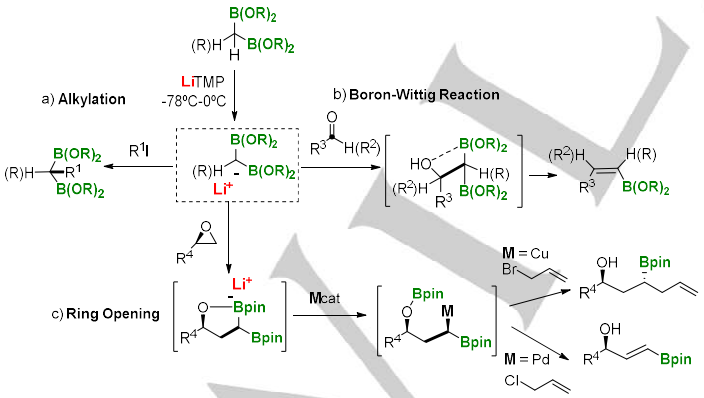
Selective C-C coupling of vinyl epoxides with diborylmethide lithium salts

Riccardo Gava[a] and Elena Fernández*[a]

Dedication ((optional))

Abstract: Vinyl epoxides and styrene oxide can react with diborylmethide lithium salts throughout an exclusive S_N2 borylmethylation / ring opening in a regio- and diastereoselctive way, depending on the nature of the substrate. The ring opening protocol provides homoallylboronates that can be transformed into challenging diastereomeric bishomoallylic alicyclic 1,3-diols. Eventually, unprecedented 3-borylated 1,2-oxaborolan-2-ol products are prepared by borylmethylation / ring opening of 2-methyl-2-vinyloxirane followed by intramolecular cyclization.

Geminal-diborylalkanes have risen as valuable building blocks for C–C bond formation, due to the easy access to nucleophilic α -boryl carbanions via deprotonation or deborylation processes.[1] The use of lithium bases, such as lithium 2,2,6,6-tetramethylpiperidide (LiTMP), allows efficient deprotonation of geminal-diborylalkanes[2] generating partially stable diborylmethide lithium salts that undergo straightforward reactivity with electrophiles under mild reaction conditions. The reactivity explored with diborylmethide lithium salts for C–C bond formation involves alkylation reactions with aryl- or alkyl halides (Scheme 1a)[3] as well as boron-Witting reactions with carbonyl compounds[4] (Scheme 1b). Reactivity of diborylmethide lithium salts with electrophiles other than aldehydes/ketones or RX has not been explored, except for an attempt to contribute to the copper-catalyzed one-pot three-component stereoselective coupling of epoxides with allyl electrophiles and bis[(pinacolato)boryl]methane (Scheme 1c)[5a] or palladium-catalyzed coupling/dehydroboration (Scheme 1c)[5b]



Scheme 1. Synthetic strategies for C-C coupling reactions with diborylmethide lithium salts trough alkylation, boron-Wittig reaction and ring opening.

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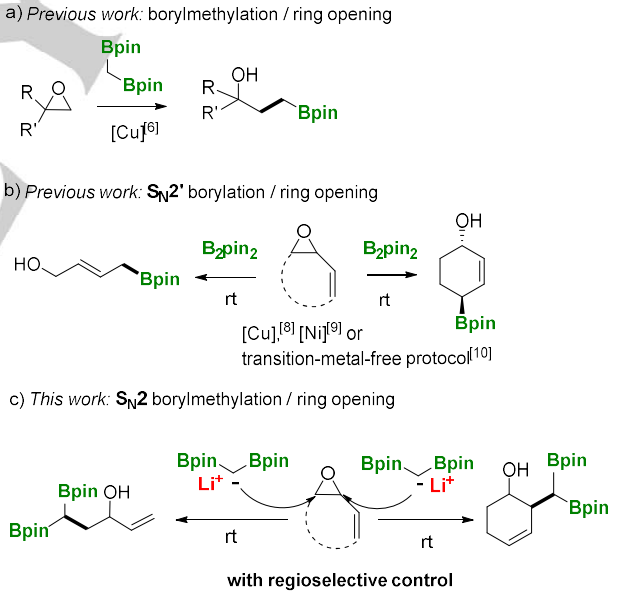
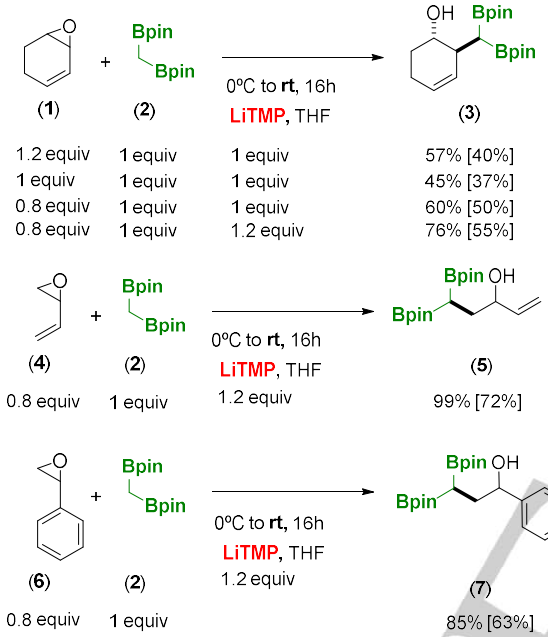
Copper(I) catalysts seem to be essential for the borylmethylation / ring opening of epoxides (Scheme 2a)[6] as well as for the borylmethylation / ring opening of vinyl cyclic carbonates through S_N2' mechanism.[7] However, the reaction of vinyl epoxides with geminal-diborylalkanes has been elusive to our days. Only the borylative ring opening reaction of vinyl epoxides has been postulated to proceed with B_2pin_2 in the presence of Cu[8], Ni[9] or in the absence of transition metal complexes[10] through a S_N2' mechanism (Scheme 2b). Now, we face here the challenge to perform the borylmethylation of vinyl epoxides with diborylmethide lithium salts that undergo direct ring opening of the epoxide keeping the conjugated double bond unreacted (Scheme 2c). Total regiocontrol on the epoxide ring opening is achieved depending on the cyclic or non-cyclic type of the vinyl epoxide substrates. Diastereoselective control in the C-C coupling is also possible when substituted diborylmethide lithium salts are involved.



Scheme 2. Reactions of epoxides and vinyl epoxides with *geminal*-diborylalkanes and B_2pin_2

We selected the commercially available vinyl epoxide 3,4-epoxy-1-cyclohexene (**1**) as model substrate to search the reaction conditions for an efficient reactivity with bis[(pinacolato)boryl]methane (**2**) in the presence of LiTMP. Scheme 3 shows that a slight excess of diborylmethane reagent and LiTMP favors the formation of 2-(bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclohex-3-en-1-ol (**3**), at room temperature. Higher temperature reaction around 50ºC or other bases, such as KHDMS, did not improve the yields. The nucleophilic ring opening takes place exclusively on the allylic

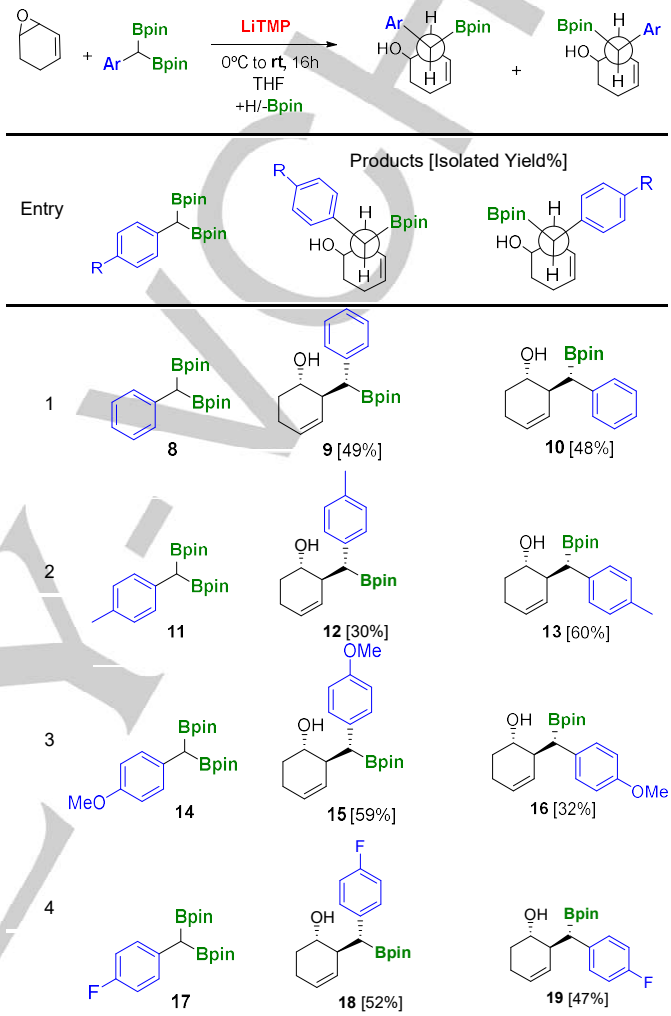
position as a matter of a S_N2 attack of the diborylmethide lithium salt, suggesting that is acting as a hard nucleophile, generating a *trans* disposition of the OH and $CH(Bpin)_2$ groups (Scheme 3). The reactivity observed by the C-C coupling of **1** with the diborylmethide lithium salt might be influenced by the conjugated nature of the strained oxirane,[11] since the ring opening of the related cyclohexene oxide did not occur under the same reaction conditions. Interestingly, by applying the optimized reaction conditions to the reactivity of **2** with the unsubstituted non cyclic vinyl epoxide 3,4-epoxy-1-butene (**4**), the nucleophilic attack of the diborylmethide lithium salt occurred exclusively at the homoallylic position (Scheme 3). The more activated substrate styrene oxide (**6**) also conducted the S_N2 attack of the diborylmethide lithium salt at the less hindered position (Scheme 3).



Scheme 3. Regioselective ring opening / cross coupling of vinyl epoxides and styrene oxide with diborylmethide lithium salts via S_N2 attack.

Having demonstrated the opposite regioselective S_N2 ring opening / cross coupling of 3,4-epoxy-1-cyclohexene (**1**) versus the non-cyclic vinyl epoxides **4** and styrene oxide **6** with diborylmethide lithium salts, we proceeded to investigate the scope of the reaction using a variety of geminal-diborylalkanes (Table 1). Towards this end, a series of reagents with molecular formula $ArCH(Bpin)_2$ were prepared,[12a] being for **11**, **17** its first synthesis, and reacted with **1** to prove the general trend in the regioselective S_N2 ring opening / C-C coupling. We observed that the reaction of (phenylmethylene)bis(pinacolborane) (**8**) with **1** in the presence of LiTMP resulted in a quantitative S_N2 attack at the allylic position of the cyclic vinyl epoxide although two diastereoisomeric products **9** and **10** were generated in almost 1/1 ratio. The characterization of the products determined that only one Bpin moiety remained in the final product, probably as a consequence of a H-deborylative process favoured by the sterically hindered multisubstituted carbon (Table 1, entry 1). When alternative $ArCH(Bpin)_2$ reagents were used introducing electron withdrawing or electron donating substituents in the aryl group, similar reactivity was observed (Table 1, entries 2-4). In all cases both diastereoisomers could be isolated in pure form and the structural configuration was confirmed by X-Ray Diffraction of the crystalline product **17** (Figure 1).

Table 1. Regioselective ring opening / C-C cross coupling of 3,4-epoxy-1-cyclohexene with $ArCH(Bpin)_2$ via LiTMP assistance.[a]



[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), geminal-diborylalkane (1 equiv), LiTMP (1.2 equiv), THF (1 mL), rt, 16h. [Isolated yields %].

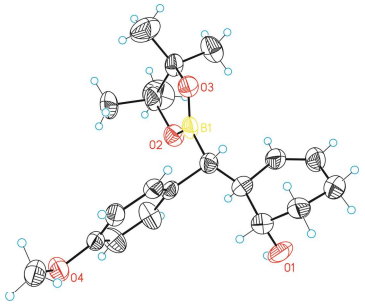
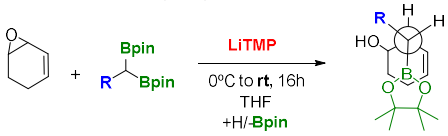


Figure 1. X-Ray Diffraction of product **15**.

Remarkably, when the geminal-diborylalkane reagents contained an alkyl group instead of an aryl group, their reaction with **1** showed the regioselective S_N2 ring opening / C-C coupling but only one exclusive diastereoiosmer was formed along the H-deborylative process (Table 2). Reagents such as (2-

phenylethane-1,1-diyl)bis(pinacolborane) (**20**) and (3-phenylpropane-1,1-diyl)bis(pinacolborane) (**22**) generated the products **21** and **23** in moderate yield as a sole diastereoisomer (Table 2, entries 1-2), while reagents octane-1,1-diylbis(dimethylborane) (**24**) and (bis(pinacolboranyl)methyl)trimethylsilane (**26**)[12b] contributed to higher isolated yields of the single diastereoisomers **25** and **27**, (Table 2, entries 3-4) being the last one full characterised by X-Ray Diffraction (Figure 2). Interestingly, the fact that protodeboronation reaction can be stereoselective when an alkyl group is attached to the diborylmethide lithium salt, is in agreement with a recent observation in diastereoselective protodeboronation between 1,1-diborylalkanes and N-*tert*-butanesulfinyl aldimines.[13]

Table 2. Regio- and diastereoselective ring opening / C-C cross coupling of 3,4-epoxy-1-cyclohexene with RCH(Bpin)$_2$ via LiTMP assistance.[a]



Entry	Bpin R Bpin	Product [Isolated Yield%]
1	Bpin Bpin **20**	OH H Bpin **21** [43%]
2	Bpin Bpin **22**	OH H Bpin **23** [40%]
3	Bpin Bpin **24**	OH H Bpin **25** [67%]
4	Bpin Me_3Si Bpin **26**	OH $SiMe_3$ H Bpin **27** [76%]

[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), geminal-diborylalkane (1 equiv), LiTMP (1.2 equiv), THF (1 mL), rt, 16h. [Isolated yields %].

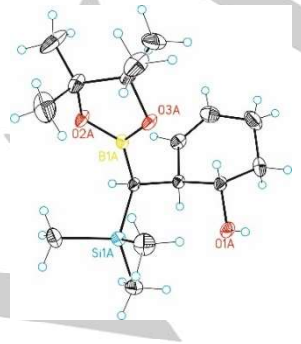
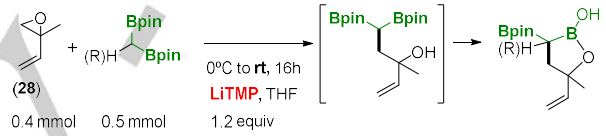


Figure 2. X-Ray Diffraction of product **27**.

We also conducted the nucleophilic ring opening / cross coupling of 2-methyl-2-vinyloxirane (**28**), with diborylmethide lithium salt, and we proved not only that the nucleophilic attack occurred exclusively at the homoallylic position, but also that the new product suffered an intramolecular cyclization to give the substituted 3-borylated 1,2-oxaborolan-2-ol product **29** (Table3, entry 1). 1,2-Oxaborolanes are important synthons[14] but their synthesis has mainly been explored through carboboration protocols.[15-18] Compound **29** represents an unprecedented cyclic organoborane involving a simple C-B-O five-membered ring with a geminal C-B moiety, where the vinyl and methyl substituents keep unaltered from the 2-methyl-2-vinyloxirane (**28**) starting material. The reaction has been extended to prepare polysubstituted 3-borylated 1,2-oxaborolan-2-ol products by reaction of **28** with alkyldiborylmethide lithium salts **20**, **22** and **26**. Despite the fact that bulky substituents were introduced in the substituted 3-borylated 1,2-oxaborolan-2-ol products the yield was quantitative and the isolated yields were moderate to high, with a diastereoisomeric ratio 4/6 in all the cases (Table 3).

Table 3. Regioselective ring opening/cross coupling of 2-methyl-2-vinyloxirane with alkyldiborylmethide lithium salts followed by intramolecular cyclization.[a]

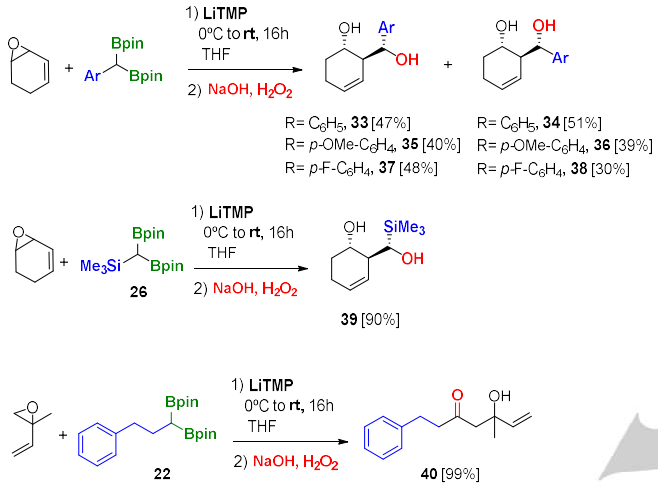


Entry	Bpin R Bpin	Product [Isolated Yield%]
1	Bpin Bpin **2**	OH B B O O **29** [75%]
2	Bpin Bpin **20**	OH B B O O **30** [56%]
3	Bpin Bpin **22**	OH B B O O **31** [74%]
4	Bpin Me_3Si Bpin **26**	OH B O O Me_3Si **32** [70%]

[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), geminal-diborylalkane (1 equiv), LiTMP (1.2 equiv), THF (1 mL), rt, 16h. [Isolated yields %].

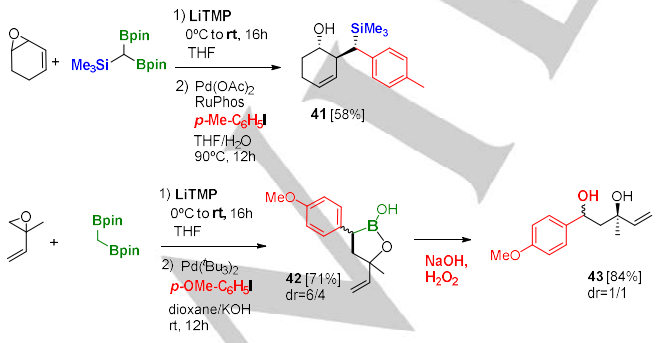
The in situ oxidation of the homoallylboronates prepared in Table 1 allows the isolation of challenging bishomoallylic alicyclic 1,3-diols (Scheme 4) in a straightforward manner. Interestingly compounds **33**, **35** and **37** have a complementary conformation to the previously reported method via Ni or transition-metal-free catalysed S_N2' borylation/ring opening of vinyl epoxides with B_2pin_2.[9a,10]

The added value of the regio- and diastereoselective ring opening / C-C cross coupling of 3,4-epoxy-1-cyclohexene with Li[RC(Bpin)$_2$] (R= trimethylsilyl)methyl group) allowed the in situ oxidative work up towards 2-(hydroxy(trimethylsilyl)methyl)cyclohex-3-en-1-ol (**39**) as a single diastereosiomer with full retention of the configuration (Scheme 4). The consecutive ring-opening / ring-closing of substrate 2-methyl-2-vinyloxirane when reacts with diborylmethide lithium salts **22**, generates the 3-borylated 1,2-oxaborolan-2-ol product **31**, that under oxidative work up conditions ends up in the formation of polyfunctional allylic alcohol 5-hydroxy-5-methyl-1-phenylhept-6-en-3-one (**40**), containing a tertiary β-hydroxyl group,[19] characteristic of high therapeutic value (Scheme 4).



Scheme 4. Ring opening/cross coupling followed by in situ oxidation with NaOH/H_2O_2

The single diastereosiomer **27** formed from rection of epoxide 3,4-epoxy-1-cyclohexene (**1**) and (bis(pinacolboranyl)methyl)trimethylsilane (**26**), in the presence of LiTMP, was further functionalized by cross coupling reaction with pCH_3-C_6H_4I in the presence of Pd(OAc)$_2$/RuPhos (Scheme 5). The corresponding product 2-(*p*-tolyl(trimethylsilyl)methyl)cyclohex-3-en-1-ol (**41**) preserved the configuration along the Pd catalyzed reaction.



Scheme 5. Functionalization by cross coupling with ArI.

Similarly, the 3-borylated 1,2-oxaborolan-2-ol compound **29** formed from 2-methyl-2-vinyloxirane (**28**) and bis[(pinacolato)boryl]methane (**2**), in the presence of LiTMP, was subsequently coupled with 4-bromoanisole in the presence of Pd(P^{t}Bu$_3$)$_2$, at room temperature, giving the coupled product **42** (Scheme 5), in d.r =6/4. The oxidative work up of **42**, generated 1-(4-methoxyphenyl)-3-methylpent-4-ene-1,3-diol (**43**) in good yield. This method represents a new access to polyfunctional 1,3-diols which are considered interesting skeleton for bioactive trisubstituted tetrahydropyrans[20] which have been mostly prepared via condensation of an allylic alcohols with aldehydes in the presence of Lewis acids.

We conclude that diborylmethide lithium salts react with vinyl epoxides and styrene oxide along borylmethylation / ring opening via exclusive S_N2 mechanism. Regioselection is achieved by substrate influence and diastereoselection on the homoallylboronate products depends on the geminal-diborylalkane used. Unprecedented ring opening followed by ring closing provides access to unexpected cyclic geminal diboronates. Further functionalization opens a new methodology to generate diastereomeric secondary and tertiary alcohols of high added value.

Experimental Section

Experimental Details can be found at the Supporting Information Document.

Acknowledgements

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Keywords: • Geminal-diborylalkanes • diborylmethide lithium salts • cyclic germinal diboronates • homoallylboronates • S_N2 mechanism

[1] a) N. Miralles, R. J. Maza, E. Fernández, *Adv. Synth. Catal.*, **2018**, *360*, 1306; b) J. Wang, Ch. Wu, *Tetrahedron Lett.*, **2018**, *59*, 2128; c) R. Nallagonda, K. Padala, A. Masarwa, *Org. Biomol. Chem.*, **2018**, *16*, 1050.

[2] a) D. S. Matteson, R. J. Moody, *J. Am. Chem. Soc.* **1977**, *99*, 3196; b) D. S. Matteson, R. J. Moody, *Organometallics* **1982**, *1*, 20.

[3] a) K. Hong, X. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 10581; b) Z.-Q. Zhang, C.-T. Yang, L.-J. Liang, B. Xiao, X. Lu, J.-H. Liu, Y.-Y. Sun, T. B. Marder, Y. Fu, *Org. Lett.* **2014**, *16*, 6342; c) Y. Lee, J. Park, S. H. Cho, *Angew. Chem. Int. Ed.* **2018**, *57*, 12930.

[4] a) K. Endo, M. Hirokami and T. Shibata, *J. Org. Chem.*, **2010**, *75*, 3469; b) K. Endo, A. Sakamoto, T. Ohkubo and T. Shibata, *Chem. Lett.*, **2011**, *40*, 1440; c) J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.*, **2015**, *17*, 1708; d) E. Lacascia, A. B. Cuenca, E. Fernández, *Chem. Eur. J.*, **2016**, 22, 18737; e) T. C. Stephens, G. Pattison, *Org. Lett.*, **2017**, *19*, 3498.

[5] a) S. A. Murray, M. Z. Liang, S. J. Meek, *J. Am. Chem. Soc.*, **2017**, *139*, 14061; b) S. A. MurrayE. C. M. Luc, S. J. Meek, *Org. Lett.*, **2018**, *20*, 469.

[6] A. Ebrahim-Alkhalil, Z.-Q. Zhang, T.-J. Gong, W. Su., X.-Y. Lu, B. Xiao, Y. Fu, *Chem. Commun.*, **2016**, *52*, 4891.

[7] N. Miralles, J. E. Gómez, A. W. Kleij, E. Fernández, *Org. Lett.*, **2017**, *19*, 6906.

[8] M. Tortosa, *Angew. Chem., Int. Ed.*, **2011**, *50*, 3950.

[9] a) S. Crotti, F. Bertolini, F. Macchia and M. Pineschi, *Org. Lett.*, **2009**, *11*, 3762; b) M. Pineschi, *Synlett.*, **2014**, *25*, 1817.

[10] 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.

[11] J. He, J. Ling, P. Chiu, *Chem. Rev*., **2014**, *114*, 8037.
[12] a) H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang and J. Wang, *Org. Lett.*, **2014**, *16*, 448; b) J. Kim, S. H. Cho, *ACS Catalysis*, **2019**, *9*, 230.
[13] X. Li, D. G. Hall, *Angew. Chem. Int. Ed.* **2018**, *57*, 10304.
[14] a) D. Hongxun, Zh. Weike, B. Junchi, *Tetrahedron Lett.*, **1987**, *28*, 2599; b) W. Zhou, S. Liang, S. Yu, W. Luo, *J. Organomet. Chem.*, **1993**, *452*, 13.
[15] M. Suginome, A. Yamamoto, M. Murakami, *J. Am. Chem. Soc.*, **2003**, *125*, 6358.
[16] M. Daini, M. Suginome, *J. Am. Chem. Soc*., **2011**, *133*, 4758.
[17] M. Nogami, K. Hirano, M. Kanai, Ch. Wang, T. Saito, K. Miyamoto, A. Muranaka, M. Uchiyama, *J. Am. Chem. Soc*., **2017**, *139*, 12358.
[18] Alternative synthesis of 1,2-oxaborolanes: a) W. Zhou, S. Liang, W. Lo, *Synthesis*, **1990**, *8*, 685; b) W. Zhou, W. Lo, G. Zhang, H. Ding, S. Liang, *J. Organomet. Chem.*, **1990**, *387*, 131; c) J. Barluenga, F. Rodriguez, J. Vadecard, M. Bendix, F. J. Fañanas, F. López-Ortiz, M. A. Rodriguez, *J. Am. Chem. Soc*., **1999**, *121*, 8776.
[19] P. K. Poutiainen, T. A. Venäläinen, Mikael Peräkylä, J. M. Matilainen, S. Väisänen, P. Honkakoski, R. Laatikainen, J. T. Pulkkinen, *Bioorg. Med. Chem*, **2010**, *18*, 3437.
[20] P. Singh, A. Bhardwaj, *J. Med. Chem*. **2010**, *53*, 3707.

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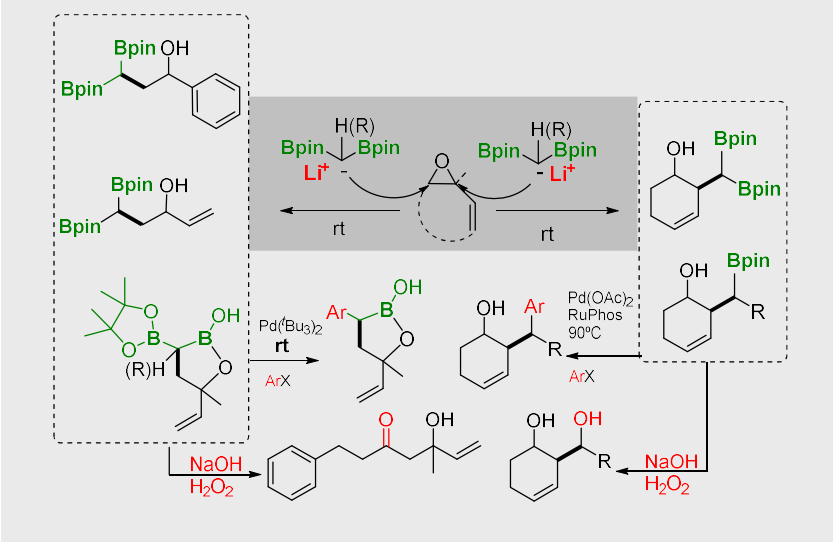

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