Organic & Biomolecular Chemistry

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Cite this: DOI: 10.1039/c5ob01523e

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

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Received 23rd July 2015,
Accepted 29th July 2015

DOI: 10.1039/c5ob01523e

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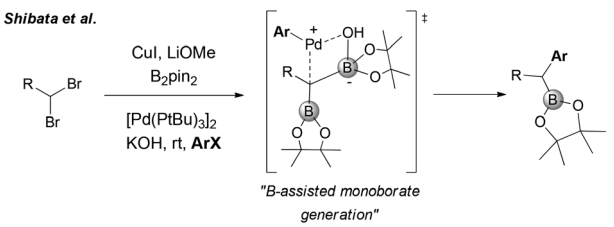
We have experimentally proved the unsymmetrical 1,1-diboration of diazo compounds, formed *in situ* from aldehydes and cyclic and non-cyclic ketones, in the absence of any transition metal complex. The heterolytic cleavage of the mixed diboron reagent, Bpin–Bdan, and the formation of two geminal C–Bpin 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 multisubstituted sp^3-carbon and generation of a Bdan stabilized carbanion, easily conducts a selective protodeboronation sequence.

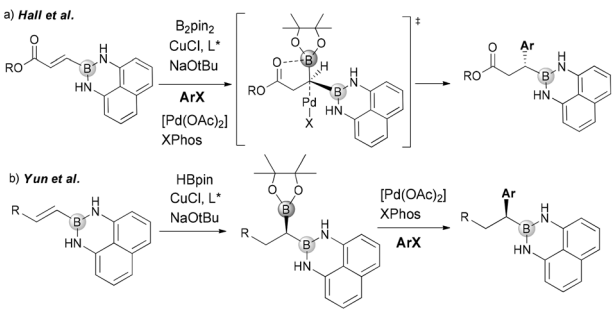
Introduction

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.[3]

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 stereoselectively introduced using a copper catalyst modified with a chiral ligand. Interestingly, although in both cases the enantioselection is transferred along the Suzuki–Miyaura cross-coupling[5] (*via*



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



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

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† Electronic supplementary information (ESI) available. CCDC 1409206–1409208. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob01523e

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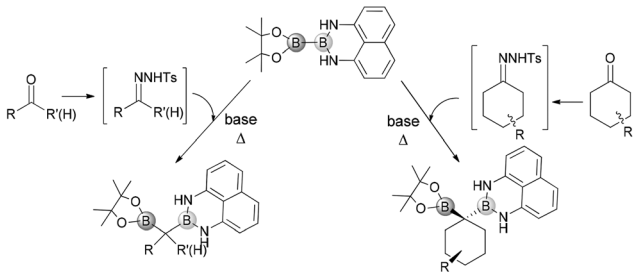


Scheme 3 Metal-free carbon insertion of *N*-tosylhydrazones into Bpin–Bdan.

the trifluoroborate salt), the configuration is inverted for β,β′-diboronylacrylates and retained for 1,1′-diborylalkanes.

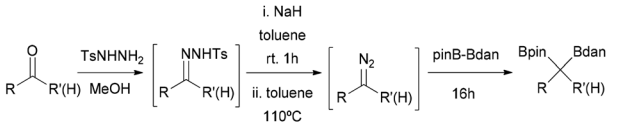
To complete the picture of the synthesis and application of 1,1-diborylalkane compounds,[6,7] two parallel strategies have proved their efficiency in formal 1,1-diboration with a symmetrical B–B bond: (a) Pt-catalysed diborylation of diazoalkanes with Bpin–Bpin[8,9] and (b) metal-free carbon insertion of *N*-tosylhydrazones into Bpin–Bpin.[10]

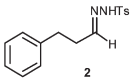
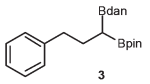
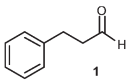
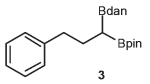
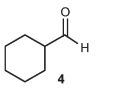
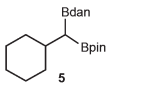
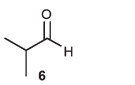
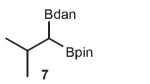
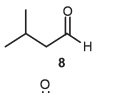
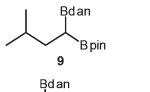
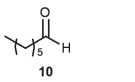
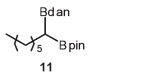
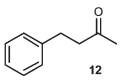
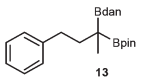
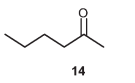
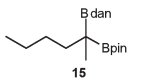
Inspired by the last strategy, we planned here to study the heterolytic B–B bond cleavage, from the Bpin–Bdan diboron reagent, employing *N*-tosylhydrazones derived from aldehydes and ketones. In particular, for *N*-tosylhydrazones derived from cyclic ketones, we looked at the potential of diastereoselection 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.

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 1 h, 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 71% yield (Table 1, entry 1). Interestingly, when *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 an 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

Table 1 1,1-Diboration of aldehydes and ketones with Bpin–Bdan, *via* *N*-tosylhydrazone/diazo intermediate 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.), 1 h, rt; for diazoalkane generation and insertion: BpinBdan (1.2 eq.), 110 °C, 16 h. [b] Yield calculated by NMR spectroscopy with ferrocene as the internal standard. [c] Isolated yield calculated based on the aldehyde or ketone substrate.

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.

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 indicate the occurrence of a concerted, yet asynchronous mechanism with a free energy barrier of 30.8 kcal mol^{-1} (Fig. 1). As the nucleophilic diazo carbon attacks at the electron deficient boron of the 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

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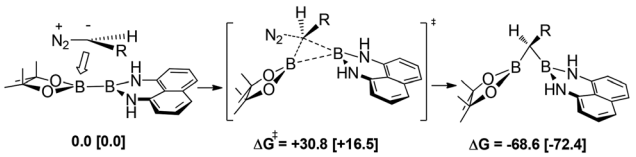


Scheme 4 Proposed mechanism for diazo compound type insertion of $CH_3(H)CN_2$ into Bpin–Bdan. Calculated free energies (and electronic energies in brackets) in kcal mol^{-1}.

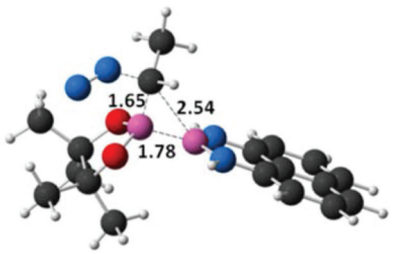
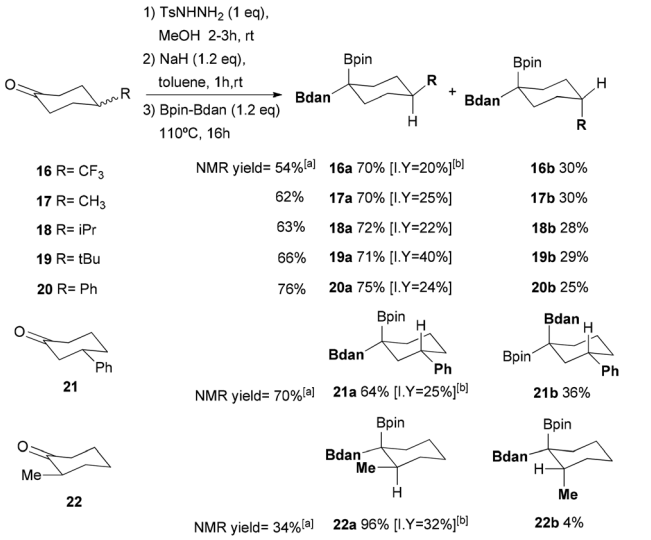


Fig. 1 Molecular structure and main geometric parameters of the transition state for diazo compound type insertion into the Bpin–Bdan molecule. Distance in angstroms.

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 the Bpin moiety, prior to the 1,2-migration 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 Fig. 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 at the other boron of the 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 Bpin-Bpin, finding the same concerted, yet asynchronous, mechanism and a very similar free energy barrier, 29.7 kcal mol^{-1} (see the ESI†).

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 compound **16a** was



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

obtained as a major diastereoisomer in a (70/30) proportion (Scheme 5). A similar diastereoselection has been observed for the 1,1-diboration of 4-methyl-, 4-*tert*-butyl-, 4-isopropyl-, and 4-phenylcyclohexanones with a 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** (Fig. 2) the diequatorial (*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, logically, without diastereoselection due to the symmetry of the diboron reagent.[10b] When we conducted the 1,1-diboration of 3-Ph-cyclohexanone (**21**) with BpinBdan, the diastereomeric ratio 64/36 was in favor of the stereoisomer **21a** with Bdan and Ph in *cis* relative configuration (Scheme 5). Unfortunately, 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 providing the highest stereoselection of 96/4 in favor of the diastereomer with Bdan and Ph in a *trans* configuration (Scheme 5). As a

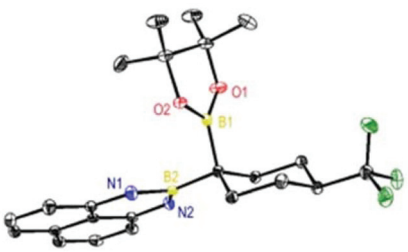


Fig. 2 X-Ray structure determination for major product **16a**.

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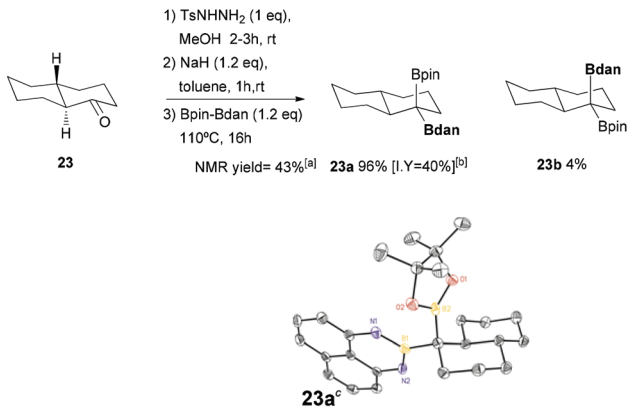
proof of concept, we selected *trans*-1-decalone (**23**) to be transformed into the corresponding diazo compound and explore its insertion into the Bpin–Bdan molecule. To our delight, the new multisubstituted sp^3-carbon was formed with moderate yield but outstanding diastereoselectivity, towards the isomer with the Bdan moiety in the equatorial position **23a** (Scheme 6).

The DFT analysis of the origin of diastereoselective preferences is summarized in Schemes 7 and S1 (ESI).† For 4-(trifluoromethyl)cyclohexanone (**16**), we considered two possible chair conformations with the CF_3 substituent in the 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 at 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 the axial position (**16b′**) is higher in energy (~5 kcal mol^{-1}) due to the destabilizing 1,3-diaxial interactions with a cyclohexane structure (see Scheme 7 and Fig. S2†). Thus, the computed lowest energy path conducts the experimentally obtained diastereoisomer with Bdan and CF_3 substituents in the equatorial position and *trans* to each other (**16a**, see the X-ray structure in Fig. 2).

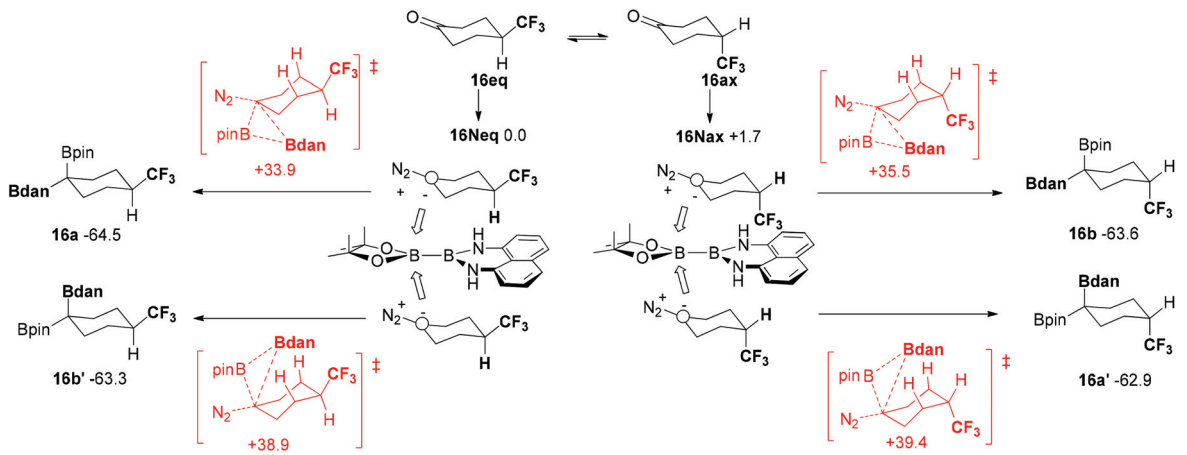
Starting at the diazo conformer with an axial CF_3 (**16Nax** in Scheme 7, right), we observed similar free energy barriers to those from **16Neq**, 33.9 and 37.7 kcal mol^{-1} for Bdan addition in equatorial (**16b**) and axial positions (**16a′**), respectively. This indicates that the substituent in the *para* position has little influence on the 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 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 diastereoisomerism shows a similar pattern to **16** (see Scheme S1 in the ESI†), but bringing the substituent from the *para* to the *ortho* position has a direct influence on the 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 Fig. S3 and Scheme S1†), resulting in a significant increase of diastereoselectivity for *ortho*-substituted cyclohexanones.

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 the equatorial position and Bpin in the axial position, as the preferred isomer.



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



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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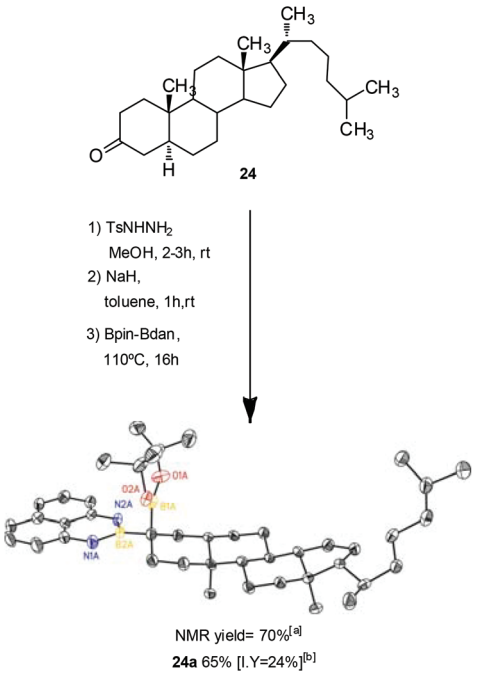

Scheme 8 1,1-Diboration of 5-α-cholestan-3-one (**24**) and X-ray structure determination of major isomer **24a**. [a] Yield determined by NMR spectroscopy with ferrocene as the internal standard. [b] Isolated yield based on the ketone.

Our next goal was to establish a selective C–Bpin functionalization from the enriched diastereoselective *gem*-diborated products. It has been recently described that the alkoxide-assisted deborylation and generation of a boron-stabilized carbanion, from 1,1-bis(pinacolboronate)esters, allow 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 using the α-Bdan moiety is reflected in the HOMO orbital, which shows strong delocalization of the carbanion p-type electron density into the π-channel of the Bdan moiety (Fig. 3, left). Analogously, the Bdan could be also activated

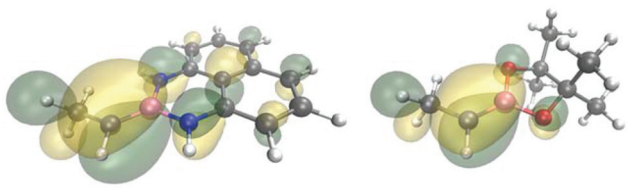

Fig. 3 Representation of HOMO orbitals, formally corresponding to the carbanion lone pair, for α-(1,8-naphthalenediaminato)boronate anion (left) and α-(pinacolato)boronate (right).

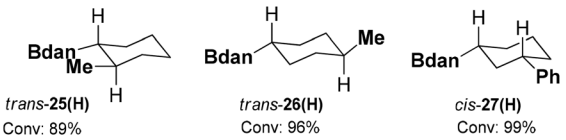

Fig. 4 Alkoxide-assisted protodeboronation process.

(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 a less negative charge (−0.14*e*) than the Bdan fragment (−0.21*e*), as inferred from the corresponding HOMO orbitals (Fig. 3). Thus, selective functionalization of the Bpin position is expected.

Alike computational results, the exclusive diastereoisomer **22a** was efficiently protodeboronated into the corresponding *trans*-**25(H)** (Fig. 4) in the presence of 5 eq. KO^{t}Bu 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 (Fig. 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]

Conclusions

In summary, we proved the metal-free 1,1-diboration of an 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 the Bdan moiety stabilize better than the transient carbanion species.

Acknowledgements

Research supported by the Spanish Ministerio de Economia y Competitividad (MINECO) through projects CTQ2013-43395P and CTQ2011-29054-C02-01.

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