Chemistry
A European
Journal

Chemistry
Europe
European Chemical
Societies Publishing

Accepted Article

Title: Generation of α-Boryl Radicals and Their Conjugate Addition to Enones: Transition-Metal-Free Alkylation of gem-Diborylalkanes

Authors: Chaoqiang Wu, Zhicheng Bao, Bowen Dou, and Jianbo Wang

To be cited as: *Chem. Eur. J.* 10.1002/chem.202004581

Link to VoR: https://doi.org/10.1002/chem.202004581

WILEY-VCH

Chemistry - A European Journal
10.1002/chem.202004581

Generation of α-Boryl Radicals and Their Conjugate Addition to Enones: Transition-Metal-Free Alkylation of *gem*-Diborylalkanes

Chaoqiang Wu, Zhicheng Bao, Bowen Dou, and Jianbo Wang*

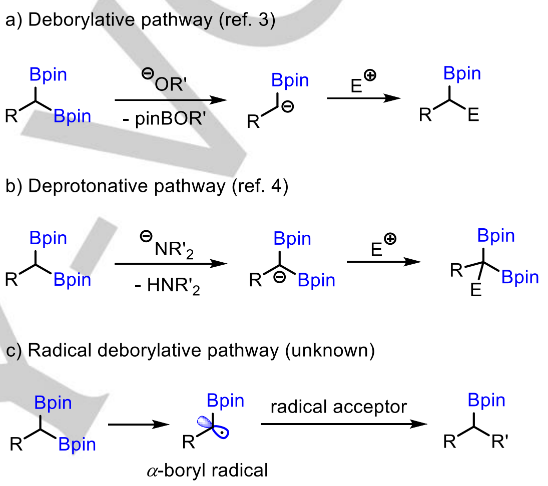
C. Wu, Z. Bao, B. Dou, Prof. Dr. J. Wang
Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry
Peking University
Beijing 100871, China
E-mail: wangjb@pku.edu.cn

Supporting information for this article is given via a link at the end of the document.

Abstract: A transition-metal-free method for the alkylation of *gem*-diborylalkanes with α,β-unsaturated ketones has been developed. It is demonstrated that the α-boryl radicals can be generated efficiently from *gem*-diborylalkanes with the aid of catechol and oxidants. The α-boryl radicals formed through such process can be engaged in conjugate addition reaction with α,β-unsaturated ketones. This transformation is a straightforward method for the synthesis of δ-borylketones.

Organic molecules containing multiple boryl groups at the same sp^3 carbon center are highly versatile intermediates in organic synthesis. Particularly, *gem*-diborylalkanes as novel alkylboronic nucleophiles have recently attracted considerable attentions as they can be applied in versatile C–C bonds forming reactions for the construction of diverse and complex molecular structures.[1,2] *gem*-Diborylalkanes are readily available and they are generally air- and moisture-stable. From *gem*-diborylalkanes diverse substituted derivatives can be easily accessed, making them attractive and practical for structure diversifications. Typically, there are two reaction modes for the functionalization of *gem*-diborylalkanes. First, in the presence of metal alkoxide bases, α-boryl carbanion species can be generated *via* deborylative pathway, which can be subsequently trapped by various electrophiles, leading to the formation of diverse alkyl boronates (Scheme 1a).[3] Alternatively, with the aid of lithium amide bases, diborylalkane carbanion species can be obtained *via* deprotonative pathway and react with various electrophiles for the synthesis of complex *gem*-diborylalkane derivatives (Scheme 1b).[4] However, to the best of our knowledge the reaction mode of *gem*-diborylalkanes based on radical process, such as the radical deborylative pathway shown in Scheme 1c, remains unknown in the literature. We have conceived that a radical process would significantly expand the diversity of the reaction modes of *gem*-diborylalkanes.

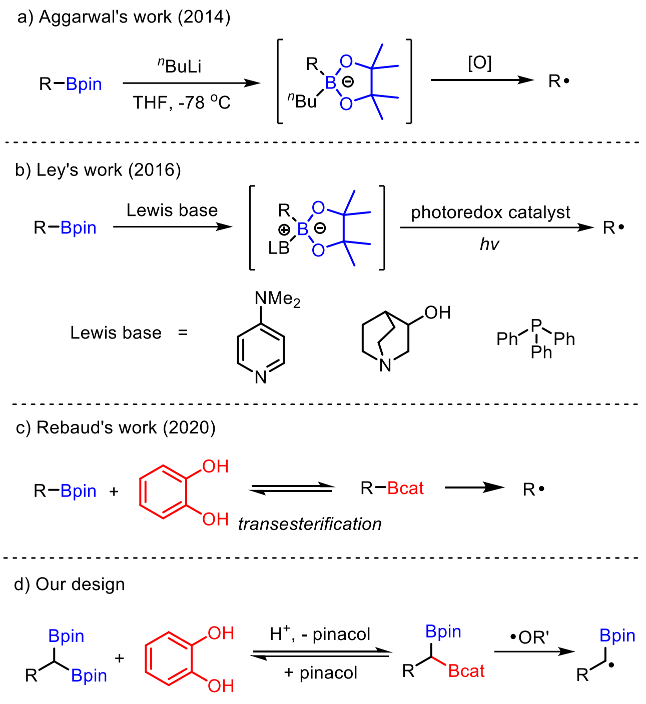
The carbon radicals bearing α-boronate substituents, namely the α-boryl radicals, have attracted significant attentions attributed to their unique characters.[5] These radical species are stabilized by the delocalization of the spin density onto the empty π-orbital of the adjacent boron atom.[6] The α-boryl radicals of alkylboronate esters have been typically generated by the addition of carbon-centered radicals to vinylboronates. Other methods include iodine-atom-transfer of α-iodoboronic esters[7] and xanthate method using boryl xanthate.[8] On the other hand, organoboron compounds have been demonstrated as efficient carbon-centered radical precursors through radical deborylative process.[9] In this context, alkylboronic acids and alkyl trifluoroborates have been widely explored as the alkyl radical precursors. However, the corresponding alkyl pinacolboronates as alkyl radical precursors are rare due to their high oxidation potentials. In 2014, Aggarwarl and co-workers developed a protocol for the radical protodeboronation of alkyl pinacolboronates by the activation of the boron moiety with *n*-butyl lithium or TBAF (Scheme 2a).[10] Ley and co-workers later demonstrated that the Lewis base-activated alkyl pinacolboronates can be transformed into the corresponding alkyl radicals *via* single electron oxidation by photoredox catalysts (Scheme 2b).[11]



Scheme 1. General reaction modes of *gem*-diborylalkanes.

While Lewis bases are essential activating reagents for the generation of alkyl radicals from the alkyl pinacolboronates through single-electron oxidation, it is known that alkyl radicals can be readily generated from alkyl catecholboronates with suitable radical initiators, such as alkoxy radicals. The high reactivity of *B*-alkylcatecholboranes toward homolytic substitution by oxygen-centered radical is attributed to the delocalization of the radical onto the benzene ring of the perboryl radical intermediate, which is generated from the complexation of *B*-alkylcatecholborane with the alkoxyl radical.[12] Inspired by this process, we considered that the *gem*-diborylalkanes may be transformed into the corresponding catecholboronate intermediates *via* transesterification equilibrium in the presence of catechol and acid, which can be further converted into α-boryl radicals with suitable radical initiators. The α-boryl radicals thus generated may be subjected

10.1002/chem.202004581



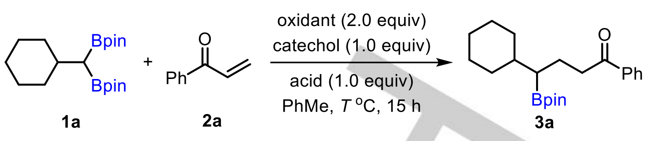
Scheme 2. Transition-metal-catalyzed thia-Sommelet-Hauser rearrangement.

to the reaction with suitable radical acceptors, such as α,β–unsaturated ketones. While our study was ongoing, Renaud and co-workers reported their study on a deboronative radical reactions with pinacol alkylboronic esters based on a transesterification strategy using catechol (Scheme 2c).[13] Herein we report our study on a transition-metal-free alkylation method of *gem*-diborylalkanes *via* α-boryl radical species (Scheme 2d).

At the outset of our study, we chose *gem*-diborylalkane **1a** as the substrate and enone **2a** as the radical acceptor for the optimization of the reaction conditions (Table 1). With DTBP (di-*t*-butyl peroxide) as the radical initiator and TFA (trifluoroacetic acid) as the acidic additive, the desired product **3a** could be obtained at 80 °C with toluene as solvent, albeit in low yield (Table 1, entry 1). While TBHP (*tert*-butyl hydroperoxide) was used as radical initiator instead of DTBP, the reaction was significantly improved to 65% yield (Table 1, entry 2). The reaction yield was diminished when acetic acid was used as the additive due to its weaker acidity (Table 1, entry 3). Then the effect of the **1a** to **2a** ratio was examined and 3.0 equiv of **2a** offered better result (Table 1, entries 4-6). A higher yield was obtained when the temperature was increased to 100 °C, with the desired product **3a** obtained with 85% isolated yield (Table 1, entry 7). For solvent effects, other solvents such as DCE (1,2-dichloromethane), MeCN and 1,4-dioxane, were screened but the reaction yields could not be improved (Table 1, entries 8-10). Finally, control experiment indicated that catechol is indispensable for the reaction (Table 1, entry 11).

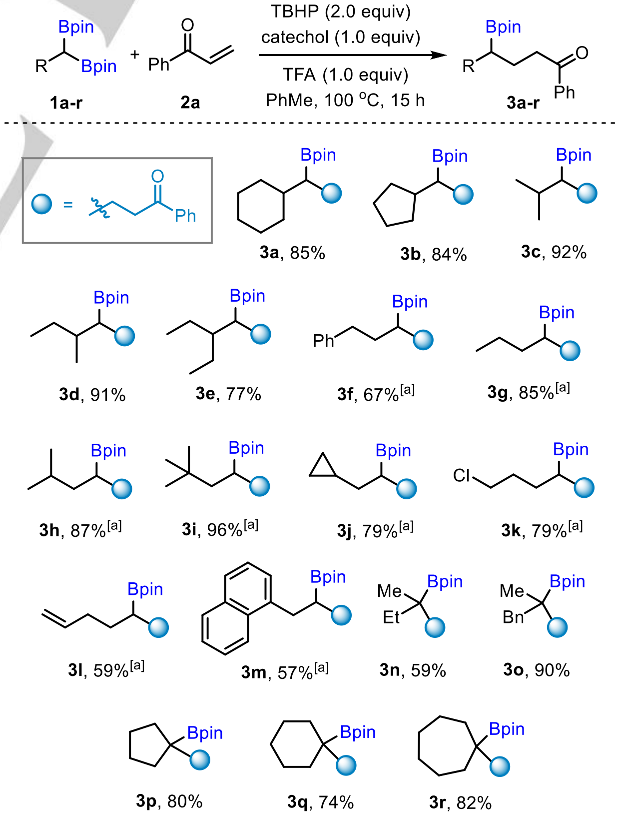
With the optimized reaction conditions in hand, we next proceeded to investigate the scope of the reaction with various *gem*-diborylalkanes. As shown in Scheme 3, the reaction worked well with a series of *gem*-diborylalkanes (**1a-r**), affording the corresponding products (**3a-r**) in moderate to excellent yields. Secondary alkyl groups substituted *gem*-diborylalkanes,

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant	Acid	**1a**:**2a**	*T* (°C)	Solvent	Yield (%)[b]
1	DTBP	TFA	1:1	80	PhMe	34
2	TBHP	TFA	1:1	80	PhMe	65
3	TBHP	AcOH	1:1	80	PhMe	40
4	TBHP	TFA	2:1	80	PhMe	66
5	TBHP	TFA	1:2	80	PhMe	71
6	TBHP	TFA	1:3	80	PhMe	80
7	TBHP	TFA	1:3	100	PhMe	86 (85)[c]
8	TBHP	TFA	1:3	100	DCE	68
9	TBHP	TFA	1:3	100	MeCN	25
10	TBHP	TFA	1:3	100	1,4-dioxane	0
11[d]	TBHP	TFA	1:3	100	PhMe	0

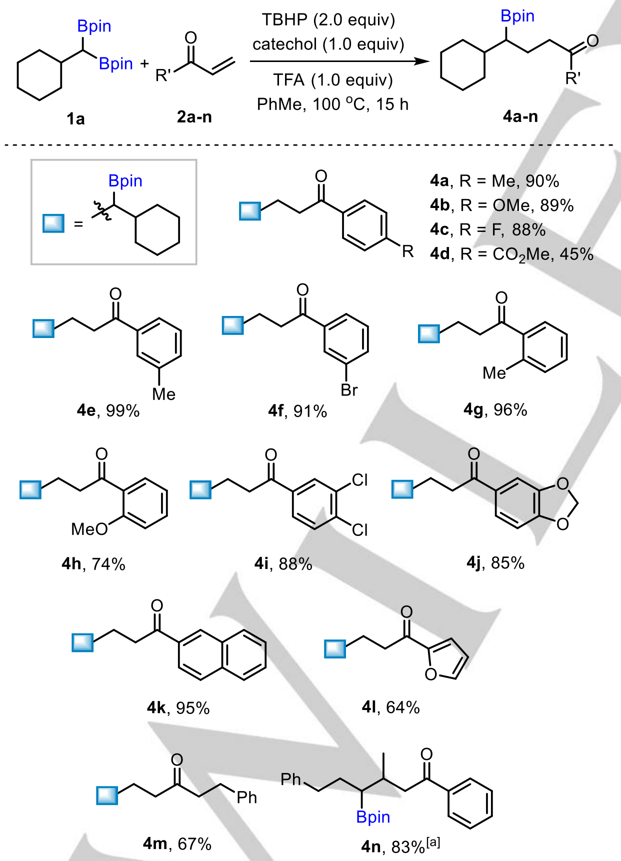
[a] The reaction was carried out with **1a** and **2a** in 3 mL toluene (0.3 mmol, 0.1 M) for 15 h. [b] Yield determined by ^{1}H NMR spectroscopy analysis using CH_2Br_2 as an internal standard. [c] Yield in the bracket refers to isolated product. [d] Catechol was not added. DTBP: di-*t*-butyl peroxide; TBHP: *tert*-butyl hydroperoxide; DCE: 1,2-dichloromethane.



Scheme 3. Substrate scope of the *gem*-diborylalkanes. The reaction was carried out with **1** and **2a** in toluene (0.3 mmol, 0.1 M) at 100 °C for 15 h. All the yields refer to isolated yields if not otherwise noted. [a] DTBP was used instead of TBHP.

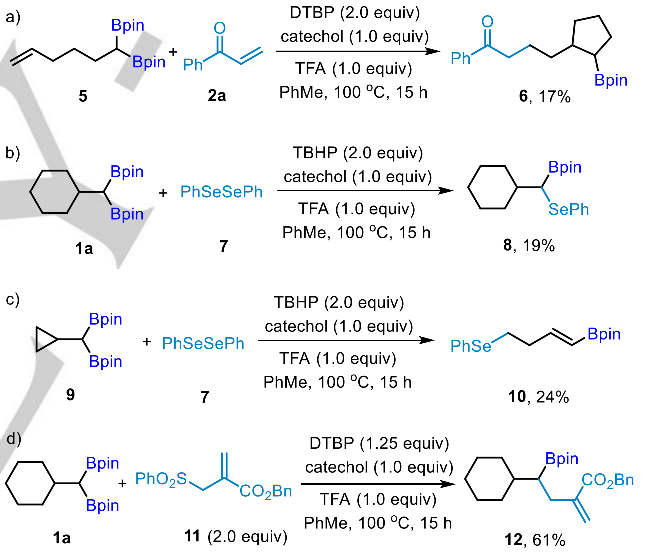
including cyclohexyl, cyclopentyl, isopropyl, isobutyl, all can be converted into the corresponding products (**3a**-**e**) under standard reaction conditions successfully with good yields. For *gem*-diborylalkanes with simple long chain alkyl groups, DTBP should be used instead of TBHP for efficient transformations (**3f**-**m**). Furthermore, dialkyl groups substituted *gem*-diborylalkanes (**3n**, **3o**) and cyclic *gem*-diborylalkanes with five-membered ring, six-membered ring and seven-membered ring (**3p**, **3q**, **3r**) could also afford the corresponding products with good yields under the same reaction conditions.

Next, the scope of enones was also investigated under the standard conditions. As shown in Scheme 4, the reaction worked well with a series of enones (**2a**-**n**), affording the corresponding products (**4a**-**n**) in moderate to good yields with good functional group tolerance. Aryl enones bearing electron-donating groups such as alkyl (**2a**, **2e**, **2g**) and alkoxy (**2b**, **2h**, **2j**), all can be converted into the corresponding products successfully. Notably, the reaction tolerates halogen substituents on the aromatic rings, including fluoro (**2c**), chloro (**2i**) and bromo (**2f**), which provides the possibility for additional transformations through transition-metal-catalyzed coupling reactions. For electron-withdrawing group substituted aryl enone, such as methoxycarbonyl (**2d**), the corresponding product (**4d**) could also be obtained albeit with lower yield. In addition, heteroaryl enone (**2l**) and alkyl enone (**2m**) could also afford the desired product with moderate yield. However, β-methyl substitutued aryl enone (**2n**) could not react with *gem*-diborylalkane **1a** under the standard reaction conditions, presumably due to steric effect. However, when less bulky *gem*-diborylalkane **1f** was used, the reaction occurred to afforded the product **4n** in 83% yield.



Scheme 4. Substrate scope of the enones. The reaction was carried out with **1a** and **2** in toluene (0.3 mmol, 0.1 M) at 100 °C for 15 h. All the yields refer to isolated yields if not otherwise noted. [a] *gem*-diborylalkane **1f** was used instead of *gem*-diborylalkane **1a**.

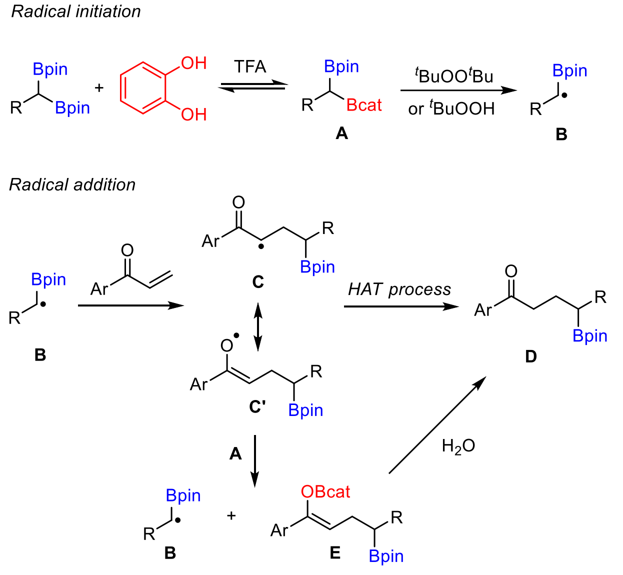
To gain insight into the reaction mechanism, several control experiments were carried out (Scheme 5). Firstly, 5-vinyl-substituted *gem*-diborylalkane **5** was treated under standard reaction conditions and cyclization product **6** was obtained, which indicated that 5-exo-trig ring-closing of α-boryl radical is involved in the reaction process (Scheme 5a). Next, diphenyl diselenide **7** was added as radical trapping agent instead of enones under the standard reaction conditions, and α-boryl radical trapped product **8** was indeed obtained (Scheme 5b). When cyclopropyl-substituted *gem*-diborylalkane **9** was treated with radical trapping agent diphenyl diselenide **7**, vinyl boronate **10** was obtained due to the ring-opening of α-boryl radical followed by the trapping with diphenyl diselenide (Scheme 5c). Finally, using allyl sulfone **11** as the radical trapping agent, the corresponding product **12** could be obtained (Scheme 5d). Thus, these control experiments support the involvement of α-boryl radical intermediate in the reaction.



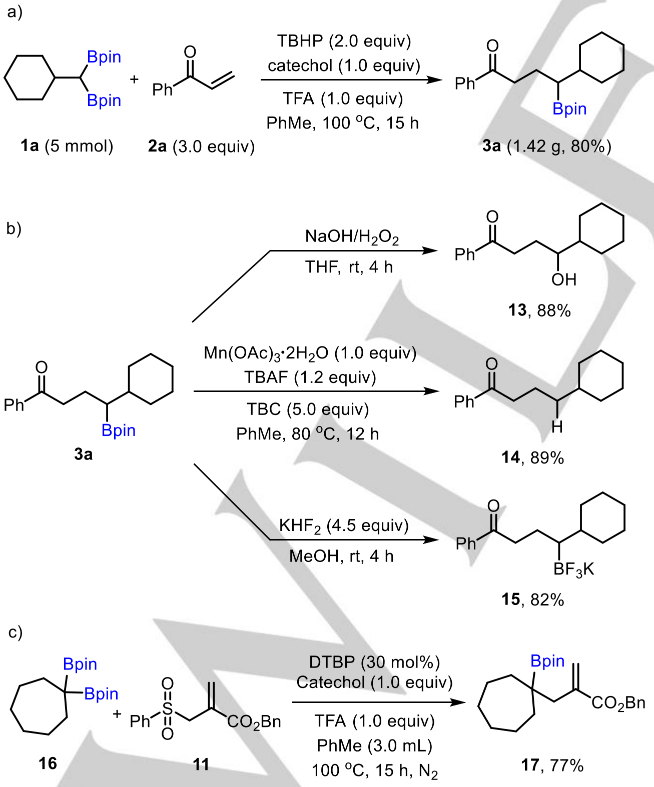
Scheme 5. Experiments for mechanistic understanding.

Based on the result of control experiments and previous report,[14] a plausible mechanism was proposed as shown in Scheme 6. Initially, *gem*-diborylalkane can be transferred into the corresponding catecholboronate intermediate **A** *via* transesterification equilibrium in the presence of catechol and TFA. With DTBP or TBHP, α-boryl radical species **B** can be generated from the corresponding catecholboronate intermediate **A** through the interaction of the catecholboronate moiety with alkoxy radical. With enone as the radical acceptor, α-boryl radical species **B** can undergo radical conjugation addition reaction to generate radical species **C** (**C'**). Finally, the ultimate product **D** is formed from the radical species **C** (**C'**) *via* HAT (hydrogen atom transfer) process with hydrogen atom source in the reaction system.[15] An alternative pathway from radical species **C** (**C'**) follows a radical chain mechanism. The radical species **C** (**C'**) reacts with catecholboronate intermediate **A** to generate α-boryl radical species **B** and boron enolate **E**.[16] The latter is hydrolyzed to afford the final product.

To demonstrate the practical usefulness of this reaction, a *gram*-scale experiment was performed with *gem*-diborylalkane **1a** and enone **2a** under the standard reaction conditions. As show in Scheme 7, the reaction proceeded to afford the corresponding boronate product **3a** with 80% isolated yield, which is similar to the corresponding small-scale experiment, demonstrating the potential of this reaction for the preparation of complex alkyl boronates in organic synthesis (Scheme 7a). Further, several functional group transformations were also performed with the alkyl boronate product **3a**. The product **3a** can be oxidized to the corresponding alcohol with hydrogen peroxide or reduced to alkane following the reported procedure.[10] Furthermore, the corresponding potassium trifluoroborate can also be formed in the presence of potassium fluoride, which may undergo various subsequent transformations (Scheme 7b). Moreover, the cyclic *gem*-diborylalkane **16** was subjected to the reaction with allyl sulfone **11**, the corresponding product **17** could be obtained in 77% yield (Scheme 7c).



Scheme 6. Proposed reaction mechanism.



Scheme 7. Gram-scale experiment and transformations of the *δ*-borylketone product **3a**.

In summary, we have developed a transition-metal-free method for the alkylation of *gem*-diborylalkanes with *α,β*-unsaturated ketones. This transformation represents the first example of generating *α*-boryl radicals from *gem*-diborylalkanes, which open new possibilities to expand the reaction modes of *gem*-diborylalkanes. It is also demonstrated that the *α*-boryl radicals generated in this way undergo conjugate addition to enones to afford *δ*-borylketones. The reaction has wide substrate scope and can be scaled up efficiently, showing its potential applications in organic synthesis for the preparation of complex alkyl boronates.

Experimental Section

General procedure for the conjugate addition reaction

A 10 mL Schlenk tube equipped with a stir bar was charged with 1,1-diborylalkane (0.3 mmol, 1.0 equiv) and catechol (33 mg, 0.3 mmol, 1.0 equiv). The tube was evacuated and filled with N2 (three cycles). Toluene (3 mL), vinyl ketone (0.9 mmol, 3.0 equiv), TBHP (82 μL, 70% aq. solution, 0.6 mmol, 2.0 equiv) or DTBP (110 μL, 0.6 mmol, 2.0 equiv) and TFA (22 μL, 0.3 mmol, 1.0 equiv) were added via syringe successively. The reaction mixture was stirred at 100 ºC for 15 h. Then the solution was cooled down to room temperature and filtered through a short plug of silica gel, eluting with ethyl acetate. The solvent was then removed in vacuo to leave a crude mixture, which was purified on a silica gel column to afford the pure product.

Acknowledgements

This research is supported by NSFC (21871010).

Keywords: diborylalkane • boryl radical • conjugate addition • *α,β*-unsaturated ketone • alkylboronate

[1] For reviews, see: a) R. Nallagonda, K. Padala, A. Masarwa, *Org. Biomol. Chem.* **2018**, *16,* 1050-1064; b) N. Miralles, R. J. Maza, E. Fernández, *Adv. Synth. Catal.* **2018**, *360,* 1306-1327; c) C. Wu, J. Wang, *Tetrahedron Lett.* **2018**, *59,* 2128-2140; d) R. Gava, E. Fernández, *Org. Biomol. Chem.* **2019**, *17*, 6317-6325; e) Y. Hu, W. Sun, C. Liu, *Synlett* **2019**, *30*, 1105-1110.

[2] For recent examples, see: a) C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 5481-5494; b) X. Liu, C. Sun, S. Mlynarski, J. P. Morken, *Org. Lett.* **2018**, *20*, 1898-1901; c) C. Hwang, W. Jo, S. H. Cho, *Chem. Commun.* **2017**, *53*, 7573-7576; d) C. E. Iacono, T. C. Stephens, T. S. Rajan, G. Pattison, *J. Am. Chem. Soc.* **2018**, *140*, 2036-2040; e) S. Namirembe, C. Gao, R. P. Wexler, J. P. Morken, *Org. Lett.* **2019**, *21*, 4392-4394; f) H. Lee, Y. Lee, S. H. Cho, *Org. Lett.* **2019**, *21*, 5912-5916; g) J. Kim, S. H. Cho, *ACS Catal.* **2019**, *9*, 230-235; h) K. Michigami, T. Sakaguchi, Y. Takemoto, *ACS Catal.* **2020**, *10*, 683-688; i) Y. Lee, J. Park, S. H. Cho, *Angew. Chem.* **2018**, *130*, 13112-13116; *Angew. Chem. Int. Ed.* **2018**, *57*, 12930-12934; j) R. Gava, E. Fernández, *Chem. Eur. J.* **2019**, *25*, 8013-8017; l) B. Lee, P. J. Chirik, *J. Am. Chem. Soc.* **2020**, *142*, 2429-2437; m) W. Sun, L. Wang, Y. Hu, X. Wu, C. Xia, C. Liu, *Nat. Commun.* **2020**, *11*, 3113.

[3] For recent examples, see: a) X. Liu, T. M. Deaton, F. Haeffner, J. P. Morken, *Angew. Chem.* **2017**, *129*, 11643-11647; *Angew. Chem. Int. Ed.* **2017**, *56*, 11485-11489; b) W. Sun, L. Wang, C. Xia, C. Liu, *Angew.*

Chem. **2018**, *130*, 5599-5603; *Angew. Chem. Int. Ed.* **2018**, *57*, 5501-5505.

[4] For recent examples, see: a) T. C. Stephens, G. Pattison, *Org. Lett.* **2017**, *19,* 3498-3501; b) S. A. Murray, E. C. M. Luc, S. J. Meek, *Org. Lett.* **2018**, *20,* 469-472; c) C. E. Iacono, T. C. Stephens, T. S. Rajan, G. Pattison, *J. Am. Chem. Soc.* **2018**, *140,* 2036-2040; d) X. Li, D. G. Hall, *Angew. Chem.* **2018**, *130*, 10461-10465; *Angew. Chem. Int. Ed.* **2018**, *57*, 10304-10308; e) Y. Lee, J. Park, S. H. Cho, *Angew. Chem.* **2018**, *130*, 13112-13116; *Angew. Chem. Int. Ed.* **2018**, *57*, 12930-12934; f) R. Gava, E. Fernández, *Chem. Eur. J.* **2019**, *25,* 8013-8017; g) S. Namirembe, C. Gao, R. P. Wexler, J. P. Morken, *Org. Lett.* **2019**, *21,* 4392-4394.

[5] a) M. Kischkewitz, K. Okamoto, C. Mück-Lichtenfeld, A. Studer, *Science* **2017**, *355*, 936-938; b) M. Ueda, Y. Kato, N. Taniguchi, T. Morisaki, *Org. Lett.* **2020**, *22*, DOI: 10.1021/acs.orglett.0c01807; c) A. Noble, R. S. Mega, D. Pflsterer, E. L. Myers, V. K. Aggarwal, *Angew. Chem.* **2018**, *130*, 2177-2181; *Angew. Chem. Int. Ed.* **2018**, *57*, 2155-2159; d) G. J. Lovinger, J. P. Morken, *J. Am. Chem. Soc.* **2017**, *139*, 17293-17296; e) M. Silvi, C. Sandford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 5736-5739; f) M. R. Heinrich, L. A. Sharp, S. Z. Zard, *Chem. Commun.* **2005**, 3077-3079.

[6] a) N. Kumar, N. Eghbarieh, T. Stein, A. I. Shames, A. Masarwa, *Chem. Eur. J.* **2020**, *26*, 5360-5364; b) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **2015**, *137*, 6762-6765; c) J. C. Walton, A. J. McCarroll, Q. Chen, B. Carboni, R. Nziengui, *J. Am. Chem. Soc.* **2000**, *122*, 5455-5463.

[7] N. D. C. Tappin, W. Michalska, S. Rohrbach, P. Renaud, *Angew. Chem.* **2019**, *131*, 14378-14382; *Angew. Chem. Int. Ed.* **2019**, *58*, 14240-14244.

[8] Q. Huang, J. Michalland, S. Z. Zard, *Angew. Chem.* **2019**, *131*, 17092-17098; *Angew. Chem. Int. Ed.* **2019**, *58*,16936 -16942.

[9] For reviews, see: a) K. Duan, X. Yan, Y. Liu, Z. Li, *Adv. Synth. Catal.* **2018**, *360,* 2781-2795; b) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415-3434; (c) V. Darmency, P. Renaud, *Top. Curr. Chem.* **2006**, *263*, 71-106.

[10] R. Rasappan, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 810-814.

[11] a) F. Lima, M. A. Kabeshov, D. N. Tran, C. Battilocchio, J. Sedelmeier, G. Sedelmeier, B. Schenkel, S. V. Ley, *Angew. Chem.* **2016**, *128*, 14291-14295; *Angew. Chem. Int. Ed.* **2016**, *55*, 14085-14089; b) F. Lima, U. K. Sharma, L. Grunenberg, D. Saha, S. Johannsen, J. Sedelmeier, E. V. Van der Eycken, S. V. Ley, *Angew. Chem.* **2017**, *129*, 15332-15336; *Angew. Chem. Int. Ed.* **2017**, *56*, 15136-15140; c) F. Lima, L. Grunenberg, H. B. A. Rahman, R. Labes, J. Sedelmeierb, S. V. Ley, *Chem. Commun.* **2018**, *54,* 5606-5609.

[12] For review, see: A.-P. Schaffner, P. Renaud, *Eur. J. Org. Chem.* **2004**, 2291-2298.

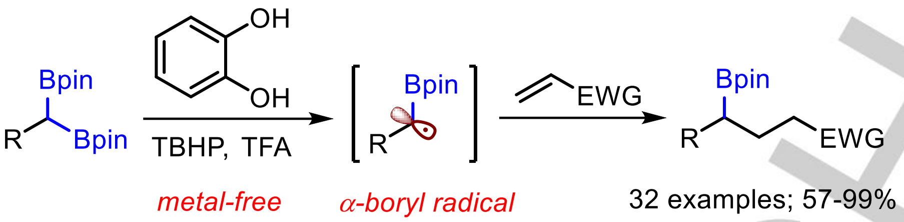
[13] E. André-Joyaux, A. Kuzovlev, N. D. C. Tappin, P. Renaud, *Angew. Chem.* **2020**, *132*, 13963-13968; *Angew. Chem. Int. Ed.* **2020**, *59*, 13859 -13864.

[14] C. Ollivier, P. Renaud, *Chem. Eur. J.* **1999**, *5,* 1468-1473.

[15] a) G. Povie, G. Villa, L. Ford, D. Pozzi, C. H. Schiesserb, P. Renaud, *Chem. Commun.* **2010**, *46,* 803-805; b) G. Villa, G. Povie, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133,* 5913-5920.

[16] A. Beauseigneur, C. Ericsson, P. Renaud, K. Schenk, *Org. Lett.* **2009**, *11*, 3378-3781.

Entry for the Table of Contents



α-Boryl radicals are generated with the aid of catechol and oxidant from *gem*-diborylalkanes The α-boryl radicals are subsequently engaged in conjugate addition reaction with α,β-unsaturated ketones to afford δ-borylketones.