Access to 1,1-diborylalkenes and concomitant stereoselective reactivity

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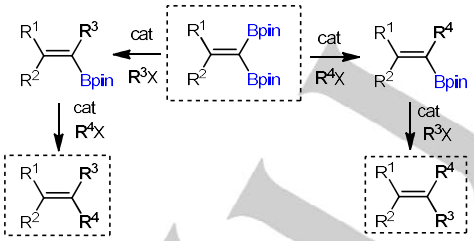
Dedication ((optional))

Abstract: *Gem*-diborylalkenes have emerged as efficient reagents for selective cross-coupling reactions, reduction approaches and Michael additions. The synthesis of the 1,1-diborylalkenes involves condensation of polyborated compounds with aldehydes or ketones followed by B-O elimination, geminal diboration of 1,1-dihaloalkenes, 1-haloalkenes as well as terminal alkynes, dehydrogenative borylation of alkenes, borylation of alkynylboronates and hydroboration of alkynylboronates. These new set of reactions become general for a wide range of substrates and they can be understood by complementary mechanisms.

1. Introduction

The presence of two geminal boron moieties in an alkene compound makes the molecule very versatile since each boryl moiety can be differentiated and transformed in a stepwise manner, allowing the synthesis of a diverse array of multisubstituted alkenes.[1] 1,1-Diborylalkenes can undergo a 2-fold cross-coupling reaction with different electrophiles allowing for stereoselective synthesis of unsymmetrically substituted alkenes. Access to both diastereoisomers can be achieved just by reversing the order of employed electrophiles. In addition, the entire process of transforming the 1,1-diborylalkenes into multisubstituted alkenes can be performed in a one-pot procedure. It is important to highlight that the first cross coupling reaction can be assisted by the presence of the geminal B.



Scheme 1. Stereoselective transformation of 1,1-diborylakenes

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Jordi Royes received his B.S. in Chemistry at the Univ. Rovira i Virgili (Spain) in 2015. He completed the Master in Synthesis and Catalysis and Molecular Design in 2016 preparing a research project based on strategic trimethylsilyldiazomethane insertion into pinB-SR followed by selective alkylations, under the supervision of Dr. Fernández and Cuenca. Since then he has been working in the field of organoboron chemistry for his PhD and during his second year is developing an applied project in Janseen-Toledo with Dr. Trabanco.

Ana B. Cuenca completed her PhD degree in 2002 under the direction of Prof. G. Asensio. She worked as a postdoctoral researcher with Prof. Quirion at the IRCOF-CNRS in Rouen (2002-04), and then completed a 2nd postdoctoral stay at the MIT (USA) under the supervision of Prof. S. L. Buchwald (2004-06). She served as an associate professor at the U. Valencia (2006-13). In 2013 she joined Prof. E. Fernández group where she explored new organic B-mediated reactions. From Sept-2016 she is an assistant professor at IQS-School of Engineering (Barcelona).

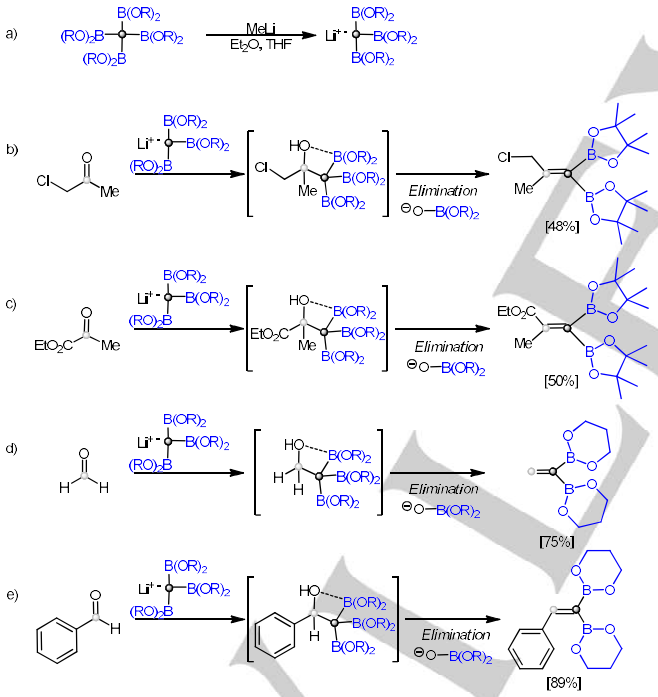
Elena Fernández did PhD studies in catalytic hydroformylation of sugars with Prof. S. Castillón (1991-1995) and she moved at the University of Oxford (UK) (1995-1997) for a postdoctoral position with Prof. John M. Brown where her studies culminated with an approach towards the first catalytic asymmetric hydroboration-amination reaction. Elena accepted a lecturer position at the University Rovira i Virgili, becoming part of the permanent staff in 2000. She is full professor from ANECA since 2011. Her group's research interests are based on new concepts about activation and reactivity of organoboron compounds.

2. Synthesis of 1,1-diborylalkenes

Diverse access to *gem*-diborylalkenes has been developed depending on the strategy of the C-B bond formation. The original procedure used poliborated carbanion nucleophiles that react with aldehydes or ketones, to condense and eliminate B-O species. Another strategy is based on the conceptual stepwise procedure involving initial preparation of an monoboryl-containing organometallic compound from an organic molecule[2] followed by introduction of the second boryl moiety. The other main strategy involves simultaneous introduction of two boryl groups into an organic molecule using an non-symmetric B-B reagent.

2.1. Condensation of polyborated compounds with aldehydes or ketones followed by B-O elimination

As Matteson described in 1974,[3] triborylmethide ions can be easily formed from a reaction of tetraborylmethane when react with methyllithium (Scheme 2a). (where $(OR)_2$ = $(OMe)_2$ or pinacol) are extremely reactive towards ketones (tolerating functional groups such as α-chloro, carbethoxy and tertiary amino substituents) (Scheme 2b,c). Acetaldehyde and benzaldehyde also undergo the condensation (Scheme 2d,e).

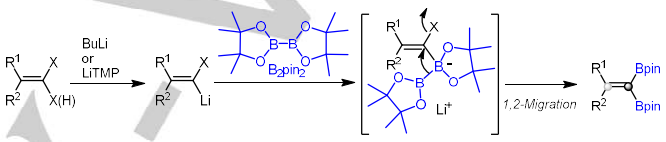


Scheme 2. Condensation of polyborated compounds with aldehydes or ketones followed by B-O elimination.

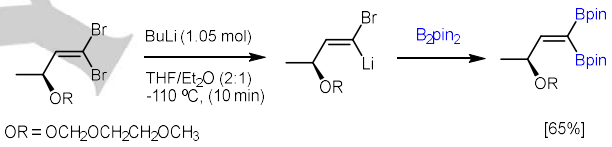
Matteson also probed that the new 1,1-diborylakenes could react with hydrogen peroxide affording the corresponding carboxylic acids. While this represented a double oxidation, it was also the first time that selective monosubtitution of one boryl moiety took place by the reaction of *gem*-diborylalkenes with Br_2, to produce α-bromoalkene boronic esters.

2.2. Geminal diboration of 1,1-dihaloalkenes or 1-haloalkenes

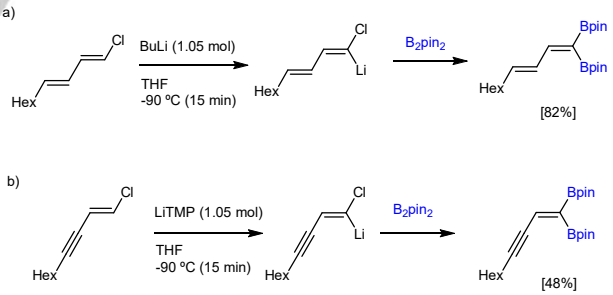
Hiyama and Shimizu discovered in 2001[4] that alkylidene-type lithium carbenoids can react with bis(pinacolato)diboron (B_2pin_2) allowing for conversion of 1,1-dihaloalkenes or 1-haloalkenes into 1,1-diborylalkenes (Scheme 3). BuLi or LiTMP are usually employed to form alkylidene-type lithium carbenoids even in a stereoselctive manner, particularly when the substrate contains a control element, such as an alkoxy group, (Scheme 4) that assists the stereoselective bromine-to-lithium exchange. The *gem*-diboration of lithium carbenoids, prepared from conjugated chloroalkenes, proceed smoothly producing conjugated compounds with two boryl groups at the terminal positions (Scheme 5), highlighting the selective 1,1-borylative process in the presence of unsaturated functional groups.



Scheme 3. Geminal diboration of alkenylidene-type carbenoids with B_2pin_2.



Scheme 4. Stereoselective preparation of an alkenylidene-type carbenoids and further reactivity with B_2pin_2

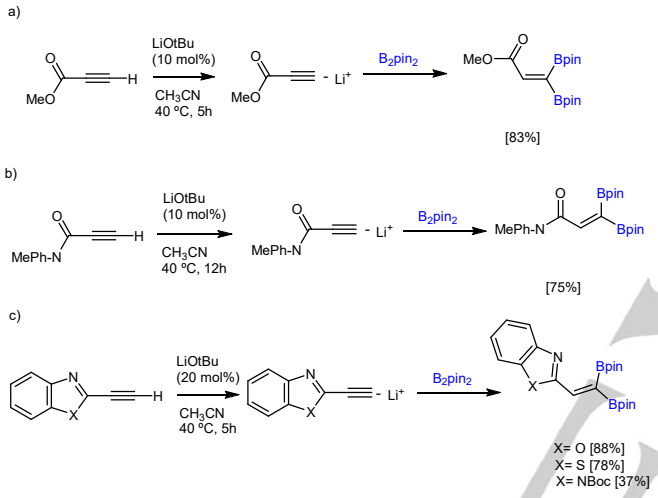


Scheme 5. Gem-diboration of conjugated chloroalkenes with B_2pin_2

The *gem*-diboration clearly involves 1,2-migration of the boryl group in the intermediate alkenyl-B-B species which takes place with inversion of configuration at the C-sp^2 center. As sp^2 carbon atoms hardly undergo normal nucleophilic substitution, the nucleophilic substitution here is considered in terms of boryl assisted nucleophilic substitution.

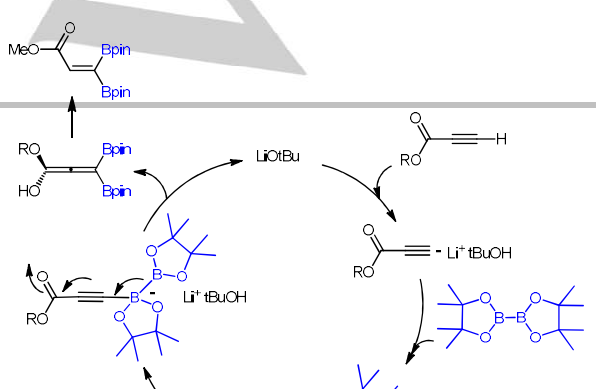
2.3. Geminal diboration of terminal alkynes

Ohmiya and Sawamura reported in 2015[5] a base-catalyzed reaction between terminal alkynes and bis(pinacolato)diboron towards the direct synthesis of functionalized 1,1-diborylalkenes. Activated terminal alkynes were selected to probe this new concept including those containing a propiolate, a propiolamide or a 2-azole substituents (Scheme 6a-c). The mild and transition-metal free reaction conditions are attractive features of this method, which can be carried out on gram scale. The optimized Brønsted base that acts as catalytic system, was selected from a screening of bases, identifying LiOtBu as the most effective, followed by NaOtBu, KOtBu, and lithium hexamethyl disilazide (LHMDS) which resulted less efficient. Aprotic solvents such as CH_3CN, hexane, toluene, THF, and dichloromethane favoured the reaction outcome, while protic solvents were responsible for a significant reduction in yield.



Scheme 6. Base-catalyzed 1,1-diboration of activated terminal alkynes.

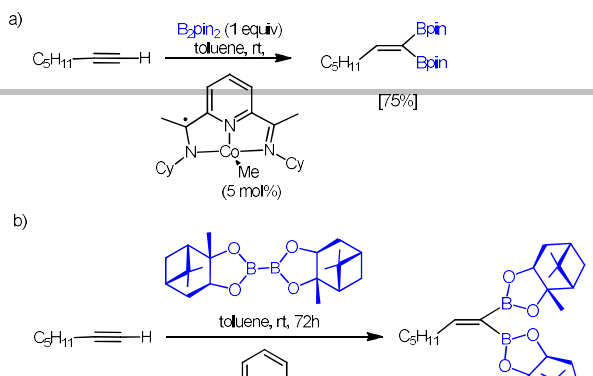
The authors suggested a catalytic cycle that might be initiated by the deprotonation of the activated terminal alkyne with LiOtBu to form a lithium acetylide which then reacts with B_2pin_2 to form an alkynyl borate intermediate (Scheme 7). Migration of the terminal boryl group of the intermediate adduct to the sp-hybridized carbon atom of the alkyne moiety, followed by the protonation of the carbonyl oxygen atom might give a 1,1-diborylallenol intermediate, which immediately isomerized to the final 1,1-diborated alkene product. The boron migration–protonation step regenerates LiOtBu, making the overall process catalytic in this reagent.



Scheme 7. Suggested mechanism for the LiOtBu-catalyzed 1,1-diboration of activated terminal alkynes.

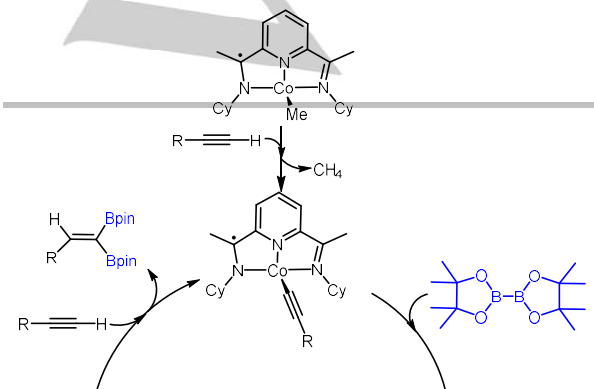
A cobalt-catalyzed method for the 1,1-diboration of terminal alkynes with B_2pin_2 has also been described by Chirik and co-workers.[6] The reaction proceeds efficiently at room temperature with excellent 1,1-selectivity and broad functional group tolerance (Scheme 8a). In particular, common organic functional groups such as tert-butyldimethylsilyl ether, acetal, ester, phthalimide, nitrile, and secondary amides were all compatible with the reaction conditions. Interestingly from a chemoselective point of view, a substrate bearing a terminal olefin underwent 1,1-diboration of the alkyne without affecting the vinylic moiety. For substrates belonging to the aryl- and heteroaryl acetylene family, the 1,1-diboration required an increased amount of B_2pin_2 to suppress the competitive homodimerization. The reaction was also very efficient for bis[(+)-pinanediolato]-diboron, producing the corresponding 1,1-diborated product with good yields, albeit at longer reaction times (72h, Scheme 8b).

When the non-symmetrical diboron reagent Bpin-Bdan (dan = 1,8-diaminonaphthalene) was used, the 1,1-diboration of the terminal alkynes led to a stereoselective formation of trisubstituted olefins of well-defined configuration (Scheme 8c), with the Bdan moiety placed selectively *trans* to the alkyl substituents of the alkene. The reaction required in this particular case a temperature of 50 ºC, presumably due to the more difficult activation of the pinB−Bdan reagent by the cobalt catalyst.



Scheme 8. Co-catalyzed 1,1-diboration of terminal alkynes with B_2pin_2, bis[(+)-pinanediolato]-diboron and Bpin-Bdan

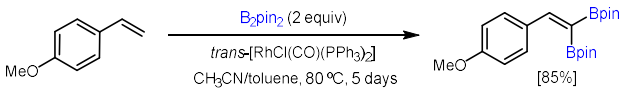
The mechanism for the cobalt-catalyzed 1,1-diboration of terminal alkynes can be understood, as suggestion by the authors,[6] as the initial transformation of the cyclohexylsubstituted pyridine(diimine) cobalt methyl complex into a cobalt acetylide (I) specie by reaction with the terminal alkyne (Scheme 9). The cobalt acetylide (I) might then react with B_2pin_2, via oxidative addition, to form an alkynyl diboronate cobalt(III) complex. Reductive elimination leads to the alkynylboronate specie still coordinated to the Co(I) intermediate. This species then inserts into the remaining C-B bond in a regioselective manner to give a vinylcobalt intermediate, which provides the desired 1,1-diborylalkene upon reaction with another terminal alkyne substrate (Scheme 9). It appears that the presence of the *N*-cyclohexyl-substituents on the supporting ligand is relevant for the observed reactivity, particularly for the formation of the key cobalt-acetylide intermediate. In fact, analogous experiments with aryl-substituted bis(imino)pyridine cobalt compounds showed preferential formation of the cobalt hydride over the cobalt acetylide. The isolation and full characterization by X-ray diffraction analysis of cobalt intermediates confirmed the suggested catalytic cycle, as seen in the formation of the vinylcobalt species by treating the cobalt acetylide complex with B_2pin_2



Scheme 9. Suggested mechanism for the Co-catalyzed 1,1-diboration of terminal alkynes with B_2pin_2.

2.4. Dehydrogenative borylation of alkenes

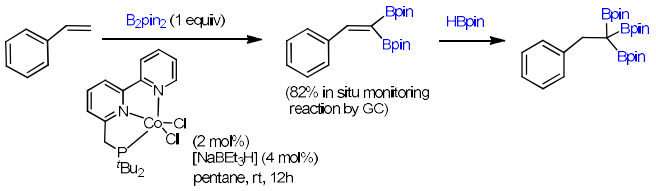
Marder and co-workers were pioneer in observing the rhodium catalyzed transformation of 4-vinylanisole into vinyl-bis(boronate) esters.[7] The catalyst used was *trans*-[RhCl(CO)$(PPh_3)_2$] (5 mol%) that activated 2 equiv of B_2pin_2 to obtain 85% of the 1,1-diborylalkene. The authors discovered his new reactivity manifold while investigating the Rh complex as a catalyst for the dehydrogenative borylation of alkenes towards vinylboronate esters. Presumably, the excess of B_2pin_2 favoured the double replacement of the terminal H's of the 4-vinylanisole by two Bpin moieties, in a single catalytic reaction, working at 80ºC (Scheme 10). The reaction time could be significantly reduced (10 min) when microwave heating was used instead.[8] Although the detailed mechanism of the dehydrogenative borylation of alkenes reaction remains unknown, it most likely involves an insertion of the alkene into a Rh–B bond, followed by β-hydride elimination to give a mono-vinylboronate that undergoes a second dehydrogenative borylation process. The process is not ideal since other borylated products are formed during the borylation reaction.



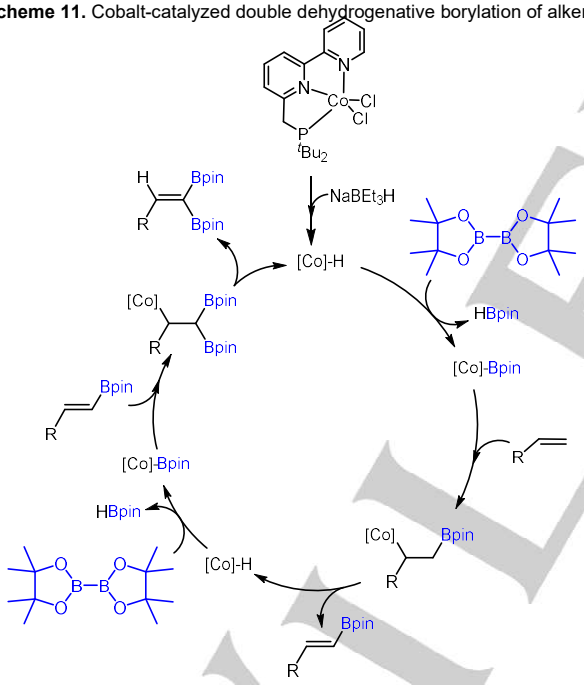
Scheme 10. Rhodium-catalyzed double dehydrogenative borylation of alkenes.

Huang and co-workers explored the cobalt-catalyzed dehydrogenative borylation of alkenes using the B_2pin_2 reagent.[9] The reaction was not selective towards the 1,1-diborylalkene, as other mono- and triborylated products were also formed under the

reaction conditions. The reaction could be carried out by using a [$CoCl_2$(^{t}BuPNN)] (2 mol%) pre-catalyst in the presence of $NaBH_4$ (4 mol%) as activator, requiring only 1 equiv of B_2pin_2 to produce the double dehydrogenative borylation at room temperature (Scheme 11). Mechanistic studies suggested that the reaction of the precatalyst [$CoCl_2$(^{t}BuPNN)] with 2 equiv of $NaBEt_3H$ produces the Co(I)-H species that upon transmetallation with B_2pin_2 forms the Co(I)-Bpin intermediate and HBpin as byproduct (Scheme 12). The insertion of the alkene into the Co-Bpin bond generates a β-boryl-substituted Co(I) species which undergoes β-hydride elimination to give the monoborylakene and Co(I)-H. A second transmetallation with B_2pin_2 forms the Co(I)-Bpin that reacts with the monoborylakene to produce the 1,1-diborylakene through a second dehydrogenative borylation. The resulting 1,1-diborylalkene compound can be further hydroborated with the HBpin formed in situ during the dehydrogenative borylation (Scheme 11).

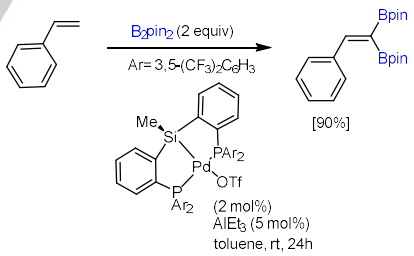


Scheme 11. Cobalt-catalyzed double dehydrogenative borylation of alkenes.

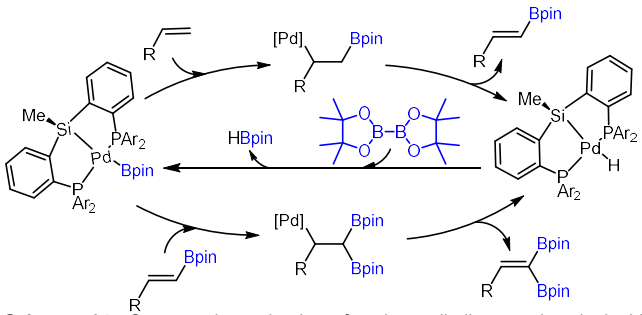


Scheme 12. Suggested mechanism for the cobalt-catalyzed double dehydrogenative borylation of alkenes.

Both protocols, based on Rh and Co catalysts, have demonstrated the feasibility of developin *gem*-diborylation of terminal olefins. In both cases, the protocol limitations include a substrate scope that did not go beyond vinylarenes. In addition, the presence of M-H and M-Bpin species along the catalytic cycles allows for the formation of by-products, based on mono and triborylated compounds. Iwasawa and co-workers launched a concise method to prepare 1,1-diborylakenes from simple alkenes and diboron reagents, involving a monoborylpalladium(II) complex as the key catalytic species.[10] The catalytic system is based on a palladium complex bearing a PSiP-pincer type ligand. Interestingly, the treatment of a 1:2 mixture of alkenes and B_2pin_2 with 1-10 mol% of the palladium complex, activated by $AlEt_3$ (5 mol%) regioselectively afforded two types of diborylalkenes, 1,1-diborylalkenes and 1,2-diborylakenes, depending on the substituents of the alkenes. The use of the terminal alkenes bearing electronically activated bulky substituent afforded 1,1-diborylalkenes in high yields (Scheme 13) due to complete suppression of the sacrificial hydroboration of the alkene. It has been suggested by the authors that the PSiP-pincer palladium pre-catalyst (bearing the 3,5-bis(trifluoromethyl)phenyl groups on phosphorus) undergoes transmetallation with $AlEt_3$ followed by β-hydride elimination to generate a monohydridopalladium complex. This active species then reacts with B_2pin_2 to give HBpin and monoborylpalladium complex bearing the PSiP-pincer ligand. The borylpalladium might then undergo the alkene insertion and β-hydride elimination to give the monoborylated product with regeneration of palladium hydride. The latter then immediately reacts with B_2pin_2 to regenerate the key catalytic borylpalladium species. A second borylation of the monoborylated product, in the presence of excess B_2pin_2 provides the diborylation product (Scheme 14).



Scheme 13. Palladium-catalyzed double dehydrogenative borylation of alkenes.

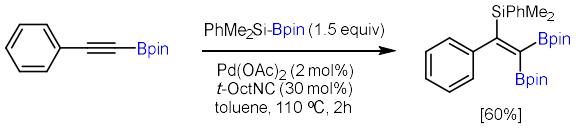


Scheme 14. Suggested mechanism for the palladium-catalyzed double dehydrogenative borylation of alkenes.

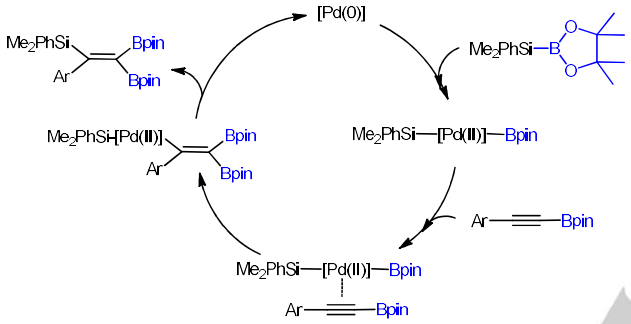
2.5. Borylation of alkynylboronates

Nishihara and co-workers explored the palladium-catalyzed silaboration of alkynylboronates. When conducted at 110 ºC, the reaction led, within hours, to the formation of a *gem*-doborylated

species with high control on the stereoselectivity (Scheme 15).[11] The catalytic palladium(0)-isonitrile system can be generated *in situ* from $Pd(OAc)_2$ and 1,1,3,3-tetramethylbutylisonitrile. The palladium(0) species might activate the silaborane reagents via an oxidative addition, and the resulting $PhMe_2$-Pd(II)-Bpin intermediate could then insert the alkynylboronate so as to stereoselectively place the two boryl moieties at the terminal carbon (Scheme 16). Eventually, the reductive elimination gives access to the 1,1-diboryl-2-silyl alkene.

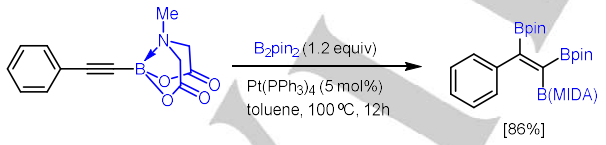


Scheme 15. Palladium-catalyzed silaboration of 1-alkynylboronates



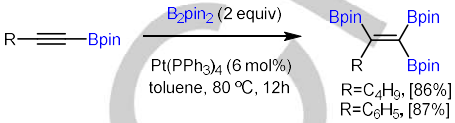
Scheme 16. Suggested mechanism for the palladium-catalyzed silaboration of alkynylboronates.

The same authors also conducted the synthesis of *gem*-diborylated alkenes having two types of boryl groups, employing this time platinum-catalyzed diboration of alkynyl MIDA-boronates with B_2pin_2 as reagent.[12] The reaction takes place in toluene at 100ºC, reaching after 12h a high yield of the triborated product (Scheme 17). The substrate phenylethynyl MIDA boronate can be easily prepared by treatment of phenylethyne with an equimolar amount of EtMgBr, followed by a reaction with $B(OMe)_3$ at −78 °C for 1 h, and concluding with the addition of an excess of MIDA at 130 °C.



Scheme 17. Palladium-catalyzed diboration of alkynyl MIDA-boronates

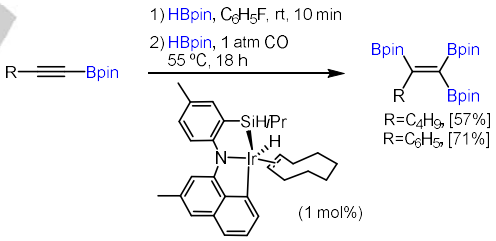
Original work by Srebnik and co-workers, demonstrated that platinum (0) could promote the diboration of 1-alkynylboronates with B_2pin_2 as reagent, working in toluene at 80ºC overnight (Scheme 18).[13] The catalyst precursor was $Pt(PPh_3)_4$ which is believed to activate the diboron reagent through the oxidative addition, generating the active Pt(II)-diboryl species.[14] Although the formation of the trisboronatedvinyl systems proceeds quantitative (via a diboration), the authors discovered that in order to avoid the formation of diboryl side-products, the process required the in situ catalyst formation for 3h prior to the addition of the reactants.



Scheme 18. Platinum-catalyzed diboration of 1-alkynylboronates

2.6. Hydroboration of alkynylboronates

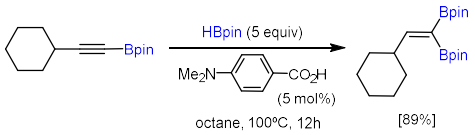
A two-step reaction to convert terminal alkynes into triborylalkenes has also been reported using pinacolborane (HBpin). Ozerov and co-workers[15] have observed that terminal alkynes can be converted into alkynylboronates in the presence of a catalytic iridium SiNN pincer complex. For a second step, a treatment of the reaction mixture with CO was required to generate a new catalyst capable of mediating the dehydrogenative diboration of an alkynylboronate with pinacolborane (Scheme 19). The authors confirmed that the mechanism of the diboration remains unclear, although noting that it does not proceed via intermediacy of a hydroborated products nor via diboration with B_2pin_2



Scheme 19. Hydroboration of alkynylboronate towards triborylalkenes.

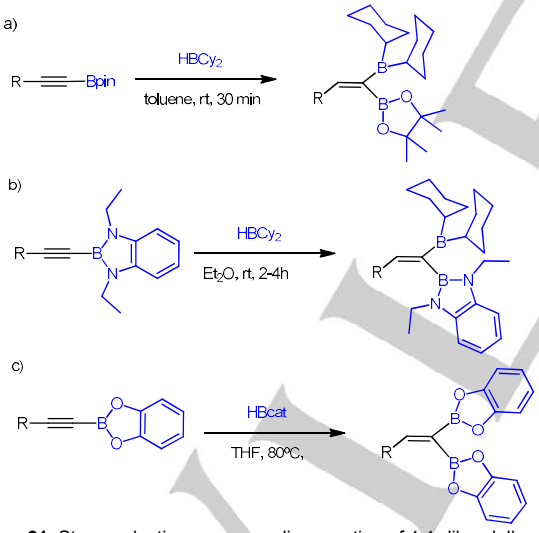
The use of pinacolborane has also been applied in the carboxylic acid-catalyzed hydroboration of various terminal and internal alkynes in the absence of any transition-metal catalysts. This unprecedented catalytic hydroboration exhibits a large functional group compatibility, giving the corresponding alkenyl diboronates in good to high yields with exclusive regio- and stereoselectivity. Jin and co-workers[16] have demonstrated that alkenyl pinacolboronate esters can be hydroborated with HBpin in the presence of a catalytic amount of acetic, formic or benzoic acids to afford the corresponding 1,1-diborylakene with exclusive regioselectivity. At the same time, the use of sterically hindered acids (pivalic acid and 2,2,2-triphenylacetic acid) as well as certain rather strong acids (such as trifluoroacetic acid) decreased the yield of the desired product. Additionally, the

solvent examination screen revealed that the use of nonpolar solvents is preferred for obtaining high yields. Interestingly, other hydroborating reagents, such as 9-BBN and HB(cat), are incompatible with this organocatalytic reaction.



Scheme 20. Hydroboration of alkynylboronates with HBpin

Alternative hydroborating reagents can be used in a non-catalyzed hydroboration of alkynylboronates. This is the case of $HBCy_2$, which can undergo a straightforward addition to terminal alkynylboronates, even at room temperature (Scheme 21a).[17,18] The reaction of $HBCy_2$ with equimolar amounts of alkynylboronates that contain 1,3,2-benzodiazaborole moieties can also be carried out with diethyl ether as solvent, at room temperature leading to the regioselective formation of 1,1-diborylalkenes (Scheme 21b).[19] Additionally, Siebert and co-workers explored the hydroboration of catecholatoborylethyne with catecholatoborane (HBcat). In this case, the process required raising the temperature to 80 ºC in order to reach a quantitative yield of the B-H addition product (Scheme 21c).[20] The *cis*-addition of the catecholborane proceeds regioselectively favoring the formation of the 1,1-isomer.



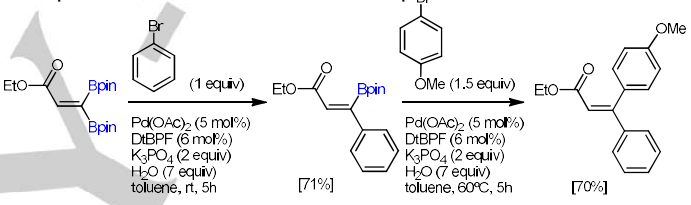
Scheme 21. Stereoselective cross-coupling reaction of 1,1-diborylalkenes.

3. Reactivity of 1,1-diborylalkenes

3.1. Selective cross-coupling reactions

The selective synthesis of 1,1-diborylalkenes is particularly attractive because these species enable, for instance, the construction of useful π- conjugated molecules through the Pd-catalyzed multiple carbon−carbon formation.[21] Particularly important is the fact that the two geminal boron substituents of the 1,1-diborylalkenes can be differentiated and transformed in a stepwise manner.

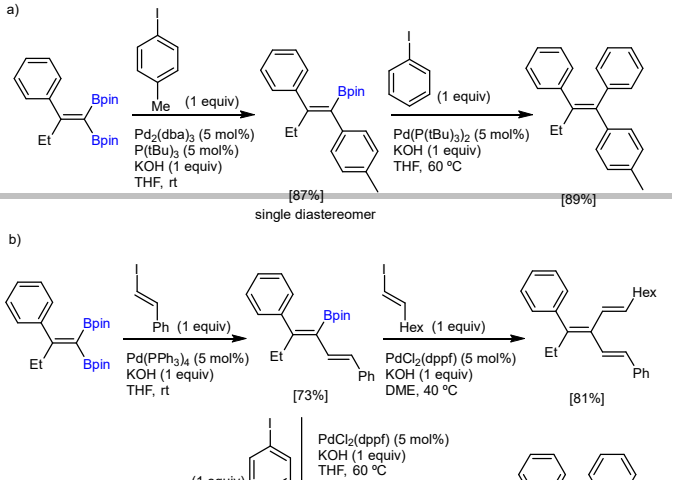
This is the case of the Suzuki–Miyaura coupling between the β,β-diborylacrylate and bromobenzene in the presence of $Pd(OAc)_2$ catalyst precursor modified with DtBPF (DtBPF=1,1'-bis(di-tert butylphosphino)ferrocene) and K_3PO_4 as a base. Sawamura and co-workers demonstrated that the cross coupling occurs selectively at the boron site *trans* to the ester group to give the corresponding alkenylboronate (with E/Z>99:1) in high yield (Scheme 22).[5] This stereoselectivity is probably due to the steric effect of the ester group, since no interaction exists between the B atoms and the ester O atom in the substrate. A second cross-coupling with 4-bromoanisole can be performed to give an isomerically pure trisubstituted alkene in good yield (Z/E>99:1). Remarkably, the first cross coupling reaction takes place at room temperature, while the second one requires 60ºC.



Scheme 22. Pd-catalyzed consecutive carbon−carbon formation with β,β-diborylacrylate

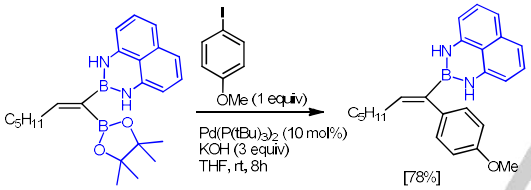
In general, 1,1-diborylalkenes can undergo stereoselective cross-coupling reaction with aryl iodides to afford the corresponding (*E*)-alkenylboronates as single diastereomers. A subsequent coupling of the monoboronate provides an efficient and completely stereocontrolled access to triarylated alkenes.[22-26] Applying this concept, Hiyama and co-workers[1] developed the stereocontrolled approach to 1,1,2-triaryl-1-alkenes based on sequential cross-coupling reaction of 1,1-diborylalkenes (Scheme 23a). Once again, the first cross coupling reaction takes place at room temperature, while the second one requires 60ºC.

The same authors extended this stereocontrolled coupling reaction between 1,1-diborylalkenes and alkenyl iodides or bromides, giving rise to 3-borylated 1,3-dienes in good yields with high *E*-selectivity (Scheme 23b). Successive Pd-catalyzed coupling reactions with alkenyl or aryl iodides results in a stereocontrolled formation of [3]dendralene[27] or triphenylated 1,3-dienes.



Scheme 23. Pd-catalyzed consecutive carbon−carbon formation with β,β-diborylacrylate

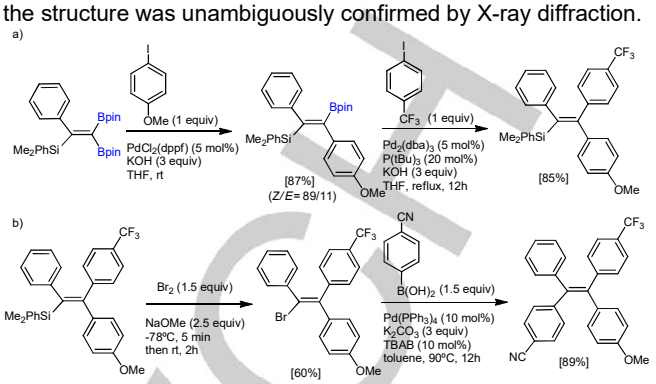
The differential reactivity of the two boron substituents in 1,1-diborylakenes bearing two different boryl uints, such as Bpin and Bdan, allows selective Suzuki−Miyaura cross coupling at the Bpin moiety (Scheme 24).[6] From a synthetic perspective, the two-step sequence of 1,1-diboration and cross coupling represents a formal 1,1-carboboration of 1-heptyne with an Ar-Bdan.[28-30]



Scheme 24. Pd-catalyzed selective Suzuki−Miyaura cross coupling at the Bpin moiety

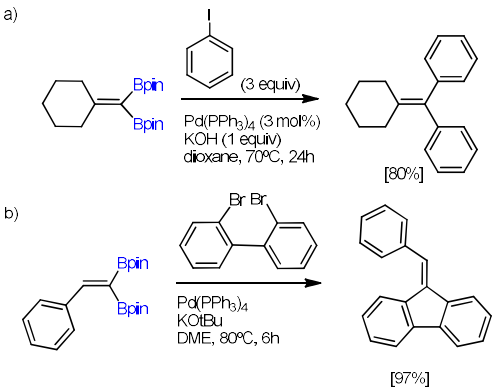
A highly chemoselective arylation by Suzuki-Miyaura coupling of 1-phenyl-1-silyl-2,2-diborylethenes[11] to afford (*Z*)-1-silyl-2-borylstilbene derivatives has recently been developed by Nishihara and co-workers.[31,32] The authors identified $PdCl_2$(dppf) to catalyze the selective alylation, at room temperature, being the *Z* stereoisomer the major triarylated product (Scheme 25a). The C-C bond formation takes place predominantly at the *cis* position of the $SiMe_2Ph$ group, thus highlighting the significant discrimination of the geminal boryl groups. It is interesting to note that the synthesis of these trans-diarylated compounds would be impracticable via *anti*-silylborylation of unsymmetrical diarylethynes[33] because the regioselectivity of the addition would not be controllable. A subsequent Suzuki-Miyaura coupling of the remaining boron moiety provides access to the triarylated compounds when using the Pd_2dba_3/P^{t}Bu$_3$ system as the catalyst (Scheme 25a).

This approach has been extended to the synthesis of tetraarylated olefins with four different substituents (Scheme 25b). To address this challenge, the authors carried out the arylation of the remaining silyl moiety by initially converting it to a bromide through a reaction with Br_2 and NaOMe in MeOH.[34] A sequential Suzuki-Miyaura coupling with the 4-cyanophenylboronic acid then afforded the tetraarylated olefins[35] in 89% yield as a sole product; the structure was unambiguously confirmed by X-ray diffraction.



Scheme 25. Pd-catalyzed consecutive carbon−carbon formation with β,β-diborylacrylate

Double cross-coupling of the 1,1-diborylakenes, has also been developed in order to jointly convert both C-B bonds into C-C bonds. Hence, Shimizu, Hiyama and co-workers[4] developed a convenient $Pd(PPh_3)_4$-catalyzed double arylation of 1,1-diborylmethylenecyclohexane with iodobenzene at 70ºC (Scheme 26a). Similarly, Jin and co-workers[16] demonstrated the synthetic usefulness of 1,1-diborylalkenes by means of a double annulative Suzuki−Miyaura coupling with 2,2′-dibromo-1,1′-biphenyl reagent in presence of $Pd(PPh_3)_4$ catalyst. The reaction produced the corresponding product 9-benzylidene-9H-fluorene in 97% yield (Scheme 26b).

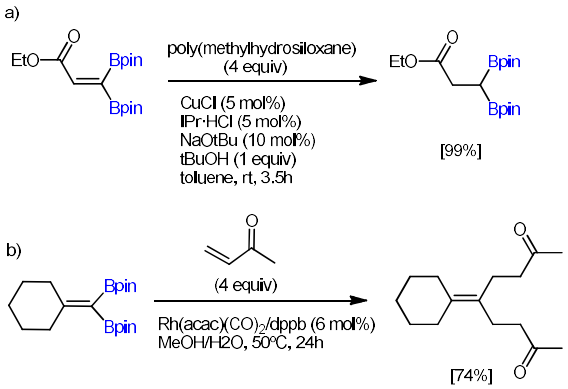


Scheme 26. Pd-catalyzed double cross-coupling of the 1,1-diborylakenes

3.2. Miscellaneous stereoselective reactivity of 1,1-diborylalkenes

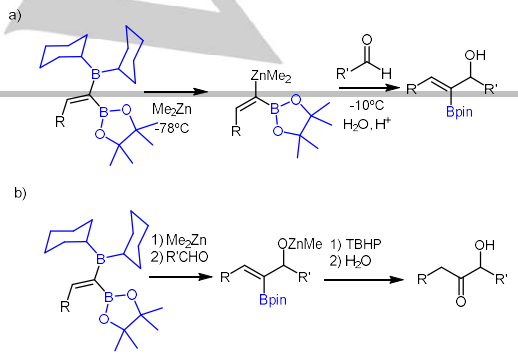
Sawamura and co-workers[5] found that β,β-diborylacrylate can be efficiently transformed into the corresponding germinal diborylalkane by copper catalyzed conjugate reduction with poly(methylhydrosiloxane) (PMHS) (Scheme 27a). The reaction

requires a copper(I) catalytic system formed *in situ* from CuCl and the N-heterocyclic carbene ligand IPr, along with added NaOtBu/tBuOH.[36-38] Interestingly, the reaction takes place at room temperature and the two geminal C-B bonds reamined untouched, representing a efficient process to obtain 1,1-diborylalkanes, which itself constitutes a very versatile organoboron building block.[39] The Rh-catalyzed Michael-type addition reaction[40] of 1,1-diborylmethylenecyclohexane to methyl vinyl ketones also proceeded smoothly to give the corresponding diketone in 74% yield (Scheme 27b).[4]



Scheme 27. a) Cu-catalyzed selective reduction of β,β-diborylacrylate compounds; b) Rh-catalyzed double Michael-addition reaction of 1,1-diborylmethylenecyclohexane

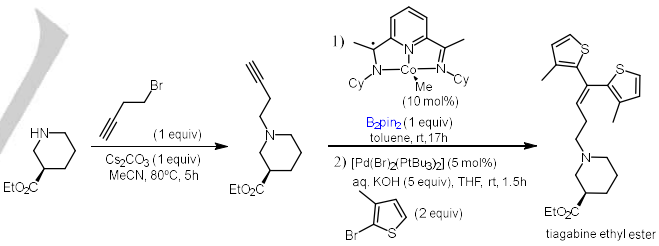
1,1-Diborylalkene compounds containing a Bpin and a dicyclohexylboryl moieties displayed two significantly different rates of transmetallation with organozinc reagents, making it possible to generate interesting zinc - boron heterobimetallic species.[41-43] Thus, Walsh and co-workers[17] demonstrated that the dicyclohexylboryl moieties efficiently transmetallates with dimethylzinc at -70ºC, leaving the Bpin moiety untouched. The origin of this reactivity difference stems from the availability of the boron *p* orbitals. While the Bpin oxygen atoms donate electron density to boron, reducing its Lewis acidity, the cyclohexyl groups donate electron density through the sigma bonds, leaving the boron *p* orbital more available, thus lowering the barrier for the transmetallation process at BCy_2.The authors also demonstrated that the resulting boron/zinc heterobimetallic reagent readily added to aldehydes, providing the B(pin)-substituted (*E*)-allylic alcohols in high yields (Scheme 28a). The efficient synthesis of Bpin-substituted allylic alcohols imply that formation of the 1,1-heterobimetallic intermediates and carbonyl additions occur smoothly. The intermediate Bpin-substituted allylic alkoxides can be subjected to *in situ* oxidation with *tert*-butylhydroperoxide (TBHP) to provide the corresponding hydroxy ketones. The 1,1-diborylalkene compounds containing Bpin and dicyclohexylboryl moieties can be converted into hydroxy ketones in good yields via one pot 4-step transformation (Scheme 28b).



Scheme 28. One-pot generation of B(pin)-substituted allylic alcohols and hydroxy ketones

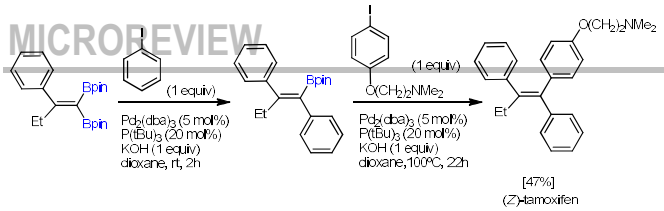
4. Synthetic applications of 1,1-diborylalkenes

The synthetic utility of the 1,1-diboryalkenes has also been applied to a highly concise synthesis of certain interesting target compounds. This is the case of tiagabine, an epilepsy medication, which was prepared starting with the alkylation of the commercially available (R)-ethylpiperidine-3-carboxylate with 4-bromo-1-butyne. The resulting alkyne precursor was subsequently subjected to a one-pot sequence consisting of cobalt-catalysed 1,1-diboration followed by a double Suzuki−Miyaura cross-coupling to yield tiagabine ethyl ester in 60% yield over 2 steps (Scheme 29).[6] The reaction conditions are compatible with the ester and amine functionality, and the integrity of the stereogenic center was preserved throughout the reaction sequence.



Scheme 29. Synthesis of tiagabine ethyl ester via one-pot 1,1-diboration/cross-coupling.

Triarylated alkenes (TAA) constitute an important class of nonsteroidal antiestrogens, as exemplified by tamoxifen, which is currently used clinically for breast cancer treatment. Since the antiestrogenic activity of TAA's depends on the configuration of the double bond, the stereocontrolled synthesis of TAA's has been the subject of intense interest. As previously shown in the Section 3.1, the 1,1-diborylalkenes represent an attractive family of precursors to be transformed to this class of compounds. A facile synthesis of (*Z*)-tamoxifen has been carried out sequentially in a one pot protocol starting with a 2,2-diborylated 1,1-etylphenylakene (Scheme 30).[1]



Scheme 30. Synthesis of (Z)-tamoxifen via one-pot sequential cross-coupling reactions.

1,1-Diborylalkenes are considered good candidates for stereoselective C-C bond formation to form polisubstituted alkenes. The diverse type of routes to achieve *gem*-diborylalkenes demonstrates the emerging interest of the area, towards general synthetic methodologies, but also to particular application to important active molecules. The stability and easy handle of those compounds justify the increasing demand of 1,1-diborylalkenes and the design of new strategic reactions.

Acknowledgements Text.

We thank MINECO through project CTQ2016-80328-P.

Keywords: 1,1-diborylalkenes • gem-diborylalkenes • diboration • dehydrogenative borylation • stereoselective cross-coupling

[1] a) M. Shimizu, Ch. Nakamaki, K. Shimono, M. Schelper, T. Kurahashi, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 12506; b) M. Shimizu, K. Shimono, M. Schelper, T. Hiyama, *Synlett* **2007**, 1969; c) M. Shimizu, T. Hiyama, *Proc. Jpn. Acad., Ser.* **2008**, *75*.

[2] I. Marek, *Chem. Rev.* **2000**, *100*, 2887.

[3] a) D. S. Matteson, P. B. Tripathy, *J. Organomet. Chem.* **1974**, *69*, 53; b) D. S. Matteson, *Synthesis* **1975**, 147.

[4] a) T. Hata, H. Kitagawa, H. Masai, T. Kurahashi, M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2001**, *40*, 790; b) T. Kurahashi, T. Hata, H. Masai, H. Kitagawa, M. Shimizu, T. Hiyama, *Tetrahedron* **2002**, *58*, 6381.

[5] A. Morinaga, K. Nagao, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2015**, *54*, 15859.

[6] S. Krautwald, M. J. Bezdek, P. J. Chirik *J. Am. Chem. Soc.* **2017**, *139*, 3868.

[7] R. B. Coapes, F. E. S. Souza, R. L. Thomas, J. J. Hall, T. B. Marder, *Chem. Commun.* **2003**, 614.

[8] I. A. I. Mkhalid, R. B. Coapes, S. N. Edes, D. N. Coventry, F. E. S. Souza, R. L. Thomas, J. J. Hall, S.-W. Bi, Z. Lin, T. B. Marder, *Dalton Trans.* **2008**, 1055.

[9] L. Zhang, Z. Huang, *J. Am. Chem. Soc.* **2015**, *137*, 15600.

[10] a) J. Takaya, N. Kirai, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 12980; b) N. Kirai, S. Iguchi, T. Ito, J. Takaya, N. Iwasawa, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 784.

[11] a) M. Iwasaki, Y. Nishihara *Chem. Rec.* **2016**, *16*, 2031; b) J. Jiao, Y. Nishihara, *J. Organomet. Chem.* **2012**, *721–722*, 3.

[12] K. Hyodo, M. Suetsugu, Y. Nishihara, *Org. Lett.* **2014**, *16*, 440.

[13] H. Abu Ali, A. E. A. Al Quntar, I. Goldberg, M. Srebnik, *Organometallics* **2002**, *21*, 4533.

[14] S. A. Westcott, E. Fernández, *Advances in Organometallic Chemistry.*, **2015**, vol 63, Chapter 3.

[15] C.-I. Lee, W.-C. Shih, J. Zhou, J. H. Reibenspies, O. V. Ozerov, *Angew. Chem., Int. Ed.* **2015**, *54*, 14003.

[16] Ho, H. E.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2014**,*16*, 4670.

[17] H. Li, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2008**, *130*, 3521.

[18] G. Molander, N. M. Ellis, *J. Org. Chem.* **2008**, *73*, 6841.

[19] L. Weber, D. Eickhoff, J. Halama, S. Werner, J. Kahlert, H.-G. Stammler, B. Neumann, *Eur. J. Inorg. Chem.* **2013**, 2608.

[20] Y. Gu, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem.* **2001**, 373.

[21] L. Xu; S. Zhang, P. Li, *Chem. Soc. Rev.* **2015**, *44*, 8848.

[22] R. B. Miller, M. I. Al-Hassan, *J. Org. Chem.* **1985**, *50*, 2121.

[23] T. Studemann, P. Knochel, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.

[24] C. Zhou, D. E. Emrich, R. C. Larock, *Org. Lett.* **2003**, *5*, 1579.

[25] P. E. Tessier, A. J. Penwell, F. E. S. Souza, A. G. Fallis, *Org. Lett.* **2003**, *5*, 2989.

[26] C. Zhou, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3765.

[27] M. Shimizu, K. Tanaka, T. Kurahashi, K. Shimono, T. Hiyama, *Chem. Lett.* **2004**, *33*, 1066.

[28] G. Kehr, G. Erker, *Chem. Commun.* **2012**, *48*, 1839.

[29] M. Suginome, *Chem. Rec.* **2010**, *10*, 348.

[30] C. Chen, T. Voss, R. Fröhlich, G. Kehr, G. Erker, *Org. Lett.* **2011**, *13*, 62.

[31] J. Jiao, K. Nakajima, Y. Nishihara, *Org Lett*, **2013**, *15*, 3294.

[32] J. Jiao, K. Hyodo, H. Hu, K. Nakajima, Y. Nishihara, *J. Org. Chem.* **2014**, *79*, 285.

[33] T. Ohmura, K. Oshima, M. Suginome, *Chem. Commun.* **2008**, 1416.

[34] R. B. Miller, M. I. Al-Hassan, *J. Org. Chem.* **1985**, *50*, 2121.

[35] M. Shimizu, T. Hiyama *Eur. J. Org. Chem.* **2013**, 8069.

[36] J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894.

[37] J. Ding, D. G. Hall, *Tetrahedron* **2012**, *68*, 3428.

[38] J. Ding,J. C. H. Lee, D. G. Hall, *Org. Lett.* **2012**, *14*, 4462.

[39] N. Miralles, R. J. Maza, E. Fernández, *Adv. Synth. Catal.*, **2017**, DOI 10.1002/adsc.201701390.

[40] M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229.

[41] M. Srebnik, *Tetrahedron Lett.* **1991**, *32*, 2449.

[42] W. Oppolzer, R. N. Radinov, *HelV. Chim. Acta* **1992**, *75*, 170.

[43] J. Rudolph, F. Schmidt, C. Bolm, *Synthesis* **2005**, 840.

[44] a) R. A. Magarian, L. B. Overacre, S. Singh, K. L. Meyer, *Curr. Med.Chem.* **1994**, *1*, 61; b) H. Wiseman, *Tamoxifen: Molecular Basis of Usein Cancer Treatment and PreVention*; Wiley: Chichester, U.K., **1994**; c) V. C. Jordan, *J. Med. Chem.* **2003**, *46*, 883; d) V. C. Jordan, *J. Med.Chem.* **2003**, *46*, 1081.

Entry for the Table of Contents

MICROREVIEW

Gem-diborylalkenes have emerged as efficient reagents for selective cross-coupling reactions. The synthesis of the 1,1-diborylalkenes involves condensation of polyborated compounds with aldehydes or ketones followed by B-O elimination, geminal diboration of 1,1-dihaloalkenes, 1-haloalkenes as well as terminal alkynes, dehydrogenative borylation of alkenes, borylation of alkynylboronates and hydroboration of alkynylboronates.

Access to 1,1-diborylalkenes and concomitant stereoselective reactivity

J. Royes, A. B. Cuenca E. Fernández**

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