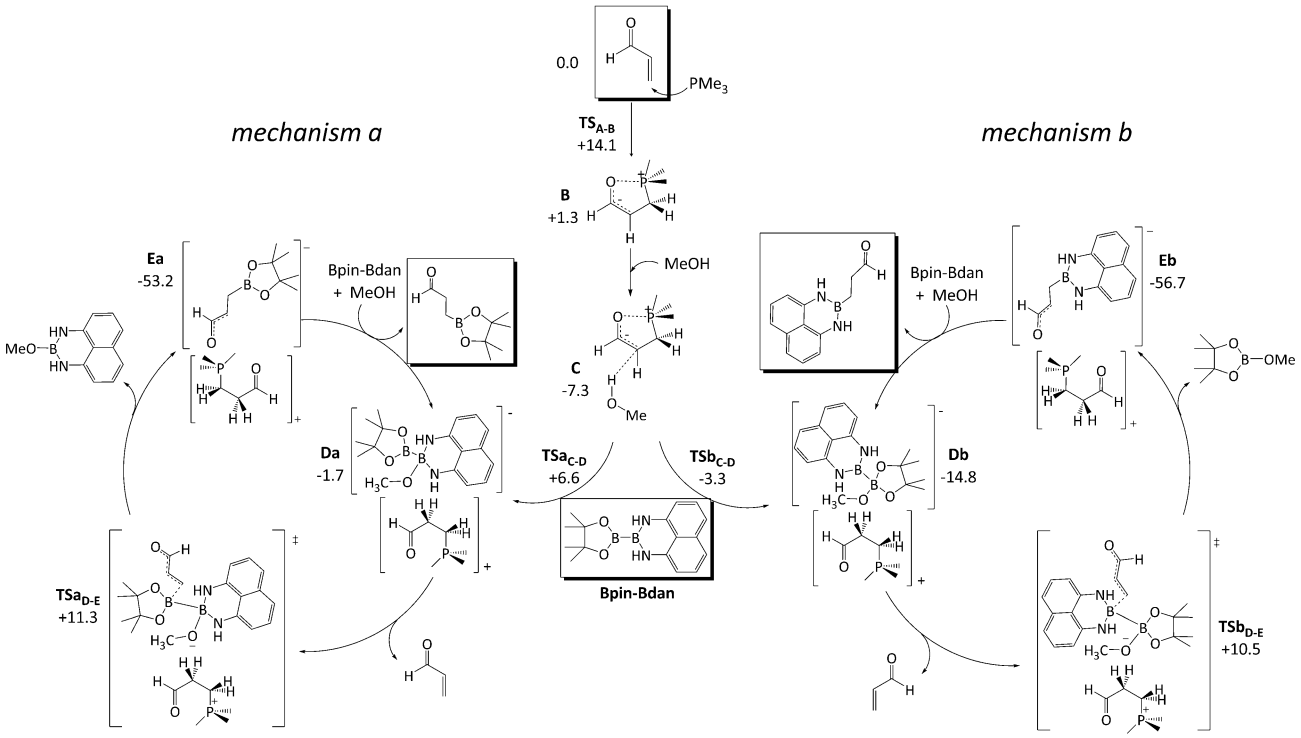


Figure 4. Suggested catalytic cycle for β-boration of acrylaldehyde with Bpin–Bdan diboron reagent in the presence of MeOH and PMe_3. Mechanism a depicts the C_β–Bpin formation and mechanism b illustrates the C_β–Bdan formation. Relative electronic energies in kcal mol^{-1}.

fer the Bpin moiety or the Bdan moiety, respectively, to the β-carbon atom of another molecule of substrate through transition state $\mathbf{TS_{D-E}}$. For both types of boryl units, the process is strongly exothermic, −51.5 kcal mol^{-1} for Bpin release in mechanism a and −41.9 kcal mol^{-1} for Bdan release in mechanism b. As it was found for the free anionic adducts depicted in the Figure 2, the activated Bpin(sp^2) moiety is more reactive than the Bdan(sp^2) one ($\Delta E^{\neq} = 13.0$ and 25.3 kcal mol^{-1}, respectively). However, if we look at the overall catalytic cycle, transition state $\mathbf{TS_{D-E}}$ is the most energetically demanding, and this is higher in energy for Bpin release ($\mathbf{TSa_{D-E}}$) than for Bdan release ($\mathbf{TSb_{D-E}}$) by ca. 1 kcal mol^{-1}. Thus, the computed overall catalytic cycle explains the observed selectivity from both the thermodynamic and the kinetic point of view. Thermodynamically, the deprotonation of methanol requires the enhanced Lewis acidity of the Bpin moiety in Bpin–Bdan by forming the [$MeO^- \rightarrow$Bpin–Bdan] adduct. Kinetically, the overall energy barrier to transfer the Bdan moiety from the ion pair to acrylaldehyde is somewhat lower than that for Bpin transfer.

In summary, we have been able to demonstrate a new activation of B(pin)–B(dan) in the absence of any metal complex. With the assistance of DFT calculations and spectroscopic studies, it was possible to postulate the exclusive formation of the Lewis acid–base adduct [$RO^- \rightarrow$B(pin)–B(dan)]. This activated intermediate reacts with α,β-unsaturated carbonyl compounds to give exclusively the C_β–Bdan carbonyl compound with high yields. In addition to the unprecedented conjugate Bdan addition to α,β-unsaturated ketones and esters, the presence of a chiral diphosphine as an additive assisted the asymmetric induction in a more efficient way than the analogous borylation with B_2pin_2. This new method allows the selective preparation of C_β–Bdan carbonyl compounds in a selective and straightforward manner.

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Keywords: boration · density functional theory · diboron reagents · nucleophilic boron

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