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Unsymmetrical 1,1-diborated multisubstituted sp^3-carbons formed via a metal-free concerted-asynchronous mechanism

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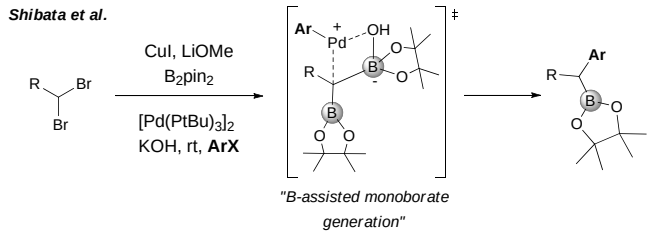
We have experimentally proved the unsymmetrical 1,1-diboration of diazo compounds, formed in situ from aldehydes and cyclic and non-cyclic ketones, in the absence of any transition metal complex. The heterolytic cleavage of the mixed diboron reagent, Bpin-Bdan, and the formation of two geminal C-Bpin and C-Bdan bonds has been rationalised based on DFT calculations to occur *via* a concerted-asynchronous mechanism. Diastereoselection is attained on substituted cyclohexanones and DFT studies provide understanding on the origin of the selectivity. The alkoxide-assisted selective deborylation of Bpin from the multisubstituted sp^3-carbon and generation of a Bdan stabilized carbanion, easily conducts a selective protodeboronation sequence.

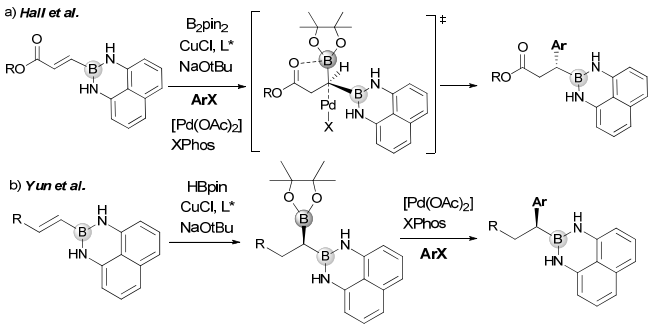
Introduction

1,1-Diborylalkanes are attracting the attention of synthetic researchers since Shibata and co-workers demonstrated in 2010 that two consecutive Suzuki-Miyaura cross-coupling (SMC) reactions can be performed in a chemo and regiospecific manner, even at room temperature.[1] This new concept, based on the protection-free selective cross-coupling on a multisubstituted sp^3-carbon, succeeded by virtue of the adjacent B atom in 1,1-diborylalkanes (Scheme 1). When chiral ligands modify the Pd complex, the reaction can take place through a stereochemical-determining transmetallation with inversion of configuration at carbon.[2] The accomplishment of a second cross-coupling reaction guarantees the formation of unsymmetrical diarylated compounds from simple 1,1-dibromoalkanes.[3c]



Scheme 1. Protection-free cross-coupling on a multisubstituted sp^3-carbon.

The unsymmetrical formation of 1,1-diborylalkane compounds has been elegantly performed by the groups of Hall[4a] and Yun,[4b] through copper mediated asymmetric borylation of β-boronylacrylates (Scheme 2a) and asymmetric hydroboration of borylalkenes (Scheme 2b), respectively. Both strategies share the fact that the substrate already contains the C-Bdan functionality (Bdan = 1,8-naphthalenediaminatoboryl) and the Bpin moiety (Bpin = pinacolboryl) is stereoselectivelly introduced by a copper catalyst modified with a chiral ligand. Interestingly, although in both cases the enantioselection is transferred along the Suzuki-Miyaura cross-coupling[5c] (*via* the trifluoroborate salt), the configuration is inverted for β,β'-diboronylacrylates and retained for 1,1'-diborylalkanes.



Scheme 2. Copper mediated unsymmetrical step wise formation of 1,1-diborylalkane compounds and further functionalization.

To complete the picture of the synthesis and application of 1,1-diborylalkane compounds,[6,7] two parallel strategies have

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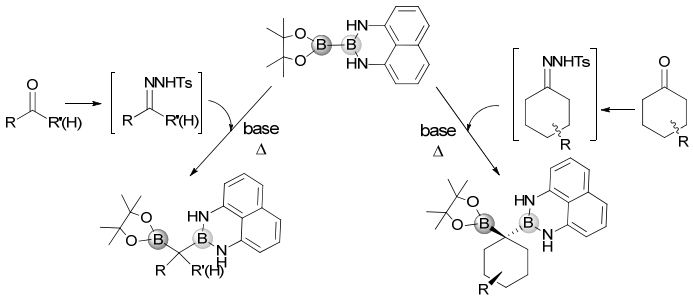
proved their efficiency in formal 1,1-diboration with symmetrical B-B bond: a) Pt-catalysed diborylation of diazoalkanes with Bpin-Bpin[8,9] and b) metal-free carbon insertion of *N*-tosylhydrazones into Bpin-Bpin.[10]

Inspired by the last strategy, we planned here to study the heterolytic B-B bond cleavage, from Bpin-Bdan diboron reagent, employing *N*-tosylhydrazones derived from aldehydes and ketones. In particular, for *N*-tosylhydrazones derived from cyclic ketones, we looked at the potential of diastereoselection when employing diazo precursors possessing diastereotopic π faces (Scheme 3). We have also elucidated, by means of DFT calculations, a plausible mechanism for the 1,1-diboration of Bpin-Bdan as well as the diastereoselective preferences, together with a prediction of the functionalization of the Bpin unit.

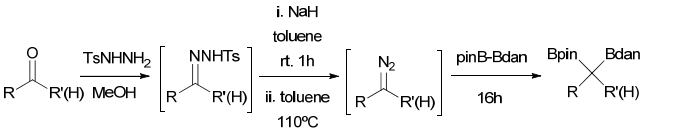


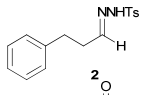
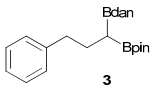
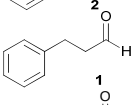
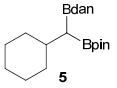
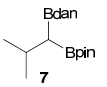
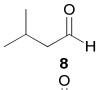
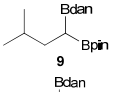
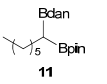
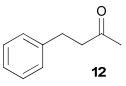
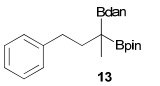
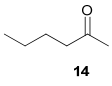
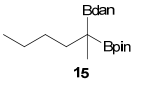
Scheme 3. Metal-free carbon insertion of *N*-tosylhydrazones into Bpin-Bdan

Results and discussion

We initiated our study by reacting hydrocinnamaldehyde (**1**) with *N*-tosylhydrazine. After isolation and recrystallization of the corresponding tosylhydrazone (**2**), the sodium salt of the tosylhydrazone was generated *in situ* by treatment with NaH (1.2 eq) at rt. After 1h, at this temperature, 1.2 eq of Bpin-Bdan was added and the reaction was heated to promote the formation of the diazo intermediate and the subsequent formal carbon insertion in the unsymmetrical B-B bond. Upon workup, the target 1,1-diborylalkane compound (**3**) was isolated in a 71% yield (Table 1, entry 1). Interestingly, when the *N*-tosylhydrazone **2** was used without purification, the final 1,1-diborylalkane product **3** was isolated in a comparable isolated yield, 75% (Table 1, entry 2). Encouraged by this promising streamlined 1,1-diboration with unsymmetrical diboron reagent, we sought to transform a series of aldehydes into 1,1-diborylalkane compounds following this one-pot insertion strategy. The aliphatic aldehydes were converted into the desired products in comparable good yields (Table 1, entries 3-6). Particularly noteworthy was the conversion of substrates **4** and **6** featuring an increased steric bulkiness around the Cα. Extension of the 1,1-diboration protocol to ketones, such as benzylacetone (**12**) and 2-hexanone (**14**) resulted in a diminished reactivity towards the corresponding 1,1-diborylalkanes **13** and **15**, respectively, most probably due to the steric hindrance.

Table 1. 1,1-Diboration of aldehydes and ketones with Bpin-Bdan, via *N*-tosylhydrazones / diazo intermediates formation.[a]

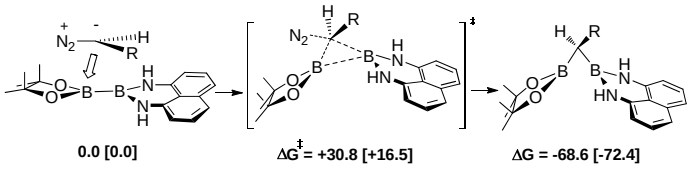


Entry	Substrate	Product	NMR yield. (%)[b]	Isolated Yield (%)[c]
1			75	71
2		" "	81	75
3			68	49
4			83	71
5			82	73
6			95	77
7			55	43
8			44	27

[a]Reaction conditions *for N-tosylhydrazone formation*: substrate (0.25 mmol), $TsNHNH_2$ (0.25 mmol), MeOH, 2-3 h, rt; *for hydrazone sodium salt formation*: NaH (1.2 eq), 1h, rt; *for diazoalkane generation and insertion*: BpinBdan (1.2 eq), 110ºC, 16h. [b]Yield calculated by NMR spectroscopy with ferrocene as internal standard; [b]Isolated yield calculated based on the aldehyde or ketone substrate

A plausible mechanistic pathway has been elucidated by DFT calculations[11] using Bpin-Bdan and $CH_3(H)CN_2$ as model diazoalkane. Scheme 4 summarizes the outcome of these calculations. We were able to locate a transition state for the formation of the two carbon-boron bonds that indicates the occurrence of a concerted, yet asynchronous, mechanism with a free energy barrier of 30.8 kcal.mol^{-1} (Figure 1). As the nucleophilic diazo carbon attacks to the electron deficient boron of Bpin moiety, the 1,2-boron migration of the Bdan moiety occurs to yield the 1,1-diboron intermediate and concomitant release of the dinitrogen. A similar mechanism has

been postulated for the metal-free insertion of diazoalkanes into HBpin, Me_2PhSi-Bpin and Bpin-Bpin.[10] In those cases, the authors proposed a process that may initiate with the formation of a Lewis acid-base interaction between the diazoalkanes and Bpin moiety, prior to the 1,2-addition of the H, Me_2PhSi, or Bpin fragment. To further analyze the diboron addition and the possible formation of a stable Lewis acid-base adduct, we performed a relaxed potential surface scan along different values of the C-Bpin bond (see Figure S1). Starting at the transition state, only in the free-energy curve, we could observe a very shallow minimum when the C-B distance was increased (at ~1.83 Å), and its estimated free energy barrier for dissociation was very low, ~1 kcal.mol^{-1}. Thus, we can conclude that the nucleophilic attack and the 1,2-boron migration occurs in a concerted but asynchronic manner. We have also characterized an analogous pathway in which the diazo carbon attacks to the other boron of Bdan moiety. As expected,[12] the lower Lewis acidity of the Bdan fragment increases the energy barrier by ~2 kcal.mol^{-1}. For comparison, we analyzed the diazoalkane insertion into symmetric BpinBpin, finding the same concerted, yet asynchronous, mechanism and a very similar free energy barrier, 29.7 kcal.mol^{-1} (see SI).



Scheme 4. Proposed mechanism for diazo compound type insertion of $CH_3(H)CN_2$ into Bpin-Bdan. Calculated free energies (and electronic energies in brackets) in kcal.mol^{-1}

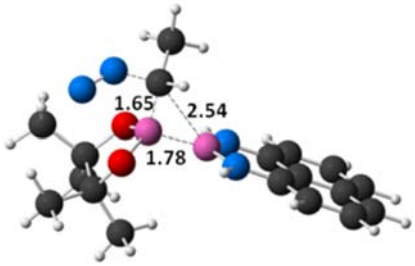
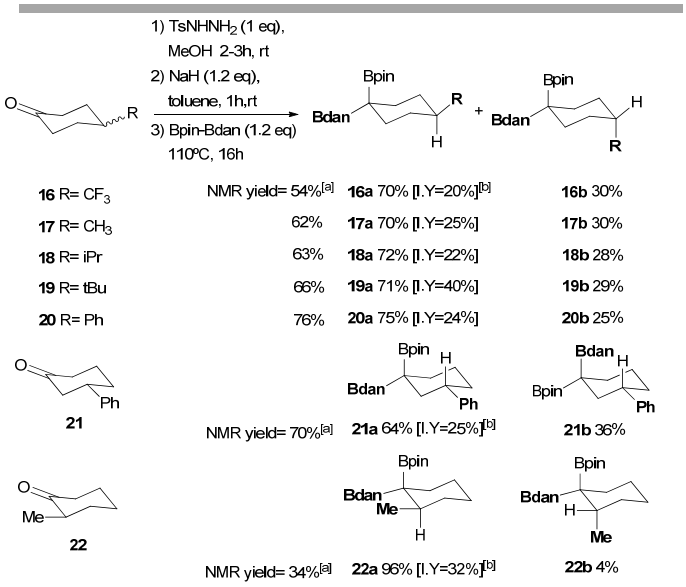
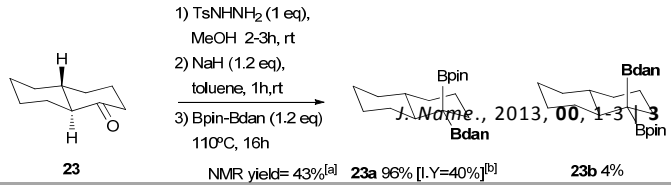


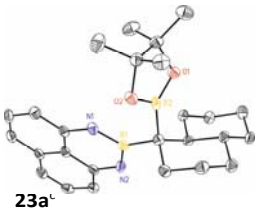
Figure 1. Molecular structure and main geometric parameters of the transition state for diazo compound type insertion into the Bpin-Bdan molecule. Distances in angstroms.

With the aim of exploring the diastereoselection in the multisubstituted sp^3-carbon formed, we selected a series of cyclic ketones to in situ generate the diazo compound and promote the insertion into the Bpin-Bdan molecule. Interestingly, when 4-(trifluoromethyl)cyclohexanone (**16**) was subjected to the diboration protocol, the corresponding insertion took place in a diastereoselective manner and compounds **16a** was obtained as a major diasteroisomer in a (70/30) proportion (Scheme 5). Similar diastereoselection has been observed for the 1,1-diboration of 4-R-cyclohexanone (R= Me, tBu, iPr and Ph) with major diastereomeric ratio observed for **20a**/**20b** (75/25) (Scheme 5). Diastereoisomers **16a**-**20a** could be isolated in a pure form. Through the X-ray analysis of suitable single crystals of **16a** (Scheme 6) the di-equatorial (*trans*) position of the Bdan fragment and the CF_3 group was unequivocally established. There is only one precedent in the literature that reports the 1,1-diboration of 4-Ph-cyclohexanone (**20**) with B_2pin_2, with comparable yields but, diboration of 3-Ph-cyclohexanone (**21**) with BpinBdan, the diastereomeric ratio 64/36 was in favor of the stereoisomer logically, without diastereoselection due to the symmetry of the diboron reagent.[10b] When we conducted the 1,1- **21a** with Bdan and Ph in *cis* relative configuration (Scheme 5). Unfortunately, the 2-Ph-cyclohexanone did not undergo any insertion reaction, likely due to steric hindrance. Interestingly, the analogue 2-Me-cyclohexanone (**22**) did react with BpinBdan through the in situ diazoalkane, providing the highest stereoselection of 96/4 in favor of the diastereomer with Bdan and Ph in *trans* (Scheme 5). As a proof of concept, we selected *trans*-1-decalone (**23**) to be transformed into the corresponding diazo compound and explore its insertion into the Bpin-Bdan molecule. To our delight, the new multisubstituted sp^3-carbon was formed with moderate yield but outstanding diastereoselectivity, towards the isomer with the Bdan moiety in the equatorial position **23**a (Scheme 6).



Scheme 5. 1,1-Diboration of substituted cyclohexanones and *trans*-decalone. [a]Yield determined by NMR spectroscopy with ferrocene as internal standard. [b]Isolated yield based on the ketone.





23a[c]

Scheme 6. 1,1-Diboration of *trans*-1-decalone (**23**). [a]Yield determined by NMR spectroscopy with ferrocene as internal standard. [b]Isolated yield based on the ketone. [c]X-Ray structural determination for major isomer **23a**

The DFT analysis of the origin of diastereoselective preferences is summarized in Schemes 7 and S1 (SI). For 4-(trifluoromethyl)cyclohexanone (**16**), we considered two possible chair conformations with the CF_3 substituent in equatorial or axial position, the equatorial conformer (**16Neq**) being 1.7 kcal.mol^{-1} lower than the axial one (**16Nax**). The species **16Neq** can attack to the Bpin-Bdan substrate through its two diastereofaces (Scheme 7, left) and the computed free energy barriers are 33.9 and 38.9 kcal.mol^{-1}. The latter path, leading the Bdan in axial position (**16b'**) is higher in energy (~5 kcal.mol^{-1}) due to the destabilizing *1,3-diaxial* interactions with cyclohexane structure (see Scheme 7 and Figure S2). Thus, the computed lowest energy path conducts to the experimentally obtained disastereoisomer with Bdan and CF_3 substituents in the equatorial position and *trans* to each other (**16a**, See X-Ray structure in Figure 2).

Starting at the diazo conformer with an axial CF_3 (**16Nax** in Scheme 7, right), we observed a similar free energy barriers to those from **16Neq**, 33.9 and 37.7 kcal.mol^{-1} for Bdan addition in equatorial (**16b**) and axial positions (**16a'**), respectively. This indicates that the substituent in *para* position has little influence on reaction center. However, the axial CF_3 shifts up the energy of both paths and the approach of Bdan through the less hindered equatorial channel (**16b**) becomes 1-2 kcal.mol^{-1} higher than the path conducting to **16a**.

Since the energy difference is not too large, we expect a non-negligible formation of the diastereoisomer **16b** with Bdan and CF_3 substituents in *cis* that agrees with the observed diastereoisomeric ratio 70/30. For 2-Me-cyclohexanone (**22**) the DFT analysis of the diastereoismerism shows a similar pattern to **16** (see S1 in SI), but bringing the substituent from *para* to *ortho* position has a direct influence on reaction center. Thus, the path leading to the minor diastereoisomer (**22b**) is destabilized by the *cis*-1,2 interactions of Bdan and methyl substituents in ~5 kcal.mol^{-1} (see Figure S3 and Scheme S1), resulting in a significant increase of diastereoselctivity for *ortho*-substituted cyclohexanones.

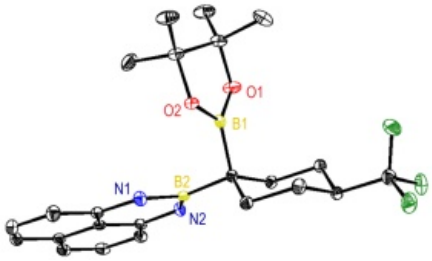
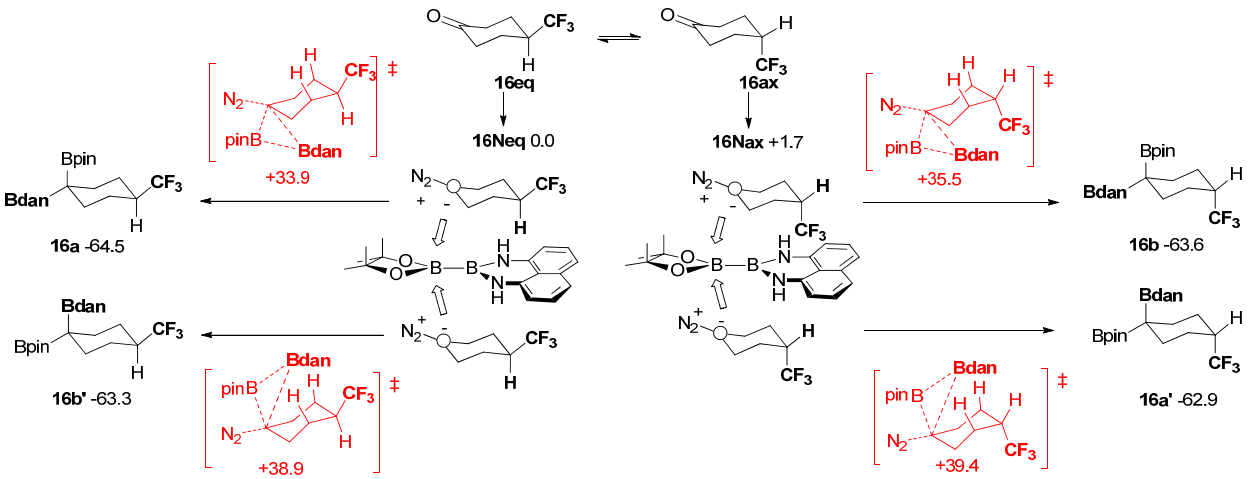


Figure 2. X-Ray structural determination for major product **16a**.



Scheme 7. Proposed diastereoisomeric pathways for the 1,1-diboration of 4-CF_3-cyclohexanone with Bpin-Bdan. Relative Gibbs free energies in kcal.mol^{-1}.

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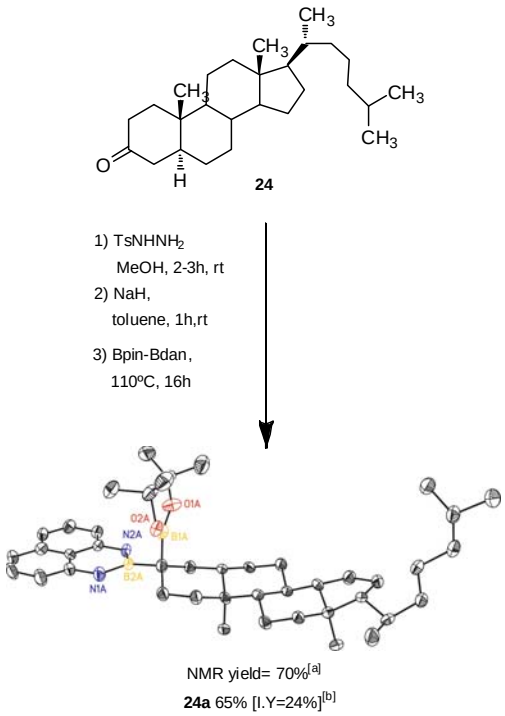
Taking advantage of the potential diastereoselection on this new metal-free 1,1-diboration of cyclic ketones, we selected 5-α-cholestan-3-one (**24**) to transform its carbonyl functional group into a chiral multisubstituted sp^3-carbon in a one-pot protocol. Scheme 8 illustrates the formation of the chiral gem-diborated product in 70% yield with a diastereomeric ratio 65/35, with the Bdan unit located in equatorial position and Bpin in the axial position, as the preferred isomer.



Scheme 8. 1,1-Diboration of 5-α-cholestan-3-one (**24**) and X-Ray structural determination for major isomer **24a**. [a]Yield determined by NMR spectroscopy with ferrocene as internal standard. [b]Isolated yield based on the ketone.

Our next goal was to establish a selective C-Bpin functionalization from the enriched diastereoselective gem-diborated products. It has been recently described the alkoxide-assisted deborylation and generation of a boron-stabilized carbanion, from 1,1-bis(pinacolboronate)esters, allowing the reactivity with alkyl halides.[13] Initially, we analyzed computationally the reactivity of 1,1-diborylalkanes with alkoxides using $CH_3(H)C(Bpin)(Bdan)$ and MeO^- as model substrates (Scheme S2). As determined previously,[12] the methoxy group interacts preferentially with the Bpin moiety forming a stable Lewis acid-base adduct. From this adduct, the deborylation to give the carbanion occurs with a moderate free energy barrier (21.9 kcal.mol^{-1}). Moreover, the stabilization of the carbanion by the α-Bdan moiety is reflected in the HOMO orbital, which shows strong delocalization of carbanion p-type electron density into the π-channel of Bdan moiety (Figure 3, left). Analogously, the Bdan could be also activated (Scheme S2), but the reaction path is shifted up in energy by ~4 kcal.mol^{-1}, and the resulting α-(pinacolato)boronate carbanion is less stable than the α-(1,8-naphthalenediaminato)boronate by 12.3 kcal.mol^{-1}. According to NBO analysis, the Bpin fragment supports less negative charge (-0.14 e) than the Bdan fragment (-0.21 e), as inferred from the corresponding HOMO orbitals (Figure 3). Thus, selective functionalization of Bpin position is expected.

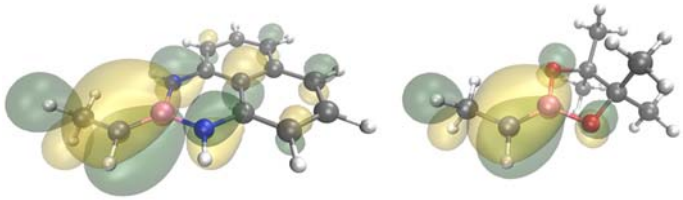


Figure 3. Representation of HOMO orbitals, formally corresponding to carbanion lone pair, for α-(1,8-naphthalenediaminato)boronate anion (left) and α-(pinacolato)boronate (right).

Alike computational results, the exclusive diastereoisomer **22a** was efficiently protodeboronated into the corresponding *trans*-**25(H)** (Figure 4) in the presence of 5 eq. K^{t}BuO at rt. Similarly we conducted the protodeboronation on the diastereomeric mixture of **17a**/**17b**[14] and **21a**/**21b** to afford principally the *trans*-**26(H)** and *cis*-**27(H)**, respectively (Figure 4). This is a new approach towards the diastereoselective C-H bond formation, which complements other efficient protodeboronations on tertiary diarylalkyl boronic esters or tertiary aryldialkyl boronic esters, with CsF-H_2O or TBAF·3H_2O, respectively.[15]

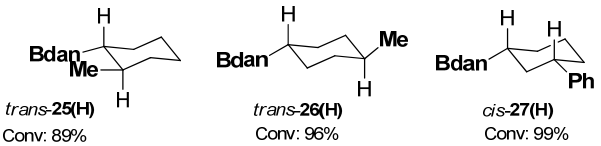


Figure 3. Alkoxide-assisted protodeboronation proces

Conclusions

In summary, we proved the metal-free 1,1-diboration of unsymmetrical Bpin-Bdan diboron reagent to aldehydes and ketones, via diazo compounds. We have disclosed that the carbon-boron formation might occur in a concerted, yet asynchronous, way. High diastereoselectivity can be achieved in *ortho* substituted cyclohexanones due to a combination of repulsive 1,3-diaxial and 1,2-cis interactions with the diboron reagent. In addition, this synthetic strategy can be used to obtain multifunctional chiral centers. Finally, it is possible to deborate selectively the Bpin group via protodeboration in the presence of bases since Bdan moiety stabilize better the transient carbanion species.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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etc.

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