ARTICLE

Alkoxide activation of tetra-alkoxy diboron reagents on C-B bond formation: a decade of unpredictable reactivity

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Jorge J. Carbó*[a] and Elena Fernández*[a]

Any attempt to facilitate a new generation of C-B bonds represents a usefull tool in organic synthesis. In addition, if that approach highlighs the nucleophilic character of boryl moieties in the absence of transition metal complexes, the challenge to create new reactive platforms becomes an opportunity. We have been deeply involved in the experimental and theoretical validation of C-B bond formation by means of alkoxide activation of tetra-alkoxy diboron reagents and here is presented a convenient guide to understand the concept and the applications.

1.Introduction

Tetra-alkoxy diboron compounds are considered stable reagents on the basis of thermodynamic properties of the B–B bond. The strength of the B–B bond, which can be measured by using the homolytic bond dissociation enthalpies (BDEs), has been found to be higher for tetra-alkoxy diboron species than for tetra-alkyl or tetra-amino diboron compounds (Figure 1).[1] Bis(pinacolato)diboron, (B_2pin_2), has a distinctive high homolytic bond dissociation enthalpy, within the tetra-alkoxy diboron compounds, making this species a reliable and easy to handle diboron reagent (Figure 1).

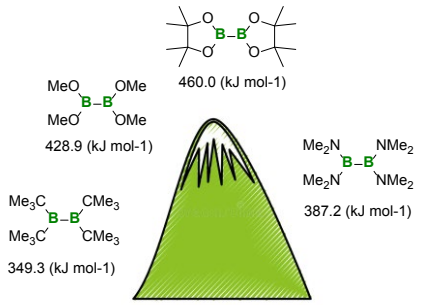


Figure 1. Relative values for bond dissociation enthalpies (BDEs) in diboron reagents.

Miyaura and co-wokers were pioneer on the use of B_2pin_2 as the source of boryl moieties for the synthesis of organoboron compounds.[2] They developed an strategic transition metal activation of the diboron reagent B_2pin_2, involving B-B cleavage via oxidative addition on Pt complexes[3] or via σ-bond metathesis on Cu complexes.[4] The strength of the newly formed Pt–B and Cu–B bonds, after the B–B cleavage, has been determined by Zheng and co-workers observing that the bond dissociation enthalpies for Pt-B or Cu-B are greatly reduced in comparison to the B-B bond dissociation enthalpy. These results are in agreement with the fact that the Pt-B and Cu-B cleavages become favourable and therefore the boryl groups can be better transferred to the substrates, allowing subsequent catalytic sequences to proceed smoothly towards the synthesis of organoboron products.[5,6] The nature of M in M-Bpin bond can gauge the reactivity of the pinacolboryl moieties.[7] Consequently, with the help of computational tools, we have analysed the structural and electronic properties of pinacolboryl fragments that are either bonded to main-group metals or coordinated to transition-metals/rare-earth metals and we have designed a map that might help to select an appropriate M-Bpin species, depending on the sought electrophilic or nucleophilic reactivity of the Bpin motifs (Figure 2a).[8] Remarkably, we also placed in the map the Lewis base adduct formed between B_2pin_2 and alkoxides as a real active source of nucleophilic boryl moieties, in the absence of transition metal complexes (Figure 2b), opening a new perspective on borylative reactions.

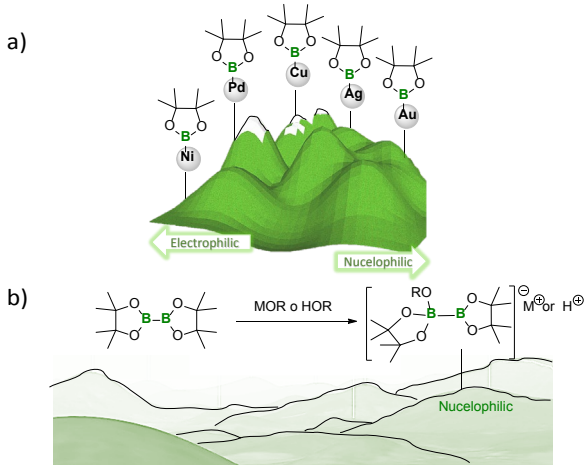


Figure 2. Electrophilic and nucleophilic character for Bpin motifs.

[a] Departament Física Química i Inorgànica, University Rovira i Virgili, Tarragona Spain.

2. Borylations through alkoxide activation of diboron reagents: our grain of sand

Experimentally, we were investigating the influence of coinage metals in catalytic borylation reactions,[9-17] by comparison with those catalyzed by platinum group metals,[18-24] by the time we performed a blank experiment on the β-boration of α,β-unsaturated carbonyl compounds with B_2pin_2, in the absence of any transition metal complex (Figure 3). To our delight, we proved that ethyl (*E*)-but-2-enoate was efficiently transformed into the β-borated product when 4 mol% of PPh_3, 15 mol% of Cs_2CO_3 as base and 2.5 mmol of MeOH were used (Scheme 1). The reactivity was extrapolated to other α,β-unsaturated esters and ketones, demonstrating the generality of the new methodology.[25] In fact this transition metal free protocol assisted by phosphines, as additives, was unpredecented, since only Hosomi and co-workers[26] showed that PBu_3 could induce 7% of conversion along the β-boration of benzylidene acetophenone into the β-borated ketone in the absence of the catalyst precursor CuOTf. The key point for the success in our methodology was the use of MeOH as co-solvent and a base to generate *in situ* the corresponding Lewis base adduct [MeO-pinB-Bpin]$^-$, (Scheme 2a).

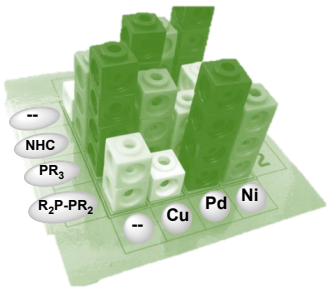
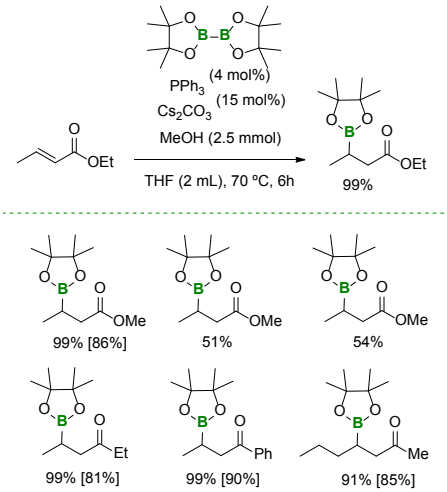
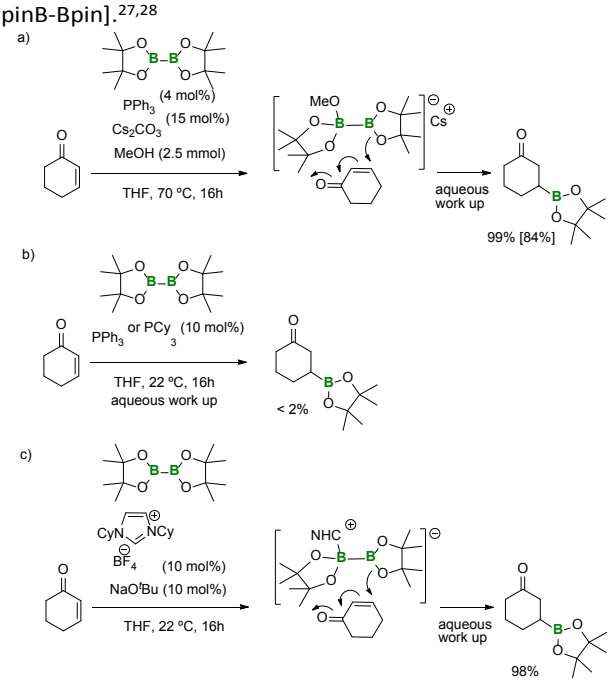


Figure 3. Influence of metals and ligands in catalytic borylation reactions



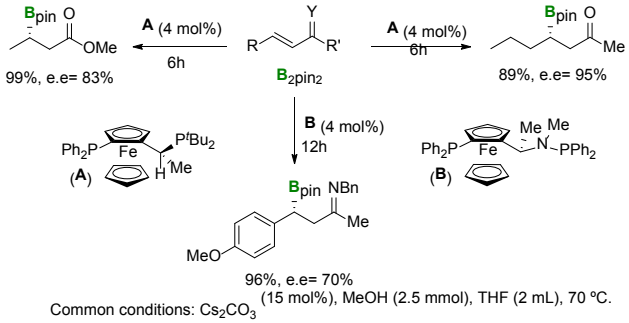
Scheme 1. Representative examples of β-boration of activated alkenes

For the sake of comparison, Hoveyda and co-workers also tried to perform the transition-metal free β-boration of α,β-unsaturated ketones with PPh_3 or PCy_3 but < 2% conversion was observed in the β-borated ketone (Scheme 2b).[27] However, they developed the alternative activation of B_2pin_2 with N-hetrocyclic carbenes (NHC), in the presence of NaO^{t}Bu as base (Scheme 2c), suggesting the Lewis base adduct [NHC--pinB-Bpin].[27,28]



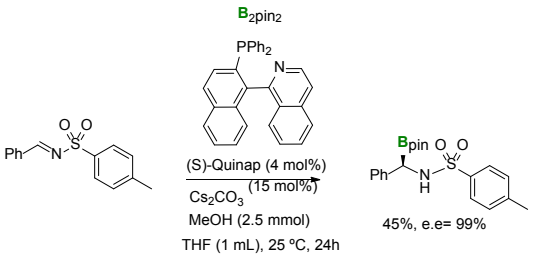
Scheme 2. Comparative strategic transition-metal free β-boration of activated alkenes

The phosphine assisted β-boration of α,β-unsaturated carbonyl compounds with B_2pin_2, allowed the asymmetry induction in the new C-B bond formation, by using standard chiral phosphines. Scheme 3 shows representative examples where the addition of 4 mol% of (*R*),(*S*)-Josiphos (**A**) promoted enantioselectivity up to 83% in β-borated esters and 95% in β-borated ketones. Similarly, α,β-unsaturated imines were transformed into the corresponding β-borated imines, being enantioselectivity induced when chiral diphosphines were involved, such as (*S*)-MeBoPhoz (**B**) (Scheme 3).[29]



Scheme 3. Representative examples of enantioselective β-boration of activated alkenes

The asymmetric borylation of tosylaldimines has also been efficiently performed in the presence of chiral diphoshines as for (*E*)-N-benzylidene-4-methylbenzenesulfonamide that generated the corresponding α-borylamine in 99% e.e. when (S)-Quinap was added in 4 mol% (Scheme 4).[30]



Scheme 4. Representative example of asymmetric borylation of tosylaldimines

The question raised at that point was how the phosphine / MeOH contributed to permit the β-boration reaction as well as the asymmetric induction on the new C-B bond formed. Although we initially suggested that the phosphines might interact with the diboron reagent to activate the B-B bond and promote the asymmetric induction,[25] a deeper study prompted us to postulate that the phosphine might play the role of pre-activation of the substrates via phosphonium enolate intermediate.[31] To probe that, we conducted stoichiometric experiments mixing PMe_3, (E)-hex-4-en-3-one and B_2pin_2 in MeOH, and we observed the quantitative formation of the ion-pair ([α-H,β-PMe_3-3-hexanone]$^+$[MeO-pinB-Bpin]$^-$ full characterized experimentally and computationally as a global minimum in the potential energy surface, taking into account its conformational flexibility. We postulated that the phosphine directly interacts with the most electrophilic carbon of the α,β-unsaturated carbonyl compound resulting in the formation of a strongly basic zwitterionic phosphonium enolate species (Figure 4). This intermediate is further protonated by the excess of MeOH, a process that is particularly favoured by the presence of bis(pinacolato)diboron that stabilizes the MeO^- anion, thus forming the Lewis acid-base adduct [MeO-pinB-Bpin]$^-$ that acts as counteranion (Figure 4). The ion-pair ([α-H,β-PR_3-3-hexanone]$^+$[MeO-pinB-Bpin]$^-$ might be the responsible for the Bpin delivery, and in the presence of chiral phosphines the nucleophilic Bpin transfer could be influenced by the chiral environment of the ion-pair.

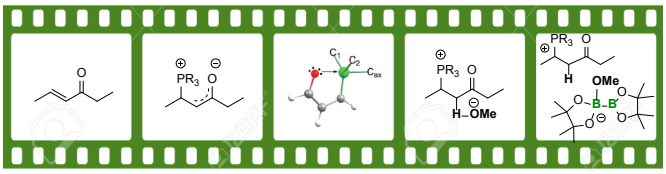


Figure 4. Sequential movie to illustrate the suggested role of phosphines in β-boration of activated alkenes

To obtain deeper insight into the reaction, the structures and stabilities of possible adducts formed within the alkene and the Lewis adduct [MeO-pinB-Bpin]$^-$ system were investigated both experimentally and computationally.[32] The energy profile for the borylation of several monosubstituted alkenes has determined the energy barrier and reaction energies (given as electronic energy and Gibbs free energy in parentheses) relative to [MeO-pinB-Bpin]$^-$ plus the respective alkene (Figure 5). The nucleophilic attack of the B(sp^2) moiety to the terminal carbon of the alkene allows to identify a TS that reflect the cleavage of the B-B bond and the formation of the new B-C bond. A dramatic decrease of the energy barrier is observed when electronic effects stabilize the TS, such as substrates with ester, ketone and aldehyde groups (Figure 5). The highest energy barrier was found for the activation of propylene and styrene. Additionally, the TS structure releases the (pin)B-OMe byproduct and the anionic borylated intermediate which reflect the role of the carbonyl group in stabilization of the negative charge developed on the internal carbon. Indeed, substrates with ester, ketone, and aldehyde groups, which allow charge delocalization, form more stable intermediates than unactivated olefins such a propylene and styrene (Figure 5).

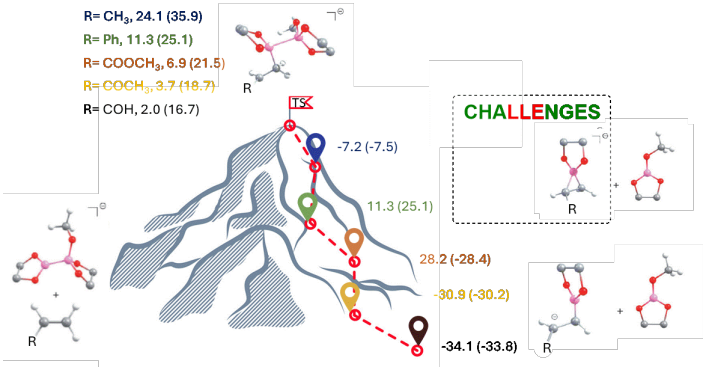


Figure 5. Energy barrier and reaction energies are given as electronic energy and Gibbs free energy (in parentheses) computed at the BP86 level relative to [MeO-pinB-Bpin]$^-$ adduct plus the respective alkene. All values in kcal mol^{-1}.

Next, we focussed on the challenging unactivated alkenes to study how the adduct [MeO-pinB-Bpin]$^-$ might interact with, since both substrates and reagent have nucleophilic characters. Our first surprise was that although the reaction conditions were very similar to those we used for conjugated boron additions to activated olefins, the observed chemoselectivity of the reaction was unpredictable.[33] The challenge became an opportunity to change the borylation process towards the simultaneous formation of two C-B bonds on the alkene. In fact, we observed the nucleophilic attack of the B(sp^2) moiety to the electron rich alkene followed by intramolecular rearrangement to intercept the second boryl moiety from the adduct [MeO-pinB-Bpin]$^-$, resulting in a straightforward diboration reaction conducted for the fist time in a transition metal-free context for B_2pin_2. By investigating the scope of substrates and the reaction conditions for this novel catalytic diboration, we concluded that both terminal and internal alkenes were efficiently transformed towards the diborated product (Figure 6).[33] Another interesting finding is that nucleophilic diboration of allenes favors the formation of 1,2-diborated products, in contrast to most transition-metal-catalyzed diborations of allenes, which usually provide the 2,3-diborated isomers as primary products.[34-36]

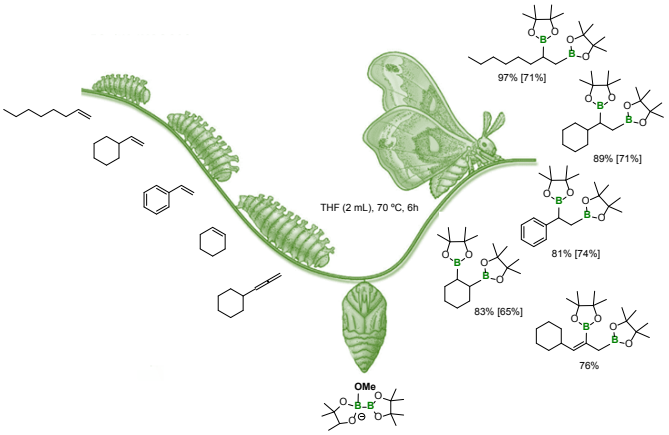
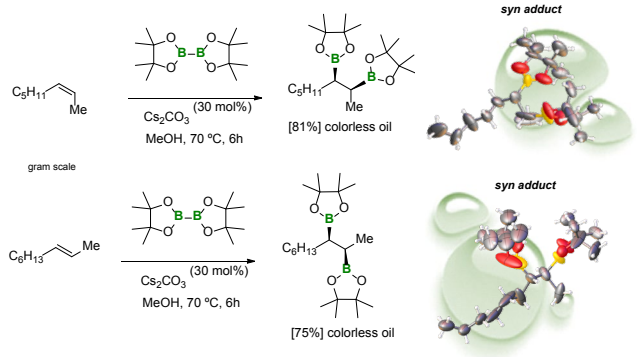


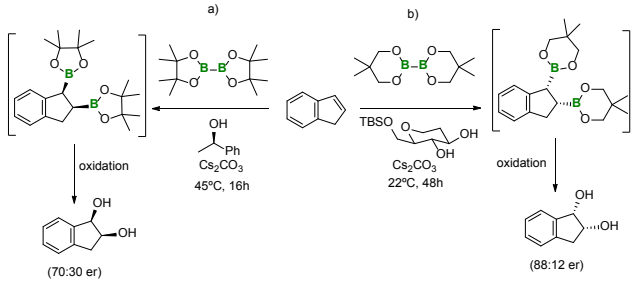
Figure 6. Illustration of the substrate scope in diboration reaction

Undeniable confirmation of the *syn*-addition mechanism for this metal-free diboration of internal alkenes was conducted through the addition of the adduct [MeO-pinB-Bpin]$^-$ to *cis* or *trans* alkenes. Using the crystalline sponge method, in collaboration with Fujita and co-workers (Scheme 5),[37] the crystal structure of those oily products proved that both reaction evolved towards the corresponding *syn* diborated products.



Scheme 5. Stereoselectivity on diboration of *cis* and *trans* alkenes

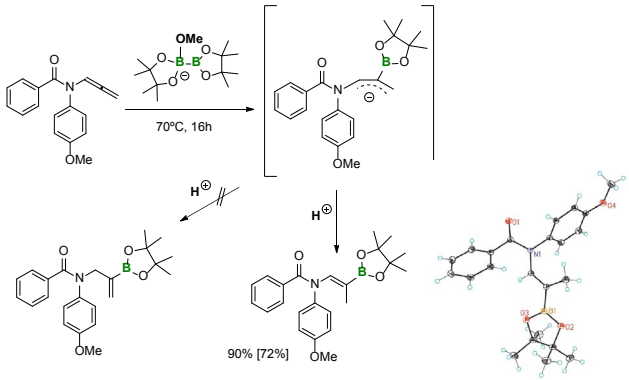
The asymmetric 1,2-diboration of cyclic and non-cyclic unactivated alkenes has been conducted using economically accessible chiral alcohols (R*OH) to form the chiral Lewis acid-base adduct [R*O-pinB-Bpin]$^-$ providing moderate enantioselectivity (Scheme 6a).[38] Alternatively, Morken and co-workers studied this process in the presence of exogenous diol catalysts that were proposed to undergo reversible boronic ester exchange with the diboron reagent bis(neopentyl glycolato)diboron, B_2neo_2 (Scheme 6b).[39,40]



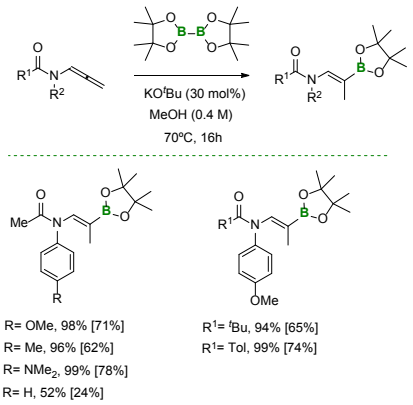
Scheme 6. Enantioselective in diboration reaction

Although, complementary efforts by Morken's group and our group have evolved in remarkable asymmetric induction protocols on transition-metal free diboration reactions, there is still room for innovative proposals to create effective enantioselectivity for a general scope of alkenes.

Alternatively, in collaboration wih Prof. Vicario, we stablished a complete stereocontrol when allenamides reacted through the distal double bond with the adduct [MeO-pinB-Bpin]$^-$, providing exclusively the *Z*-isomers.[41] The acetyl groups on the amine moiety seems to be crucial to obtain the complete stereoselectivity, which is a consequence of the formation of a stable allylic anion intermediate that is further regioselectively protonated to give the final product (Scheme 7). By changing the electron properties of the para-substituents of the aryl group in the allenamide substrates, it was proved that electron-donating para-substituents contributed to quantitative conversions with complete stereoselectivity towards the formation of the *Z*-isomer (Scheme 8). However, a trend that diminished conversions was observed when electron-withdrawing para-substituents on the aryl group were involved but fortunately, this did not affect the exclusive regioselective product formation. Replacement of the Me group by a ^{t}Bu or Tol group at the acyl moiety did not influence the reaction outcome (Scheme 8).[41]



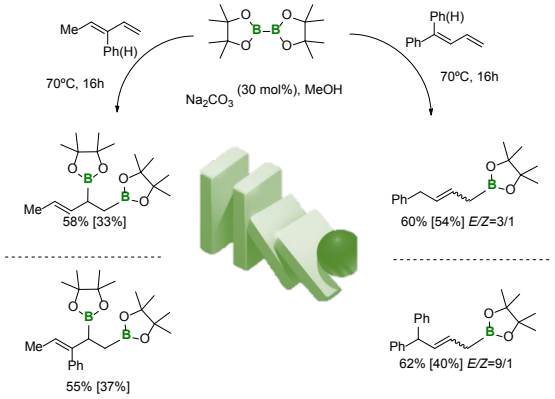
Scheme 7. Seteroselective borylation of allenamides



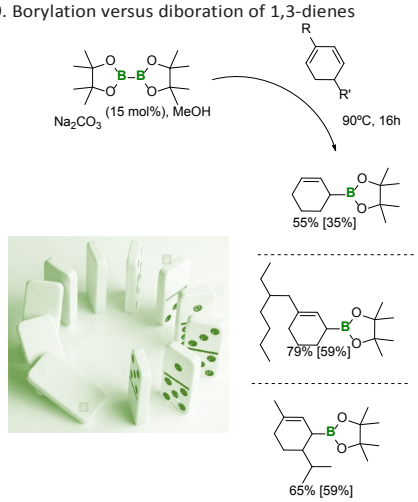
Scheme 8. Representative examples on borylation of allenamides

We moved from cumulated to conjugated dienes and the borylation reaction with adduct [MeO-pinB-Bpin]$^-$ showed the preference for S_N2'-type borylation in activated 1,3-dienes

versus 1,2-diboration of the terminal double bond in unactivated 1,3-dienes (Scheme 9).[42] A preferred *E* stereoisomeric allylic boronate product formation has also been observed, except for cyclic 1,3-dienes (Scheme 10). Interestingly, in the cyclic substrate the conjugative borylation takes place although there are no aryl substituents that direct the S_N2'-type borylation versus 1,2 diboration.[42]

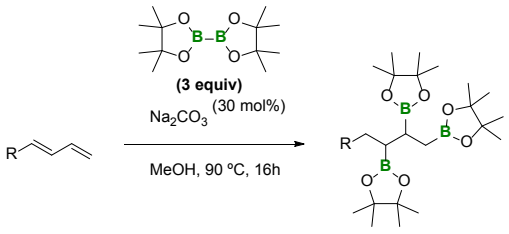


Scheme 9. Borylation versus diboration of 1,3-dienes



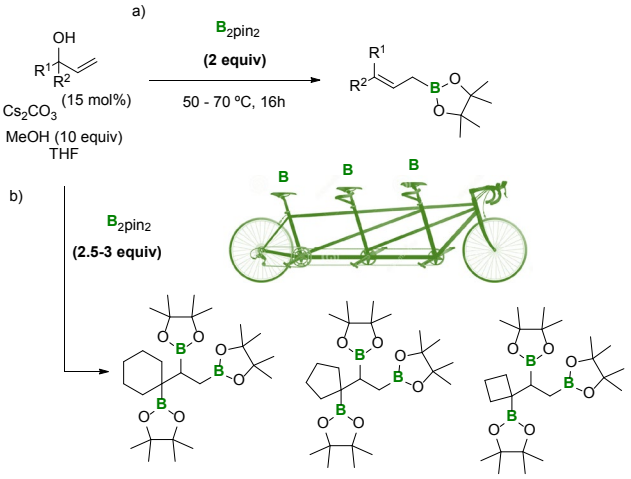
Scheme 10. Borylation versus diboration of cyclcic 1,3-dienes

Under the optimized reaction conditions to borylate 1,3-dienes with adduct [MeO-pinB-Bpin]$^-$, we explored the influence of the amount of B_2pin_2, and we found that by increasing the amount of the diboron reagent to 3 equivalents, the triborated product could be formed exclusively, probably due to the *in situ* transition-metal-free diboration of the allyl boronate (Scheme 11).[43]



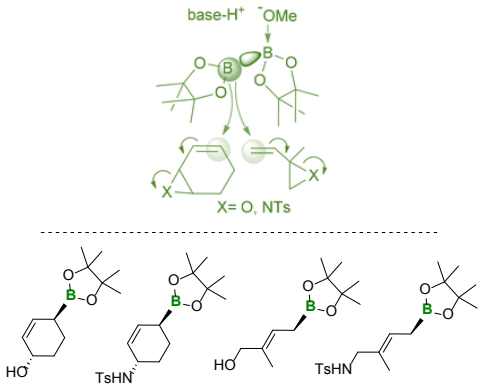
Scheme 11. Conceptual probe about suitable polyborylation of 1,3-dienes

Following a similar strategy, in collaboration with Prof. Szabó, we studied how the adduct [MeO-pinB-Bpin]$^-$ catalysed the allylic borylation of tertiary allylic alcohols allowing the synthesis of 1,1-disubstituted allyl boronates, in moderate to high yield (Scheme 12a).[44a] The unexpected tandem performance of the adduct [MeO-pinB-Bpin]$^-$ favoured the formation of 1,2,3-triborylated species from the tertiary allylic alcohols at 90 ºC (Scheme 12b), providing access within the same product to primary, secondary and tertiary boronic esters.[44a] Uchiyama and co-workers, simultaneously found a close system to perform the allylic borylation reaction, but up to 1 equiv of NaOMe and 120 ºC was required.[44b]



Scheme 12. a) Allylic borylation of tertiary allylic alcohols, b) polyborylation of tertiary allylic alcohols

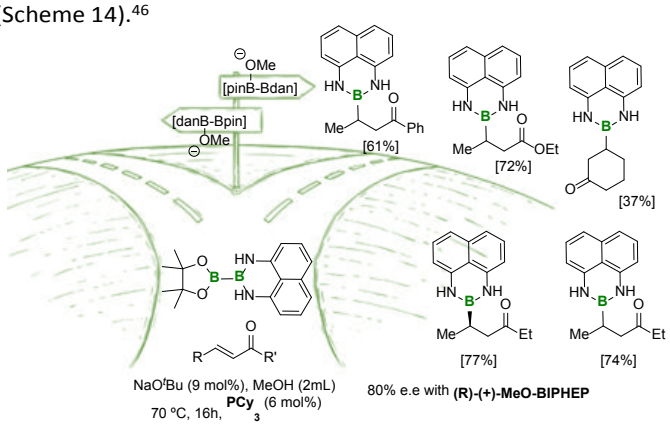
An approach towards the borylative ring-opening of vinylepoxides and vinylaziridines, by the *in situ* formed adduct [MeO-pinB-Bpin]$^-$, illustrated also the enhanced nucleophilic character of the Bpin (sp^2) towards the S_N2' conjugated B addition with the concomitant opening of the epoxide and aziridine rings.[45] The reaction proceeds with total chemo- and stereoselectivity towards *E* or *trans* isomers (Scheme 13).



Scheme 13. Borylative ring-opening of vinylepoxides and vinylaziridines

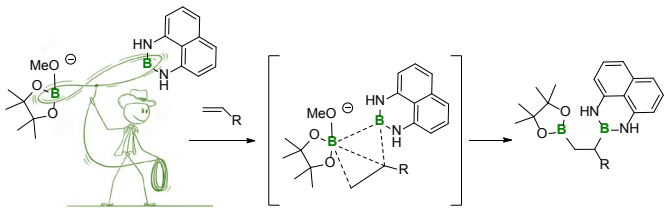
Since the alkoxide activation of symmetric diboron reagents, such as B_2pin_2, was clearly demonstrated, our next concern was to stablish how selective could be the alkoxide activation

of non-symmetrical diboron reagents. To find appropriate answers to the raised question, we explored the activation of BpinBdan diboron reagent with alkoxides (dan=1,8-diaminonaphthalene), since this potentially leads to the formation of two possible adducts: [MeO-pinB-Bdan]$^-$ or [MeO-danB-Bpin]$^-$.[46] Experimental and theoretical investigation confirmed that the adduct [MeO-pinB-Bdan]$^-$ is preferred and thus selective formation of C-Bdan bonds upon reaction with an activated C=C bond have been described. This is because the π-donation from the lone pair of nitrogen to the empty orbital of boron diminishes the Lewis acidity of Bdan moiety , and consequently the from alkoxide interaction. The activation of Bpin-Bdan with the alkoxide exclusively renders C_β-Bdan formation as no C_β-Bpin product has been detected in α,β-unsaturated ketones and esters. The presence of NaO^{t}Bu as base, and the use of phosphine PCy_3 as an additive, became beneficial, and when chiral diphosphines were used, enantioselection up to 80% e.e. was efficiently achieved (Scheme 14).[46]



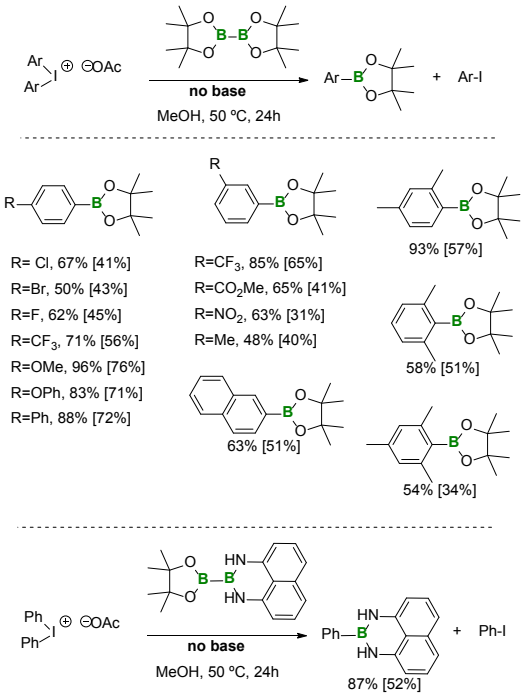
Scheme 14. Representative examples of β-boration of activated alkenes with BpinBdan

Our next challenge was to search whether the adduct [MeO-pinB-Bdan]$^-$ reacts with unactivated olefins to promote the diboration with the simulatenaous formation of C-Bpin and C-Bdan. Also the regioselectivity was a matter of concern in this particular study. But when monosubstituted alkenes reacted with BpinBdan, at 70 ºC, in MeOH / 30 mol% of Cs_2CO_3, we found that the diborated product was synthetised and the regioselectivity was almost quantitative for the diborated product with Bdan in the internal position (Scheme 15).[47] In a second set of experiments, internal olefins were subjected to the mixed diboration reaction and the 1,2-addition of Bpin and Bdan moieties to cyclic olefins took place in a *syn* fashion, although with moderate conversion.[47]



Scheme 15. Regioselective diboration of alkenes with BpinBdan

Eventually, in collaboration with Prof. Muñiz, we developed a new protocol for the alkoxide activation of B_2pin_2 and BpinBdan to react with readily available diaryliodonium acetates, which in a methanol solution engage in direct aryl–boron bond formation through a formal umpolung concept.[48] The reaction is selective, proceeds under mild conditions and does not require any additional base. It opens a new methodological venue for the use of hypervalent diaryliodonium reagents in carbon–heteroatom bond formation (Scheme 16a).[48] Using the mixed diboron reagent Bpin–Bdan the selective activation at the more electrophilic Bpin center promoted the transfer of the Bdan entity to selectively generate Ar–Bdan product (Scheme 16b). Despite the common recognition that C–Bdan bonds were totally inert toward Suzuki-Miyaura cross coupling reactions, a recent work demonstrates that C-Bdan can be transform into C-C bonds without acidic deprotection.[49] There was only one previous work devoted to the borylation of aryl iodides with B_2pin_2 promoted by Cs_2CO_3 (2 equiv) and MeOH, under 100 ºC for 2 days.[50] The presence of MeOH in the reaction seems to be the key point towards the *in situ* formation of adduct [MeO-pinB-Bpin]$^-$. Marder, Lin and co-workers investigated the stoichiometric reaction of the isolated sp^2–sp^3 diboron adduct [MeO-pinB-Bpin]$^-$ with the aryl iodides 4-methylphenyl iodide in deuterated THF at 60 ºC. This reaction was conveniently monitored by *in situ* NMR spectroscopy concluding that this adduct was responsible of the observed transformation.[51]



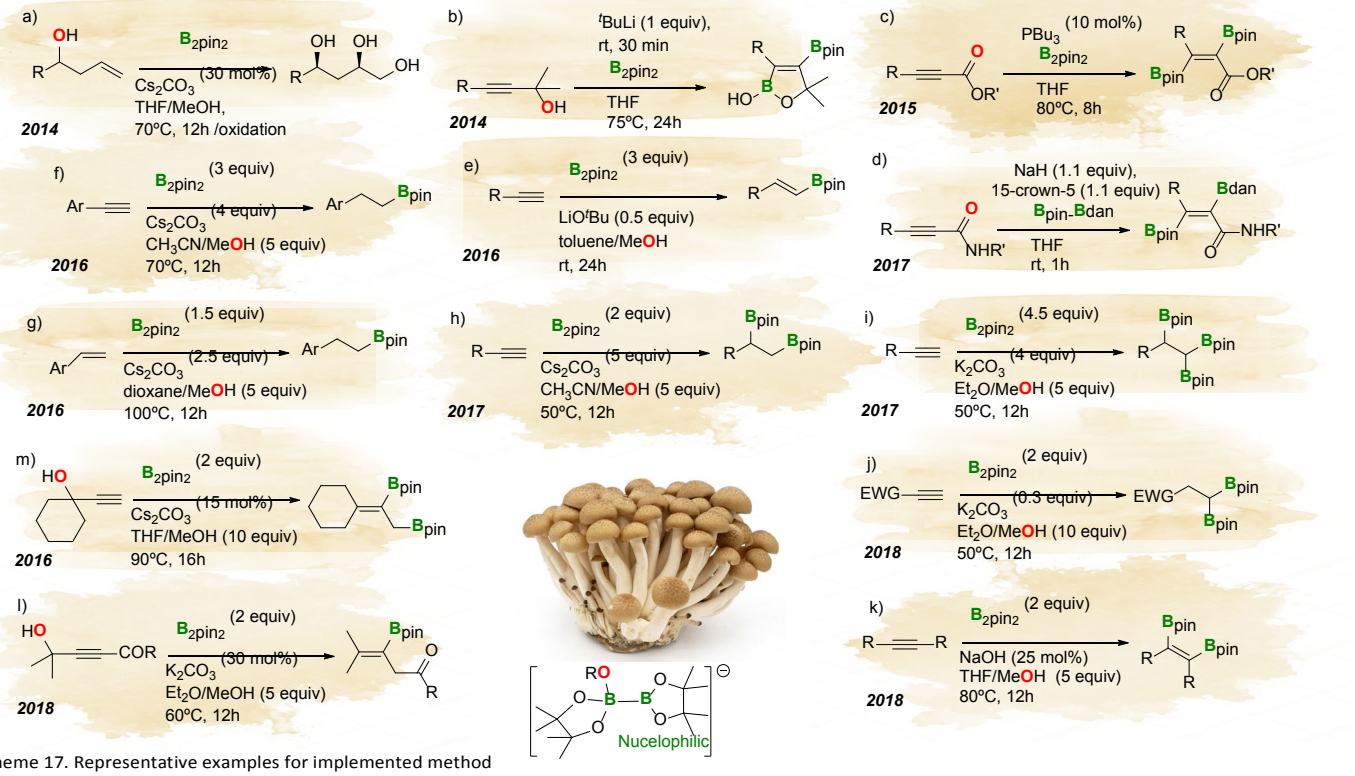
Scheme 16. Borylation of diaryliodonium acetates with alkoxide B_2pin_2 and BpinBdan

3. Swift implementation of alkoxide activation of diboron reagents towards C-B bonds synthesis

This stimulating area of work, based on the simple activation of diboron reagents with alkoxides to generate nucleophilic boryl moieties, has emerged within the last decade to a very large extent. Only relevant conceptual spots are highlighted in this section, since recent reviews have covered the field up to date.[52]

Intramolecular directed diboration is a valuable conceptual spot covered by Morken and co-workers for alkenyl alcohols proving the usefulness of the alkoxide-mediated diboron activation in the diastereoselective formation of triols from homoallylic and bis-homoallylic alcohols (Scheme 17a).[53] An alternative pseudo-intramolecular reaction of diboron reagents and propargyl alcohols, developed by Uchiyama and co-workers, provides access to the *trans*-diboration of alkynes by activating the B_2pin_2 with lithium alkoxide (Scheme 17b).[54] When the activation of B_2pin_2 was conducted with sodium alkoxide, net carboboration has been developed by Fürstner and co-workers, through the *trans*-diborated alkene intermediate.[55] *Trans*-diboration of alkynoates was suggested by Sawamura and co-workers,[56] highlighting the role of phosphine PBu_3 as additive to pre-activate the substrate and favour the allene intermediate formation (Scheme 17c). Similarly, Santos and co-workers employed primary and secondary alkylamides for intramolecular activation of Bpin-Bdan reagent, using 1.1 equiv of base and 1.1 equiv of 15-crown-5 (Scheme 17d).[57]

Yao, Deng and co-workers studied the borylation of terminal alkynes with B_2pin_2 in the presence of LiO^{t}Bu/toluene/MeOH at rt (Scheme 17e).[58] Complementarily, Song and co-wokers applied the adduct [MeO-pinB-Bpin]$^-$ to synthesise alkylboronates from arylacetylenes or vinyl arenes via borylation/protodeboronation pathway, leading to *anti*-Markovnikov products with excellent regioselectivity and broad functional group tolerance (Scheme 17f,g).[59] The same group used the activation of B_2pin_2 with alkoxides to obtain alkyl 1,2-diboronates from terminal alkylalkynes in the presence of Cs_2CO_3 (Scheme 17h).[60] However, under similar reaction conditions, but using K_2CO_3 as base, the formation of 1,1,2-tris(boronates) from terminal alkynes was observed (Scheme 17i).[60] As an extension of the domino borylation/protodeboronation strategy, Song and co-workers demonstrated that a variety of functionalized geminal-diborylalkanes can be efficiently prepared from various electron-deficient terminal and internal alkynes and B_2pin_2.[61] The reactions proceed in the presence of K_2CO_3/MeOH under mild conditions with high regioselectivity and high chemoselectivity, (Scheme 17j). Huang and co-coworkers developed the diboration of terminal alkynes with B_2pin_2 and NaOH/MeOH affording the *cis*-diborated product (Scheme 17k).[62] They also proved the addition of BpinBdan (LiOH as base), with excellent regioselectivity, adding the Bpin moiety exclusively at the terminal position.[62] Song and co-workers have reported that [MeO-pinB-Bpin]$^-$ can promote borylation/B-O elimination of propynols, delivering alkenylboronates (Scheme 17l),[63,64] in contrast to the diboration or propargylic alcohols we observed in 2016 (Scheme 17m).[44a]



Scheme 17. Representative examples for implemented method

4. Lighting the blind spots of the mechanisms with DFT calculations

Computational chemistry is a powerful tool that can provide a detailed understanding of molecular structures and reaction mechanisms.[65] In our case, a close collaboration between theoretical and experimental chemists has not only generated precise mechanistic characterization consistent with the experimental outcome but also quantitative predictions on the reactivity. Initial computational studies showed that the addition of an alkoxide, acting as a Lewis base, to the tetra-alkoxy diboron reagents forming [MeO-pinB-Bpin]$^-$ adduct involves polarization of the B-B σ-bond toward the non-quaternized sp^2 boron, which acquires a nucleophilic character (Figure 7).[33] This new concept rationalises the observed reactivity towards alkenes by the interaction between the nucleophilic B-B σ-orbital, the HOMO, and the electrophilic π*-orbital of the C=C bond, the LUMO. Then, further calculations proved the nucleophilic character of B(sp^2) fragment by analysing its transfer to a model formaldehyde substrate (Figure 8).[66] The nucelophilic attack at the carbonyl carbon by the B(sp^2) moiety has a computed, free-energy barrier of 26.2 kcal mol^{-1}, while the attack to the carbonyl oxygen has higher barrier (2.7 kcal mol^{-1}) and results in a high-energy shallow intermediate (Figure 8).

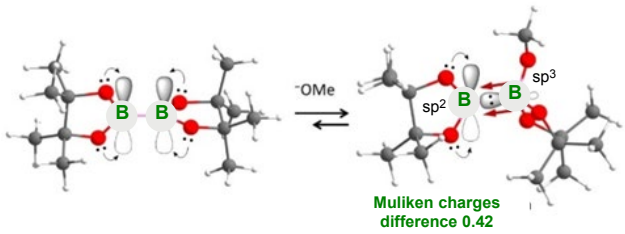


Figure 7. Alkoxide activation of B_2pin_2 through the formation of adduct [MeO-pinB-Bpin]$^-$

Compared to other nucleophilic boryl species such as boryl-copper complexes and boryl-alkali metals, the [MeO-pinB-Bpin]$^-$ adduct shows a moderate nucleophilic character. Using computational descriptors, we have built a tendency map[8] and quantitative structure-activity relationships[66] classifying and evaluating the nuleophilic and electrophilic reactivity of a broad range of trivalent boron compounds. The nucleophilic character is gauged by the charge on the boryl fragment, while another electronic parameter, the boron p/s ratio in the M-B σ-bond, was associated to the intrinsic nucleophlicity of the boryl fragment. Also a steric parameter, the *distance-weighted volume*,[67] was used to measure the effect of the fragment bulkiness on the reactivity resulting in an inverse correlation trend. Figure 9 summarizes the reactivity order for representative trivalent boron compounds.

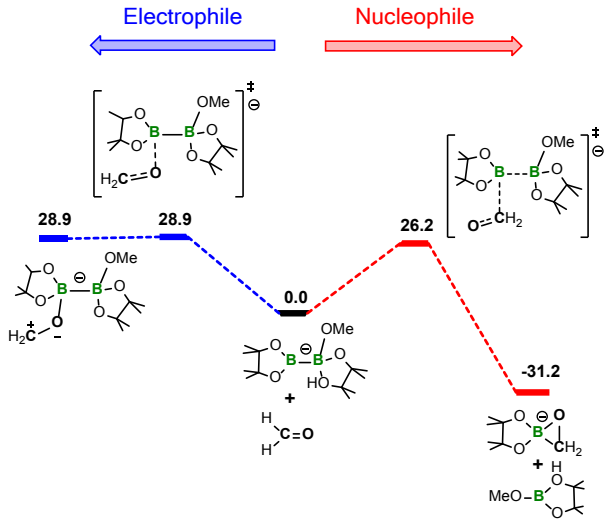


Figure 8. Computed free-energy profiles (kcal mol^{-1}) for the elecgtrophilic and nucleophilic B(sp^2) transfer from [MeO-pinB-Bpin]$^-$ adduct to formaldehyde substrate

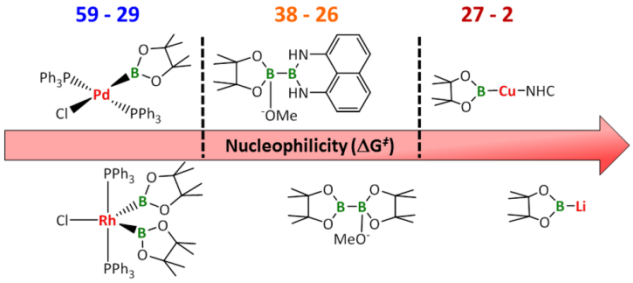
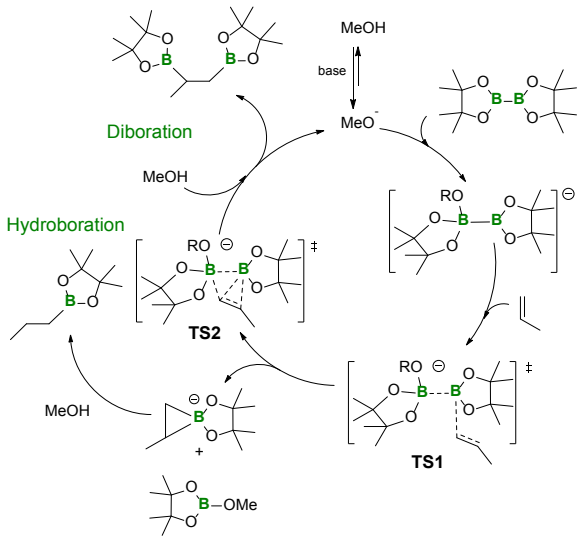


Figure 9. Reactivity order for representative trivalent boron compounds. Computed free-energy barriers for the nucleophilic boryl transfer to formaldehyde in kcal mol^{-1}

As illustrated in Figure 5, the energy barrier for the nucleophilic attack of the B(sp^2) moiety to a double bond depends dramatically on the alkene substituent.[32] Alkenes with electron withdrawing substituents showed low energy barriers and stable borylated carbanionic intermediates, which would be protonated to form the β-borated products. Accordantly, it has been experimentally observed that activated alkenes yield preferentially boron conjugate additions,[32] while the interaction of [MeO-pinB-Bpin]$^-$ adduct with unactivated alkenes results mainly in diborated products.[33] Computationally, it is not straight forward to predict a priori which product will be obtained, but detailed mechanisms have been suggested to explain the experimental outcome, as illustrated in Scheme 18, for terminal alkenes. For diboration reaction, the mechanism can be divided into three main steps: (1) the B(sp^2) atom of the [MeO-pinB-Bpin]$^-$ adduct attacks the terminal carbon of the alkene double bond, increasing the negative charge supported by the other carbon atom of the double bond; (2) through a bifurcation point in the potential energy surface, the first transition state connects with a new transition state, in which the developed negative charge of the internal alkene carbon attacks the Bsp^2 forming two C-B bonds; and (3) the alkoxy group (RO$^-$) is regenerated and the diborated product is released. Note that this

mechanism is consistent with the stereospecific *syn*-addition of diboron to internal and cyclic alkenes observed experimentally. Scheme 18 also depicts the hydroborylation processes as off-cycle reaction on the proposed mechanism for hydroboration. In the first transition state, after the nucleophilic attack of the boryl moiety to the terminal alkene follows through a boracylcle intermediate. Then, the protonation of the intermediate by the protic medium yields the hydroborated product (Scheme 18).



Scheme 18. Computationally proposed mechanisms for the diboration and hydroboration of alkenes with adduct [MeO-pinB-Bpin]⁻

An alternative mechanism for the diboration of alkenes by [MeO-pinB-Bpin]⁻ adduct have been recently proposed by Haeffner and coworkers.[68] The adduct would interact with uncomplexed acidic B_2pin_2 diboron resulting in a trimeric boron $(Bpin)_3^-$ species and a BpinOMe compound; and subsequently, the $(Bpin)_3^-$ undergoes a *syn* addition to the alkene to yield an anionic diborated intermediate. Finally, the interaction of this intermediate with BpinOMe would regenerate the [MeO-pinB-Bpin]⁻ adduct and release the *syn*-diborated product. Nevertheless, this mechanism turned out to be only marginally lower in energy (1 kcal mol^{-1}) than that depicted in Scheme 18. Moreover, under experimental conditions we expect that the high concentration of [MeO-pinB-Bpin]⁻ adduct, and the consequently low concentration of free B_2pin_2 reagent would prevent the formation of $(Bpin)_3^-$ species.

Computational studies have also unravelled the role of phosphines on organocatalytic β-boration of α,β-unsaturated carbonyl compounds with diboron reagents as illustrated in Figure 10.[31,46] The phosphine attacks on the electrophilic carbon atom of the substrate, yielding the zwitterionic phosphonium enolate, which acts as Brønsted base deprotonating the methanol solvent and generating the [MeO-pinB-Bpin]⁻ adduct. Calculations discarded the role of phosphine as a Lewis base activating the diboron due to the lack of stability of the [PR_3→pinB-Bpin] adduct. The reactivity trends as a function of the phosphine type (PMe_3 < PCy_3 < PPh_3) does not follow either their basicity or bulkiness features, indicating that a combination of stereo-electronic effects are responsible of enone preactivation (Figure 10).

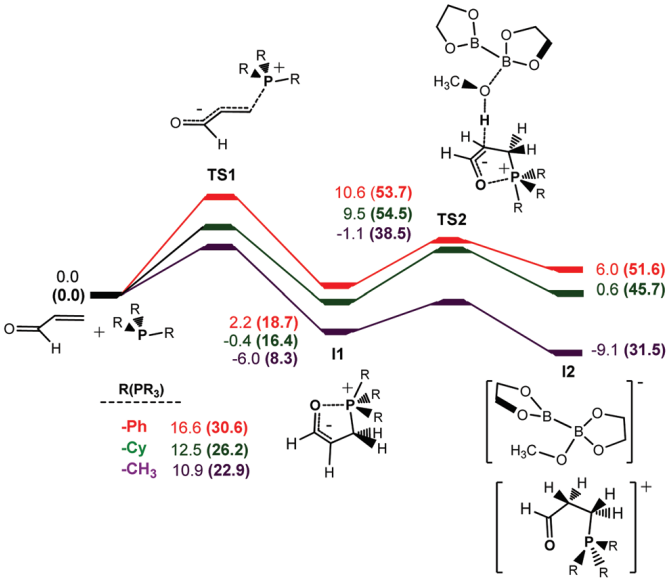
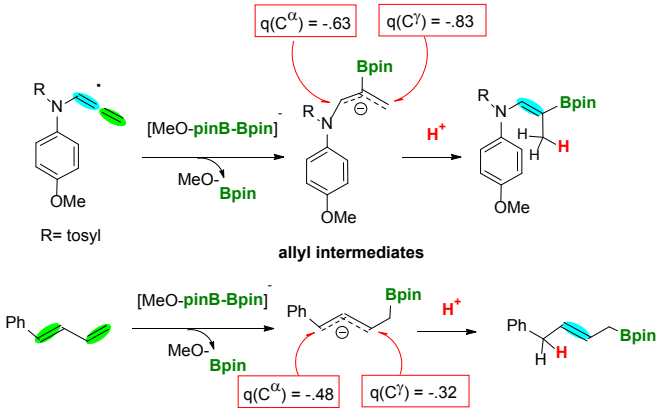


Figure 10. Computationally proposed mechanisms for the phosphines assisted organocatalytic β-boration of α,β-unsaturated carbonyl compounds with diboron reagents. Electronic energies and free-energies in parenthesis in kcal mol^{-1}

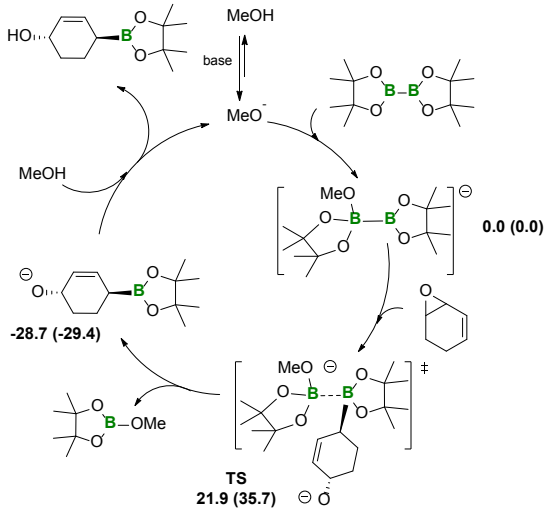
In the case of allenamides and diene substrates, the nucleophilic boryl transfer, from the [MeO-pinB-Bpin]⁻ adduct, yields the formation of allylic intermediates (Scheme 19).[41,42] The analysis of the electronic structure of these intermediates allowed to rationalize the regioselectivity. Thus, the allylic carbon supporting the larger negative charge is more reactive towards protonation, and this governs the regioselectivity in the hydroboration of the terminal double bond in allenamides[41] and in the 1,4-hydroboration of 1-phenyl substituted 1,3-dienes (Scheme 19).[42]



Scheme 19. Computationally-derived mechanisms for the hydroboration of allenamides (up) and dines (down) with B_2pin_2 in methanol/base, and analysis of electronic structure of allylic intermediate rationalising the selectivity. Atomic charges in a.u.

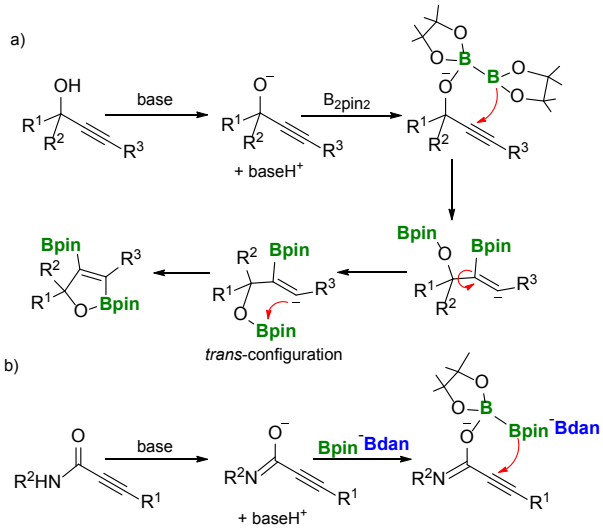
In addition for conjugated dienes we studied the observed stereochemistry, in which there is a small preference for the formation of the *E*-isomer. The steroselectivity determining step corresponds to the initial boryl transfer to the conjugated diene and the computed overall free-energy barrier for the *Z* path is only 1.7 kcal mol^{-1} higher than for the *E* path,[42] in agreement with the experimental observations. Interestingly, the *Z*-path involves the *trans-cis* isomerization of the diene, and although the *cis* isomer is more reactive, the energy penalty of its formation disfavours the reaction through this path.

The mechanism for borylative ring-opening of vinyl epoxides with B_2pin_2 has been also characterized computationally (Scheme 20).[45] Here, the boryl nucleophilic attack of the [MeO-pinB-Bpin]$^-$ adduct occurs at the conjugated C=C bond of the epoxides (or aziridines) through a S_N2' pathway. The proposed borylation mechanism would be valid for cyclic and non-cyclic vinyl epoxides and aziridines. The allylic borylation with [MeO-pinB-Bpin]$^-$ adduct of structurally-related substrates, such as tertiary allylic alcohols, might also follow a similar trend with the concomitatnt release of the hydroxi functionality (Scheme 12a).[44a]



Scheme 20. Proposed reaction mechanism for the borylative ring-opening of vinyl epoxides with B_2pin_2 in MeOH/base. Electronic energy and Gibbs free energy (in parenthesis) relative to [MeO-pinB-Bpin]$^-$ adduct in kcal mol^{-1}

More recent computational studies conducted by Uchiyama and co-workers for the *trans*-diboration of propargylic alcohols,[54] showed that the diborane can also be activated intramolecularly (Scheme 21a). From the propargylic alcohol the base generates the propargylic alkoxide, which binds to the diboron species, activating the B-B bond and then, *trans*-diboration occurs stereospecifically in two consecutive steps (Scheme 21a)[54] After the first migration of boron there is a fast carbon-carbon bond rotation process, which places the boronate group with a *trans* configuration, allowing the rapid intramolecular trapping. This reaction has a significantly lower activation energy with respect to intermolecular borylation in the alkoxide-activated diboron species. Similarly, in the case of diboration of alkynamides with mixed diboron Bpin-Bdan, the amide group can be initially deprotonated (Scheme 21b).[57] Other analogous intramolecular Lewis-base activation of boron compounds have been computationaly characterized for boron-heteroatom addition to α,β-alkenyl ketones[69] and esters.[70]



Scheme 21. Intramolecular base-assisted diboron activation for *anti*-selective diboration of a) propargylic alcohos and b) alkynamides.

The reaction depicted in Figure 14 represents an example where the addition of activated non-symmetrical diboron reagents to unsaturated substrates occurs regioselectively. Previously, we had analysed this issue in detail for reactions involving the formation of the Lewis acid-base adduct [MeO-pinB-Bdan]$^-$ resulting in the selective transfer of Bdan moiety to α,β-unsaturated carbonyl substrates[46] and to the internal carbon of terminal alkene.[47] Figure 11 illustrates our calculations for the case of terminal alkenes. The Bdan moiety is less nucleophilic than Bpin moiety, but the Bpin moiety is better Lewis acid and the coordination of the methoxy group provides lager stabilisation. Overall, in this case, the lower energy path corresponds to the formation of the [MeO-pinB-Bdan]$^-$ and the transfer of the Bdan moiety. However, we cannot discard that the balance between the stability of adduct formation and the reactivity of the boryl moiety inverts for other situations. Finally, it is worth to mention that Haeffner has compared the nucleophilic character of different diboron adducts [MeO→B(X)$_2$-B(X)$_2$]$^-$ (B_2cat_2 > B_2eg_2 > $B_2(OMe)_4$ > B_2pin_2 > B_2neop_2 > B_2hex_2; cat = cathecholato, eg = ethylene glycolato, pin = pinacolato, neo = neopentyl glycolato, hex = hexylene glycolato),[68] which could be also used to predict the most reactive borlyl moiety in non-symmetric diboron reagents [MeO→B(X)$_2$-B(X)$_2$]$^-$.

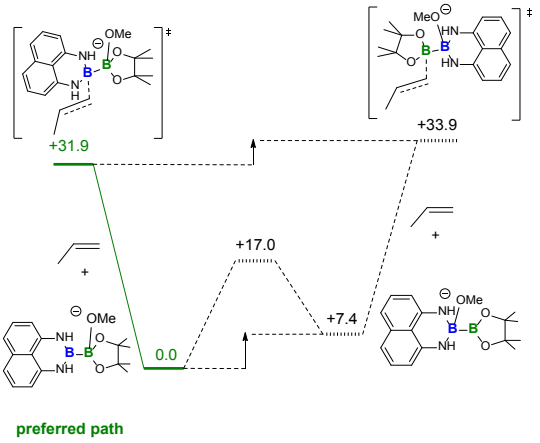
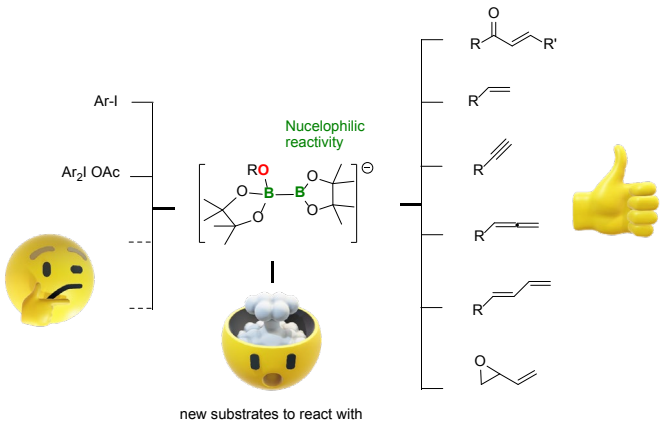


Figure 11. Calculated potential energy profile for the initial steps of the diboration of propene with mixed Bpin-Bdan reagent activated with metoxide. Electronic energies in kcal mol^{-1}

5. Outlook on future progression of the field

Amongst the most interesting inputs on alkoxide activation of tetra-alkoxy diboron reagents to promote borylative synthetic routes, would be the simplicity of the methodology. The *in situ* generation of alkoxides, normally in presence of MeOH and base, is enough to guarantee that stable diboron reagents can be activated. This would avoid the use of expensive transition metal complexes to activate the B-B bonds, particularly for scaled up protocols. A highly interesting and novel aspect concerning the formation of adduct [MeO-pinB-Bpin]$^-$ is its reactivity towards unsaturated substrates, as part of an umpolung sequence. So far, the substrate scope covers nucleophilic reactivity of [MeO-pinB-Bpin]$^-$ with alkenes, alkynes, dienes, allenes, etc., but in less extension with electrophiles such as aryl iodides as well as diaryliodonium acetates (Scheme XX). Having introduced this unpredicted reactivity it would be interesting to identify more applications and higher stereoselective challenging issues.



Scheme 22. Explored nucleophilic reactivity of adduct [MeO-pinB-Bpin]- to borylate unsaturated substrates and arylhalides

6. Conclusions

This feature article describes, from the initial experiments, how the alkoxide activation of tetra-alkoxy diboron reagents has evolved along unpredictable borylative synthetic routes, during the last decade. Technically, a blank experiment was the origin of a transition-metal-free approach on C-B bond formation where the presence of MeOH and base became essential to generate the corresponding alkoxide and promote the activation of the stable diboron reagent B_2pin_2. The suggested formation of adduct [MeO-pinB-Bpin]$^-$ and the subsequent nucleophilic character of the B(sp^2) moiety has launched an unprecedented reactivity including borylation as well as diboration protocols. The methodology has been well implemented for a large number of unsaturated substrates and stereoselectivty issues have been efficiently controlled by means of specific additives. The prove of concept has been demonstrated experimentally and computational details have provided the required insights to explain the plausible mechanisms, where umpolung sequences have predominated the reactivity provided by [MeO-pinB-Bpin]$^-$. With further development of this methodology, specially with the emergence of novel chiral versions, it can be envisaged the development of unimaginable new borylative synthetic routes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Ministerio de Economía y Competitividad and Fondo Europeo de Desarrollo Regional FEDER through project PID2019-109674GB-I00 and PGC2018-100780-B-I00.

Notes and references

1 J. Wang, W. Zheng, Y. Zheng, *RSC Adv*., 2017, **7**, 49251.
2 T. Ishiyama, N. Miyaura, *The Chemical Record*, 2004, **3**, 271.
3 a) T. Ishiyama, N. Matsuda, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.*, 1993, **115**, 11018; b) N. Miyaura, In Catalytic Heterofunctionalization; A. Togni; H. Grützmacher, Eds.; Wiley-VCH: Chichester, 2001; Chap 1.
4 a) K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* 2001, **625**, 47; b) K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett*. 2000, **29**, 982.
5 S. A. Westcott, E. Fernández, *Advances in Organometallic Chemistry*, Academic Press, Cambridge, 2015, pp. 39.
6 E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev*., 2016, **116**, 9091.
7 J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev*., 2012, **41**, 3558.
8 J. Cid, J. J. Carbó, E. Fernández, *Chem. Eur. J*., 2012, **18**, 12794.
9 J. Ramírez, R. Corberán, M. Sanau, E. Peris, E. Fernández, *Chem. Commun*., 2005, 3056.
10 R. Corberán, J. Ramírez, M. Poyatos, E. Peris, E. Fernández, *Tetrahedron: Asymmetry*, 2006, **17**, 1759.
11 V. Lillo, M. R. Fructos, J. Ramírez, A. A. A. Braga, F. Maseras, M. M. Díaz-Requejo, P. J. Pérez, E. Fernández, *Chem. Eur. J*., 2007, **13**, 2614.

12 J. Ramírez, M. Sanaú, E. Fernández, *Angew. Chem. Int. Ed*., 2008**, 47**, 5194.
13 V. Lillo, A. Prieto, A. Bonet, M.M. Díaz Requejo, J. Ramírez, P. J. Pérez, E. Fernández, *Organometallics*, 2009, **28**, 659.
14 A. Bonet, V. Lillo, J. Ramírez, M. M. Díaz Requejo, E. Fernández, *Org. Biomol. Chem.,* 2009, **7**, 1533.
15 V. Lillo, A. Bonet, E. Fernández, *Dalton Trans.*, 2009, 2899.
16 W. J. Fleming, H. Müller-Bunz, V. Lillo, E. Fernández, P. J. Guiry, *Org. Biomol. Chem.,* 2009, **7**, 2520.
17 C. Solé, E. Fernández*, Chem. Asian J.*, 2009, **4**, 1790**.**
18 V. Lillo, J. Mata, J. Ramírez, E. Peris, E. Fernández**,** *Organometallics*, 2006, **25**, 5829.
19 V. Lillo, J. A. Mata, A. M. Segarra, E. Peris, E. Fernández**,** *Chem. Commun.*, 2007, 2184.
20 V. Lillo, E. Mas-Marzá, A. M. Segarra, J. J. Carbó, C. Bo, E. Peris, E. Fernández, *Chem. Commun.*, 2007, 3380.
21 D. Penno, V. Lillo, I. O. Koshevoy, M. Sanaú, M. A. Úbeda, P. Lahuerta, E. Fernández, *Chem. Eur. J.*, 2008, **14**, 10648**.**
22 V. Lillo, M. J. Geier, S. A. Westcott, E. Fernández, *Org. Biomol. Chem.,* 2009, **7**, 4674.
23 C. Pubill-Ulldemolins, C. Bo, J. A. Mata, E. Fernández, *Chem. Asian J.*, 2010, **2**, 61**.**
24 A. Bonet,H. Gulyás, I. O. Koshevoy, F. Estevan, M. Sanaú, M. A. Úbeda, E. Fernández, *Chem. Eur. J.*, 2010, **16**, 6382.
25 A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.*, 2010, **49**, 5130.
26 H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett*., 2000, **41**, 6821.
27 K. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc*., 2009, **131**, 7253.
28 correction: K. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* 2010, **132**, 12766.
29 E. La Cascia, X. Sanz, C. Bo, A. Whiting, E. Fernández, *Org. Biomol. Chem.*, 2015, **13**, 1328.
30 C. Solé, H. Gulyás, E. Fernández, *Chem. Commun*. 2012, **48**,3769.
31 C. Pubill-Ulldemolins, A. Bonet, H. Gulyás, C. Bo, E. Fernández, *Org. Biomol. Chem.*, 2012, **10**, 9677.
32 C. Pubill-Ulldemolins, A. Bonet, C. Bo, H. Gulyás, E. Fernández, *Chem. Eur. J*. 2012, **18**, 1121.
33 A. Bonet, C.Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández *Angew. Chem. Int. Ed.*, 2011, **50**, 7158.
34 F. Yu, Ch-H. Cheng, *J. Am. Chem. Soc.* 2001, **123**, 761.
35 N. F. Pelz, A. R. Woodward, H. E. Burks, J. D. Sieber, J. P. Morken, *J. Am. Chem. Soc*. 2004, **126**, 16328.
36 A. R. Woodward, H. E. Burks, L. M. Chan, J. P. Morken, *Org. Lett.* 2005, **7**, 5505.
37 A. B. Cuenca, V. Duplant; N. Zigon, M. Hoshino, M. Fujita, E. Fernández, *Chem. Eur. J.* **2016**, 22, 4723.
38 A. Bonet, C. Solé, H. Gulyás, E. Fernández, *Org. Biomol. Chem*., 2012, **10**, 6621.
39 L. Fang, L. Yan, F. Heaffner, J. P. Morken, *J. Am. Chem. Soc*., 2016, **138**, 2508.
40 L. Yan, Y. Meng, F. Haeffner, R. M. Leon, M. P. Crockett, J. P. Morken, J. *Am. Chem. Soc*., 2018, **140**, 3663.
41 L. García, J. Sendra, N. Miralles, E. Reyes, J. J. Carbó, J. L. Vicario, E. Fernández, *Chem. Eur. J.*, 2018, **24**, 14059.
42 R. J. Maza, E. Davenport, N. Miralles, J. J. Carbó, E. Fernández *Org. Lett.*, 2019**, 21**, 2251.
43 E. Davenport, E. Fernández, *Chem. Commun*, 2018, **54**, 10104.
44 a) N. Miralles, R. Alam, K. J. Szabó, E. Fernández, *Angew. Chem. Int. Ed*. 2016, **55**, 4303; b) K. Harada, M. Nogami, K. Hirano, D. Kurauchi, H. Kato, K. Miyamoto, T. Saito, M. Uchiyama, *Org. Chem. Front*. 2016, **3**, 565
45 X. Sanz, G. M. Lee, C. Pubill-Ulldemolins, A. Bonet, H. Gulyás, S. A. Westcott, C. Bo, E. Fernández, *Org. Biomol. Chem.* 2013, **11**, 7004.
46 J. Cid, J. J. Carbó, E. Fernández, *Chem. Eur. J.*, 2014, **20**, 3636.
47 N. Miralles, J. Cid, A. B. Cuenca, J. J. Carbó, E. Fernández, *Chem. Commun*, 2015, **51**, 1693.
48 N. Miralles, R. M. Romero, E. Fernández, K. Muñiz, *Chem. Commun.*, 2015, **51**, 14068.
49 S. Kamio, H. Yoshida, *Adv. Synth. Catal.,* 2021, **363**, 2310.
50 J. Zhang, H.-H. Wu, J. Zhang, *Eur. J. Org. Chem*. 2013, 6263.
51 a) S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radius, Z. Lin, Ch. Kleeberg, T. B. Marder, *Chem. Eur. J.* 2015, **21**, 7082; b) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem. Int. Ed.* 2009, **48**, 5350.
52 a) A. B. Cuenca, R. Shishido, H. Ito, E. Fernández, *Chem. Soc. Rev*., 2017, **46**, 415; b) Y. Wen, Ch. Deng, J. Xie, X. Kang, *Molecules* 2019**, 24**, 101; c) K. K. Das, S. Paul, S. Panda, *Org. Biomol. Chem*., 2020, **18**, 8939; d) Z. Kuang, K. Yang, Y. Zhou, Q. Song, *Chem. Commun.*, 2020, **56**, 6469; 3) H. Keiichi, M. Uchiyama, *Adv. Synth. Catal*., 2021, **363**, 2340.
53 T. P. Blaisdell, T. C. Caya, L. Zhang, A. Sanz-Marco, J. P. Morken, *J. Am. Chem. Soc*., 2014, **136**, 9264.
54 Y. Nagashima, K. Hirano, R. Takita and M. Uchiyama, *J. Am. Chem. Soc.*, 2014, **136**, 8532.
55 a) H. Jin, A. Fürstner, *Org. Lett.* 2019, **21**, 3446; b) H. Jin, A. Fürstner, *Angew. Chem. Int. Ed.* 2020, **59**, 13618.
56 K. Nagao, H. Ohmiya, M. Sawamura, *Org. Lett.* 2015, **17**, 1304
57 A. Verma, R. F. Snead, Y. Dai, C. Slebodnick, Y. Yang, H. Yu, F. Yao, W. L. Santos, *Angew. Chem. Int. Ed.* 2017, **56**, 5111.
58 S. Hong, W. Zhang, M. Liu, Z.-J. Yao and W. Deng, *Tetrahedron Lett*., 2016, **57**, 1.
59 K. Yang and Q. Song, *Green Chem*., 2016, **18**, 932.
60 G. Gao, J. Yan, K. Yang, F. Chen and Q. Song, *Green Chem*., 2017, **19**, 3997.
61 G. Gao, Z. Kuang and Q. Song, *Org. Chem. Front*., 2018, **5**, 2249.
62 S. Peng, G. Liu and Z. Huang, *Org. Lett*., 2018, **20**, 7363
63 a) Z. Kuang, H. Chen, J. Yan, K. Yang, Y. Lan and Q. Song, *Org. Lett*., 2018, **20**, 5153.
64 H. Chen, T. Zhang, C. Shan, S. Liu, Q. Song, R. Bai, Y. Lan, *Org. Lett*., 2019, **21**, 4924.
65 P. Nakliang, S. Yoon, S. Choi, *Org. Chem. Front.* 2021, DOI: 10.1039/d1qo00531f, *ASAP*
66 D. García-López, J. Cid, R. Marqués, E. Fernández, J J. Carbó, *Chem. Eur. J.* 2017, **23**, 5066.
67 a) S. Aguado-Ullate, S. Saureu, L. Guasch, J. J. Carbó, *Chem. Eur. J.* 2012, **18**, 995; b) S. Aguado-Ullate, M. Urbano, I. Villaba, E. Pires, J. I. García, C. Bo, J. J. Carbó, *Chem. Eur. J*. 2012, **18**, 14026.
68 F. Haeffner, *Comput. Theor. Chem.* 2018, **1131**, 90.
69 M. G. Civit, X. Sanz, C. M. Vogels, C. Bo, S. A. Westcott, E. Fernández, *Adv. Synth. Catal.* 2015, **357**, 3098.
70 D. García-López, M. G. Civit, C. M. Vogels, J. M. Ricart, S. A. Westcott, E. Fernández, J. J. Carbó, *Catal. Sci. Technol.* 2018, **8**, 3617.

