Chemical Science

EDGE ARTICLE

Check for updates

Cite this: Chem. Sci., 2020, 11, 8020

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 31st May 2020 Accepted 5th July 2020

DOI: 10.1039/d0sc03039b

rsc.li/chemical-science

Electrophilic fluoroalkylthiolation induced diastereoselective and stereospecific 1,2-metalate migration of alkenylboronate complexes[†]

Feng Shen, 🕩 a Long Lu*b and Qilong Shen 🕩 *a

A transition metal free process for conjunctive functionalization of alkenylboron ate-complexes with electrophilic fluoroalkylthiolating reagents is described, affording β -trifluoroalkylthiolated and difluoroalkylthiolated boronic esters in good yield and excellent diastereoselectivity. The potential applicability of the method was demonstrated by the preparation of a difluoromethylthiolated mimic **12** of a potential drug molecule PF-4191834 for the treatment of asthma.

An electrophile-induced 1,2-metalate migration of an alkenylboron "ate" complex and subsequent base-promoted βelimination to form a functionalized cis-alkene, now the socalled Zweifel reaction, was first reported by Zweifel and coworkers in 1967 (Fig. 1A).1-3 The reaction was proposed to proceed *via* an initial attack of the π electron of the alkene moiety to iodine to generate a zwitterionic iodonium ion, which then undergoes a stereospecific 1,2-metalate to afford a β iodoboronic ester, followed by anti-elimination upon treatment with a base to afford a *cis*-olefin. Thus, if the iodine is replaced by an alternative electrophilic reagent and the use of a base is omitted, an interrupted-Zweifel reaction for the preparation of a stereospecific β -functionalized boronic ester could be realized. Toward this end, Aggarwal reported the first example of such a reaction by employing PhSeCl as the electrophilic reagent.4 It was proposed that PhSeCl first reacts with an alkenylboronate complex to form a zwitterionic seleniranium ion. Subsequent diastereospecific 1,2-metalate migration affords the stereospecific β-seleno-alkylboronate (Fig. 1B). Likewise, shortly after, Denmark and co-workers reported an analogous Lewisbase catalysed enantioselective and diastereoselective carbosulfenylation of an alkenylboronate complex using N-arylthiosaccharin as the electrophile (Fig. 1C).⁵

In light of these discoveries and our recent success in the development of a toolbox of electrophilic fluoroalkylthiolating reagents including three trifluoromethylthiolating reagents α -cumyltrifluoromethane sulfenate,⁶ *N*-trifluoromethylthio-

saccharin7 and N-trifluoromethylthiodibenzenesulfonimide,8 difluoromethylthiolating and two reagents N-difluoromethylthiophthalimide⁹ and S-(difluoromethyl)benzenesulfonothioate,10 we wondered whether these electrophilic fluoroalkylthiolating reagents could also trigger the proposed stereospecific 1,2-metalatation of the alkenylboronate complex to afford β -fluoroalkylthiolated borane derivatives (Fig. 1D). The trifluoromethylthio (-SCF₃) and the difluoromethylthio (-SCF₂H) groups have gained great attention recently, partially because of their high and tuneable lipophilicity¹¹ that might improve the drug candidate's cell membrane permeability and consequently, its overall pharmacokinetics.12 Thus, the development of new efficient reactions for the incorporation of the

ROYAL SOCIETY OF **CHEMISTRY**

View Article Online

View Journal | View Issue



Fig. 1 The interrupted Zweifel reaction.

[&]quot;Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: shenql@mail.sioc.ac.cn

^bShanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China. E-mail: lulong@mail.sioc.ac.cn

[†] Electronic supplementary information (ESI) available. CCDC 2006801. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc03039b

trifluoromethylthio¹³ or difluoromethylthio groups¹⁴ would be of vital importance in facilitating medicinal chemists' endeavours in new drug discovery. Herein, we report that by employing electrophilic difluoromethylthiolating reagent PhSO₂SCF₂H 2a as the electrophile, the proposed difluoromethylthiolating induced stereospecific 1,2-metalate migration of alkenyl boronate complexes occurred smoothly to afford β-difluoromethylthiolated boronic esters in good yields and excellent diastereoselectivity. Likewise, when electrophilic trifluoromethylthiolating reagent N-trifluoromethylthiosaccharin 7 was used, an analogous reaction for the diastereoselective formation of β-trifluoromethylthiolated boronic esters was successfully achieved.

We began our study by examining the reaction of the electrophilic difluoromethylthiolating reagent 2a with the alkenylboronate complex which was generated in situ by mixing 1a and PhLi in diethyl ether. It was found that the reaction in CH₃CN occurred in full conversion after 12 hours at room temperature, affording the corresponding product 3a in 53% yield (Table 1, entry 1). When the amount of PhLi was increased to 1.3 equivalents, the yield was increased to 76%, while the yield decreased to 66% when 2.0 equivalents of PhLi were used, likely due to the decomposition of the product under strong basic conditions (Table 1, entries 1-5). We then further investigated the effect of the reaction temperature and the solvent. It was found that the temperature did not affect the reaction significantly since the yields of the desired products were decreased slightly to 72% and 70%, respectively, when the reactions were conducted at 0 $^{\circ}$ C or $-15 ^{\circ}$ C (Table 1, entries 6 and 7). Likewise, the reaction was not sensitive to the polarity of the solvent since reactions conducted in less polar solvents such as THF or CH₂Cl₂ or nonpolar solvents like toluene occurred in

Table 1 Optimization of conditions for the reaction of the alkenyl boronate complex with $\mathsf{PhSO}_2\mathsf{SCF}_2\mathsf{H}^a$



Entry	Equiv. of PhLi	Solvent	Temp (°C)	Yield ^a (%)
1	1.0	CH₂CN	rt	53
2	1.1	CH ₃ CN	rt	60
3	1.2	CH ₃ CN	rt	72
4	1.3	CH ₃ CN	rt	$76(72)^{b}$
5	2.0	CH ₃ CN	rt	66
6	1.3	CH ₃ CN	0	72
7	1.3	CH ₃ CN	-15	70
8	1.3	CH ₃ CN	rt	56 ^c
9	1.3	THF	rt	73
10	1.3	CH_2Cl_2	rt	64
11	1.3	Toluene	rt	60

^{*a*} Reaction conditions: vinyl boronate **1a** (0.10 mmol) and reagent **2a** (0.15 mmol), in CH₃CN (1.0 mL) at room temperature for 12 h; Yields were determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard. ^{*b*} Isolated yield. ^{*c*} *N*-Difluoromethylthiophthalimide was used.

slightly lower 60–73% yields (Table 1, entries 9–11). We also found that reaction using *N*-difluoromethylthiophthalimide as the electrophilic difluoromethylthiolating reagent gave the same product in a slightly lower yield (Table 1, entry 8).

With optimum reaction conditions established, a range of different alkenylboronate complexes were tested under standard conditions (Scheme 1). Alkenylboronate complexes obtained by treating 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol



Scheme 1 Scope of 1,2-metalate migration of alkenyl boronates with reagent 2a.^{*a*} ^{*a*} Reaction conditions: alkenyl or aryl boronic ester (0.30 mmol, 1.0 equiv.), R₃Li (0.33 mmol, 1.1 equiv.) in Et₂O (1.5 mL) at -78 °C to room temperature for 30 min; then the solvent was swapped with CH₃CN (3.0 mL); 2a (0.45 mmol, 1.5 equiv.) was added. Isolated yield. ^{*b*} R₃Li (0.39 mmol) in Et₂O (1.5 mL) at 0 °C to room temperature for 30 min. ^{*c*} The mixture was treated with NaBO₃ (0.9 mmol, 3.0 equiv.) in THF/H₂O (v/v = 1:1, 6 mL) at room temperature for 6 h.

Chemical Science

ester with diverse aryl lithiums reacted efficiently with reagent 2a to give the corresponding β -difluoroalkylthionated boronic esters 3b-e and 3g-m in good yield and excellent diastereoselectivity. A range of aryllithiums with both the electrondonating methoxy group (3c) and electron-withdrawing groups such as a fluoride (3d) or a trifluoromethyl group (3g) or a bulky tert-butyl group at meta-position (3i) worked well. The reaction can also proceed smoothly for naphthyllithium (3h) and nbutyllithium (3i). Moreover, organolithiums generated from heteroaromatics, such as indole (3k), benzothiophene (3l), benzofuran (3m), could also be used. Notably, it is well-known that bromine is not compatible with butyl lithium. Yet, 3f with a para-bromophenyl moiety was obtained from the reaction of the alkenylboronate complex in situ generated by treat-(3,6-dihydro-2H-pyran-4-yl)lithium ing with 4bromophenylboronic acid pinacol ester. However, the alkenylboronate complex generated by treating (E)-4,4,5,5tetramethyl-2-(5-phenylpent-1-en-1-yl)-1,3,2-dioxaborolane with tert-butyllithium, failed to react with reagent 2a to give the corresponding β -difluoroalkylthionated boronic esters (3r). Next, the scope with respect to the alkenyl boronic ester component was explored. 3,6-Dihydro-2H-thiopyran-4-ylboronic acid pinacol ester (3n), or N-Ts-3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (30) and 1-phenylvinylboronic acid pinacol ester (3q) could react well to afford the corresponding products. To demonstrate the scalability of the reaction, 3p was prepared on a gram scale in 75% yield. Furthermore, bridged cyclic boronate 3s could also be obtained in moderate yield, and the anti diastereoselectivity of the reaction was confirmed by X-ray diffraction of its single crystals.

Furthermore, it was found that the resultant boronic esters could be easily oxidized to alcohols, with the difluoromethylthio group remaining intact, by treatment with 3.0 equivalents of NaBO₃ at room temperature for 6 h. For example, difluoromethylthiolated β -alcohols **4a–4d** were obtained in moderate to good yields under these conditions (Scheme 1).

In general, it is a common practice to use *E* or *Z*-alkenes in the reaction to probe whether the reaction is stereo-specific. Thus, we examined the reaction of *E*-(3'-phenylpropyl)vinyl boronic acid pinacol ester and *Z*-(3'-phenylpropyl)vinyl boronic acid pinacol ester under standard conditions. It was found that the reaction is stereospecific since the reactions of *E*- and *Z*-alkenyl boronic esters specifically produced corresponding *anti*- and *cis*-difluoromethylthiolated alcohols (**4e**



Scheme 2 Reactions of *E*- and *Z*-alkenyl boronate complexes with reagent 2a.



Scheme 3 Synthesis of α -chiral ketones by stereospecific 1,2-migration.^{a a} Reaction conditions: alkyl boronic ester (0.30 mmol, 1.0 equiv.), R₃Li (0.36 mmol, 1.2 equiv.) in Et₂O (1.5 mL) at -78 °C to room temperature for 30 min; then the solvent was swapped with CH₃CN (3.0 mL); **2a** (0.45 mmol, 1.5 equiv.) was added; and then NaBO₃ (0.9 mmol, 3.0 equiv.) in THF/H₂O (v/v = 1 : 1, 6 mL) was used; and then Jone's reagent (0.45 mmol, 1.5 equiv.) was used. Isolated yield.

and **4f**) with excellent diasteroselectivity (>20 : 1), respectively (Scheme 2).

To further expand the scope of the reaction, we studied the difluoromethylthiolative triggered stereospecific 1,2-metalate migration of *in situ* generated vinyl boronate complexes from enantio-enriched secondary alkyl boronic esters with vinyl lithium. The resulting crude alkyl boronic esters were then sequentially oxidized by NaBO₃ and Jone's oxidation to give α -chiral ketone derivatives. It was found that chirality of the secondary alkyl boronic esters was stereospecifically transferred to the final products **6a–c** with 100% es (Scheme 3).

Encouraged by the excellent diastereoselective difluoromethylthiolation of alkenyl boronic acid pinacol esters, we then extended this highly selective reaction to analogous trifluoromethylthiolation triggered 1,2-metalate migration of



Scheme 4 Scope of 1,2-metalate migration of alkenyl boronates with electrophilic trifluoromethylthiolating reagent 7.^a ^a Reaction conditions: alkenyl boronic ester (0.30 mmol, 1.0 equiv.), R₃Li (0.33 mmol, 1.1 equiv.) in Et₂O (1.5 mL) at -78 °C to room temperature for 30 min; then the solvent was swapped with CH₃CN (3.0 mL); reagent 5 (0.45 mmol) was added. ^b R₃Li (0.39 mmol, 1.3 equiv.) in Et₂O (1.5 mL) at 0 °C to room temperature for 30 min. Isolated yield.

alkenylboronate (Scheme 4). It was found that when N-trifluoromethylthiosaccharin 7 was used as the electrophilic trifluoromethylthiolating reagent, the reaction of alkenylboronate derived from PhLi occurred smoothly in CH₃CN after 12 h at 0 °C to give β -trifluoroalkylthionated boronic ester 8a in 76% yield (8a). Likewise, a variety of other aryllithiums could be successfully employed in this reaction to afford the corresponding β -trifluoroalkylthionated boronic esters (8b-h) in high yields. This reaction appears to be compatible with labile functional groups such as chlorine (8b), trifluoromethyl (8c), ketal (8d), and acetal (8e). In addition, organolithiums generated from heteroaromatics, such as benzofuran (8g) and benzothiophene (8h) could also be employed. Lastly, it was found that a single diastereoisomer with an anti configuration (8i) was isolated in 75% yield when the corresponding E-alkenyl boronic ester was used. Yet, the scope of alkenyoboronate complexes for the reaction with N-trifluoromethylthiosaccharin 7 is not as broad as that with PhSO₂SCF₂H since alkenylboronate complexes generated by treating 3,6-dihydro-2H-pyran-4boronic acid pinacol ester with *n*-butyllithium or by treating 2,2-dimethylethenylboronic acid pinacol ester with lithium benzothiophene failed to produce the desired β-trifluoroalkylthionated boronic esters 8j and 8k under the standard conditions.

To further demonstrate the great potential of this reaction, we applied this protocol as a key step in the synthesis of a difluoromethylthiolated mimic of PF-4191834, which is a potent competitive inhibitor of the 5-lipoxygenase (5 LOX) enzyme for the treatment of mild to moderate asthma¹⁵ (Fig. 2). Firstly, arylsulfide **11** was synthesized efficiently by deborylthiolation of organoboron **9** with thiosulfonate **10** in the presence of 5 mol% CuSO₄ as the catalyst. Lithium halide exchange of compound **11** with *t*-butyllithium at -78 °C for 30 min generated the corresponding aryl lithium species *in situ*, which was treated with 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester to afford the alkenyl boronate complex. Switching the solvent from diether ether to CH₃CN, followed by the addition of **1.5** equivalents of PhSO₂SCF₂H **2a**, and further reaction at room temperature for 12 h produced the difluoromethylthiolated mimic of PF-4191834



Fig. 2 Construction of PF-4191834 mimic by conjunctive crosscoupling.

12 in 70% yield. This example showed the potential of the current protocol in the preparation of biological active compounds.

In summary, a method of conjunctive three-component coupling between alkenyl boronic esters, organolithiums and electrophilic fluoroalkylthiolating reagents was successfully developed, affording β-trifluoroalkylthionated and difluoroalkylthionated boronic esters in good yield and excellent diastereoselectivity. The reaction is stereospecific since the reaction of the E-alkenyl boronic ester specifically gave an antidifluoromethylthiolated β-alcohol and the reaction of the Zalkenyl boronic ester specifically gave cis-difluoromethylthiolated β -alcohol 4f with excellent diasteroselectivity (>20 : 1). The potential applicability of the method was demonstrated by the preparation of a difluoromethylthiolated derivative of a potential drug molecule for the treatment of asthma PF-4191834 12. The reactions of the alkenyl boronate complexes with other electrophilic fluoroalkylating reagents are currently actively underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (21625206, 21632009, and 21421002) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000).

Notes and references

- 1 G. Zweifel, H. Arzoumanian and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 3652.
- 2 Reviews for 1,2-metalate migration of alkenyl boronate complexes: (a) R. J. Armstrong and V. K. Aggarwal, *Synthesis*, 2017, 49, 3323; (b) S. Namirembe and J. P. Morken, *Chem. Soc. Rev.*, 2019, 48, 3464.
- 3 Selective recent examples for reaction of vinyl boronate complexes: (a) Y. Kobayashi, M. Asano and Y. Kiyotsuka, Heterocycles, 2009, 77, 787; (b) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott and V. K. Aggarwal, Angew. Chem., Int. Ed., 2011, 50, 3760; (c) V. K. Aggarwal, M. Binanzer, M. C. de Ceglie, M. Gallanti, B. W. Glasspoole, S. J. F. Kendrick, R. P. Sonawane, A. Vázquez-Romero and M. P. Webster, Org. Lett., 2011, 13, 1490; (d) Y. Wang, A. Noble, E. L. Myers and V. K. Aggarwal, Angew. Chem., Int. Ed., 2016, 55, 4270; (e) R. J. Armstrong, W. Niwetmarin and V. K. Aggarwal, Org. Lett., 2017, 19, 2762; (f) D. J. Blair, D. Tanini, J. M. Bateman, H. K. Scott, E. L. Myers and V. K. Aggarwal, Chem. Sci., 2017, 8, 2898; (g) V. Fasano, J. Cid, R. J. Procter, E. Ross and M. J. Ingleson, Angew. Chem., Int. Ed., 2018, 57, 13293.
- 4 (a) R. J. Armstrong, C. García-Ruiz, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 786; (b) R. J. Armstrong, C. Sandford, C. García-Ruiz and

This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, 4922; (*c*) D. P. Hari, J. C. Abell, V. Fasano and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 5515.

- 5 Z. L. Tao, K. A. Robb, J. L. Panger and S. E. Denmark, *J. Am. Chem. Soc.*, 2018, **140**, 15621.
- 6 (a) X.-X. Shao, X.-Q. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457; (b) X.-X. Shao, C.-F. Xu, L. Lu and Q. Shen, *J. Org. Chem.*, 2015, **80**, 3012.
- 7 C.-F. Xu, B.-Q. Ma and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9316.
- 8 P. P. Zhang, M. Li, X.-S. Xue, C.-F. Xu, Q.-C. Zhao, Y.-F. Liu, H.-Y. Wang, Y.-L. Guo, L. Lu and Q. Shen, *J. Org. Chem.*, 2016, **81**, 7486.
- 9 D.-H. Zhu, Y. Gu, L. Lu and Q. Shen, *J. Am. Chem. Soc.*, 2015, 137, 10547.
- 10 D.-H. Zhu, X.-X. Shao, X. Hong, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2016, **55**, 15807.
- 11 (a) A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, 71, 525; (b) C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, 91, 165.
- 12 (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) G. Landelle,

A. Panossian and F. R. Leroux, Curr. Top. Med. Chem., 2014, 14, 941.

- 13 Selective reviews for trifluoromethylthiolating methods: (a)
 V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, 6, 880; (b)
 X. X. Shao, C. F. Xu, L. Lu and Q. Shen, *Acc. Chem. Res.*, 2015, 48, 1227; (c) X. H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, 115, 731; (d) C. F. Ni, M. Y. Hu and J. B. Hu, *Chem. Rev.*, 2015, 115, 765; (e) H. Chachignon and D. Cahard, *Chin. J. Chem.*, 2016, 34, 445; (f) S. Barata-Vallejo, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, 14, 7150; (g) P. P. Zhang, L. Lu and Q. Shen, *Acta Chim. Sin.*, 2017, 75, 744.
- 14 (a) H. Y. Xiong, X. Pannecoucke and T. Besset, *Chem. Eur. J.*, 2016, 22, 16734; (b) X. Pannecoucke and T. Besset, *Org. Biomol. Chem.*, 2019, 17, 1683; (c) X. Xiao, Z. T. Zheng, T. Li, J. L. Zheng, T. Tao, L. M. Chen, J. Y. Gu, X. Yao, J. H. Lin and J. C. Xiao, *Synthesis*, 2020, 52, 197.
- 15 P. D. De Koning, L. Murtagh, J. P. Lawson, R. A. Vonder Embse, S. A. Kunda and W. Kong, *Org. Process Res. Dev.*, 2011, 15, 1046.