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Introduction

Fluorine-containing compounds have unusual physicochemical properties and have had a considerable impact on the discovery of new medicines, agrochemicals, catalysts, and functional materials.¹ Thus, the development of fluorine-containing building blocks has recently been receiving increasing attention. The *gem*-difluoromethylene group is considered to be a bioisostere² of carbonyl groups and oxygen atoms of ethers and can modulate the pK_a of neighboring functional groups.³ *gem*-Difluoroalkyl groups (-CF₂-R) are key moieties in many fluorine-containing drugs, including lubiprostone,⁴ oteseconazole,⁵ vinflunine,⁶ and gemcitabine⁷ (Scheme 1a). The introduction of a *gem*-difluoroalkyl group into bioactive molecules is an effective strategy for studying structure-activity relationships and tuning the pharmacological activity of drugs and drug candidates.⁸

The efficient construction of chiral *gem*-difluoroalkyl compounds has attracted substantial research interest over the past few decades.⁹ However, the types of chiral *gem*-difluoroalkyl compounds are still limited in number because of lack of



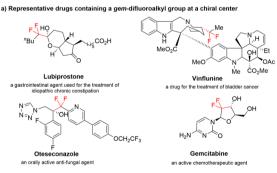
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Chiral *gem*-difluoroalkyl reagents: *gem*difluoroalkyl propargylic borons and *gem*difluoroalkyl α-allenols†

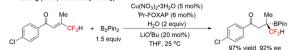
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Chiral fluorinated reagents provide new opportunities for the discovery of drugs and functional materials because the introduction of a fluorinated group significantly alters a molecule's physicochemical properties. Chiral *gem*-difluoroalkyl fragments ($R-CF_2-C^*$) are key motifs in many drugs. However, the scarcity of synthetic methods and types of chiral *gem*-difluoroalkyl reagents limits the applications of these compounds. Herein, we report two types of chiral *gem*-difluoroalkyl reagents chiral *gem*-difluoroalkyl propargylic borons and *gem*-difluoroalkyl α -allenols and their synthesis by means of methods involving rhodium-catalyzed enantioselective B–H bond insertion reactions of carbenes and Lewis acid-promoted allenylation reactions. The mild, operationally simple method features a broad substrate scope and good functional group tolerance. These two types of reagents contain easily transformable boron and alkynyl or allenyl moieties and thus might facilitate rapid modular construction of chiral molecules containing chiral *gem*-difluoroalkyl fragments and might provide new opportunities for the discovery of chiral *gem*-difluoroalkyl drugs and other functional molecules.

efficient synthetic methods. Since organoboron compounds,¹⁰ alkynes, and allenes¹¹ are common building blocks in organic synthesis, *gem*-difluoroalkyl-substituted chiral boron



 b) Previous work: asymmetric catalytic synthesis of a chiral gem-difluoroalkyl borate Zhang (2018, one example only)



c) This work: synthesis of chiral gem-difluoroalkyl propargylic boron and α -alleno



Scheme 1 Background and strategy.

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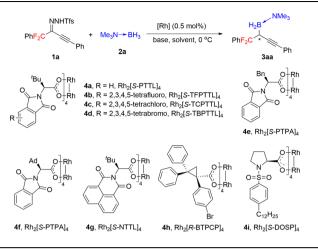
[†] Electronic supplementary information (ESI) available. CCDC 2246187. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc03266c

compounds and allenes are expected to become novel chiral gem-difluoroalkyl reagents. To our knowledge, there is only one catalytic method for the synthesis of boron-substituted chiral gem-difluoroalkyl compounds (Scheme 1b),12 while chiral gemdifluoroalkyl propargylic borons and chiral gem-difluoroalkylsubstituted allenes remain unknown. Therefore, the development of efficient, convenient methods for the synthesis of easily transformable chiral gem-difluoroalkyl-substituted boron compounds bearing alkyne and allene motifs would be highly desirable. Herein, we report a method for dirhodium-catalyzed B-H bond insertion reactions using gem-difluoroalkyl alkynyl Ntriftosylhydrazones as carbene precursors for the preparation of a wide range of novel, stable chiral gem-difluoroalkyl propargylic borons in high yields with high enantioselectivities (Scheme 1c). We also developed a method for $BF_3 \cdot Et_2O$ promoted allenylation of aldehydes with a chiral gem-difluoroalkyl propargylic boron; this method offers rapid access to a wide range of chiral gem-difluoroalkyl α -allenols with adjacent axial and central chiralities. These two types of chiral gemdifluoroalkyl reagents, which contain easily transformable boron and alkynyl or allenyl moieties, have high value for facilitating the rapid, modular construction of chiral molecules containing gem-difluoroalkyl groups. We demonstrated the synthetic potential of the gem-difluoroalkyl α -allenols by transforming one of them into chiral gem-difluoroalkyl 2,5-dihydrofuran and tetrahydrofuran derivatives.

Results and discussion

Inspired by our earlier work on asymmetric B-H bond insertion,13 we hypothesized that gem-difluoroalkyl alkynyl N-triftosylhydrazones could serve as carbene precursors for the construction of chiral gem-difluoroalkyl reagents through asymmetric B-H bond insertion reactions. We began by using gem-difluoroalkyl alkynyl N-triftosylhydrazone 1a as a model substrate, trimethylamine-borane adduct 2a as a boron source, and NaH as a base (Table 1). First, we evaluated commercially available chiral dirhodium catalysts 4a-4i (0.5 mol%) in reactions at 0 °C in Et₂O (entries 1-9). Of the tested catalysts, 4d gave the highest yield and enantioselectivity (85% yield, 89% ee, entry 4). We evaluated several alternative bases (entries 10-13) and found that they significantly decreased the yield but had little influence on the enantioselectivity. The solvent screening revealed that the weakly coordinating solvent methyl tert-butyl ether improved the yield to 99% (entry 14). In contrast, the chlorinated solvent dichloromethane substantially decreased both the yield and the enantioselectivity (entry 15). Lowering the reaction temperature to -10 °C had beneficial effects on the enantioselectivity: desired product 3aa was obtained in 99% yield with 93% ee (entry 16). However, the reaction at -20 °C gave a reduced yield and enantioselectivity (entry 17).

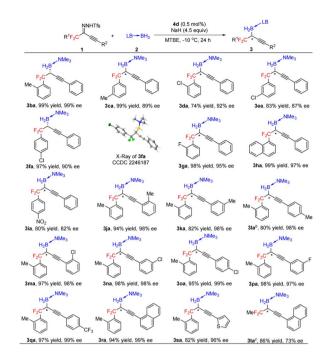
Under the optimal conditions (Table 1, entry 16), we evaluated B–H bond insertion reactions of various *gem*-difluoroalkyl alkynyl *N*-triftosylhydrazones **1** with trimethylamine–borane adduct **2a** (Scheme 2). Reactions of *N*-triftosylhydrazones bearing an aryl group attached to the alkynyl moiety (**1b–1t**) gave the corresponding B–H bond insertion products (**3ba–3ta**) Table 1Optimization of conditions for rhodium-catalyzed enantio-
selective B-H bond insertion of N-triftosylhydrazone 1a with trime-
thylamine-borane adduct $2a^{\alpha}$



Entry	[Rh]	Solvent	Base	Yield (%)	ee (%)
1	4a	Et ₂ O	NaH	41	31
2	4b	Et_2O	NaH	40	70
3	4c	Et_2O	NaH	71	85
4	4d	Et_2O	NaH	85	89
5	4e	Et_2O	NaH	52	11
6	4f	Et_2O	NaH	34	11
7	4g	Et_2O	NaH	67	63
8	4h	Et_2O	NaH	72	12
9	4i	Et_2O	NaH	15	26
10	4 d	Et_2O	NaOH	64	90
11	4d	Et_2O	K_2CO_3	60	89
12	4d	Et_2O	K_3PO_4	56	90
13	4d	Et_2O	LiOtBu	54	86
14	4d	MTBE	NaH	99	89
15	4 d	DCM	NaH	28	36
16^b	4d	MTBE	NaH	99	93
17 ^c	4 d	MTBE	NaH	59	86

^{*a*} Reaction conditions: 4/1a/2a = 0.0005 : 0.15 : 0.1 (mmol), 0.45 mmol base, 2.5 mL solvent; all the reactions were complete within 24 h. DCM, dichloromethane; MTBE, methyl *tert*-butyl ether. Isolated yields are given. The ee values were determined by HPLC. ^{*b*} Performed at -10 °C. ^{*c*} Performed at -20 °C.

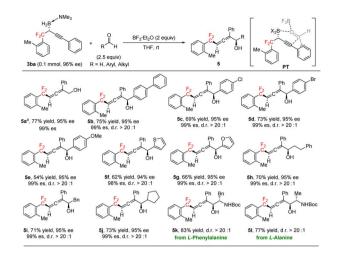
in 74–99% yields with 73–99% ee. The steric properties of the substituent on the aryl group clearly affected the enantioselectivity of the reaction. A substrate with an *ortho*-methyl group gave the expected product **3ba** in high yield with high enantioselectivity, whereas the corresponding *meta*-methylsubstituted compound showed lower enantioselectivity (**3ca**). However, the position of a chlorine substituent had little effect on the enantioselectivity (**3da–3fa**). Furthermore, a substrate with an *ortho*-fluorine substituent gave the corresponding product (**3ga**) with good results. Transformation of a 1naphthyl-substituted *N*-triftosylhydrazone afforded product **3ha** with satisfactory results. Substrate **1i**, which has a *para*-nitro group, gave access to the corresponding product (**3ia**) in 80% yield with 82% ee. We also evaluated substrates bearing an aryl or a heteroaryl group attached to the alkynyl moiety. Substrates



Scheme 2 Preparation of chiral gem-difluoroalkyl propargylic borons by rhodium-catalyzed B-H bond insertion reactions. ^a Reaction conditions: 4d/1/2 = 0.0005:0.15:0.1 (mmol), 0.45 mmol NaH, 2.5 mL MTBE, -10 °C. All reactions were complete within 24 h. Isolated yields are given. The ee values were determined by HPLC. ^b Performed at room temperature. ^c Catalyst 4b was used.

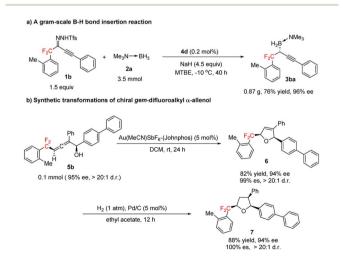
with an electron-donating methyl group or an electronwithdrawing fluorine or chlorine atom or a trifluoromethyl group on the 1-phenyl ring were tolerated (3ja-3qa). Compounds with a 1-naphthyl or 1-thienyl group attached to the alkynyl moiety showed high yields and enantioselectivities (3ra, 3sa). When 4b was the catalyst, a substrate with a methyl group attached to the gem-difluoromethylene group afforded 3ta in good yield with moderate enantioselectivity. We also evaluated reactions of 1a with a series of borane adducts 2 and found that only trialkylamine-borane adducts afforded good results (see the ESI[†] for details). The structure and absolute configuration of (R)-3fa were determined by X-ray diffraction analysis of a single crystal.

Chiral α -allenols,¹⁴ which have both axial and central chiralities, not only are found in hundreds of natural products but also serve as valuable synthetic intermediates in a wide range of transformations. gem-Difluoroalkyl-substituted chiral α-allenols have great potential as novel chiral gem-difluoroalkyl reagents with possible applications for drug discovery. To the best of our knowledge, chiral gem-difluoroalkyl-substituted allenes have not been reported. Serendipitously, we found that $BF_3 \cdot Et_2O$ -promoted addition reactions between (R)-3ba and aldehydes generated chiral gem-difluoroalkyl a-allenols, which have axial and central chiralities (Scheme 3; see the ESI[†] for optimization of the reaction conditions). Having discovered this, we evaluated a broad array of aldehydes, including formaldehyde and aromatic and aliphatic aldehydes in reactions with (R)-3ba. The addition reaction between formaldehyde and



Scheme 3 Preparation of chiral gem-difluoroalkyl a-allenols through addition reactions of gem-difluoroalkyl propargylic boron with aldehydes.^a (CH₂O)_n (10 equiv.).

(R)-3ba gave chiral gem-difluoroalkyl α -allenol 5a in good yield with excellent regioselectivity and well-retained ee. Aromatic aldehydes with a 4-phenyl, 4-chloro, or 4-bromo substituent gave corresponding α -allenols **5b–5d** in good yields with excellent regio-, diastereo-, and enantioselectivities. However, the yield of 5e from the reaction of 4-methoxy benzaldehyde was relatively low. 2-Thenaldehyde and 2-furfural gave good results (5f, 5g). Aliphatic aldehydes were also appropriate substrates, generating the desired products (5h-5j) in good yields with high regio- and diastereoselectivities. In addition, a-chiral amino aldehydes derived from natural amino acids reacted smoothly with (R)-3ba under the standard conditions, diastereoselectively providing gem-difluoroalkyl β -amino α -allenols 5k and 5l, which have three contiguous chiral centers. We propose that this reaction proceeds via transition state PT (Scheme 3). Coordination of BF₃·Et₂O to the carbonyl group of the aldehyde enhances the electrophilicity of the carbonyl carbon atom,15 and



Scheme 4 Gram-scale B-H bond insertion reaction and transformations of gem-difluoroalkyl a-allenol 5b.

the concerted addition process ensures the high diastereoselectivity.

Next, we explored the synthetic potential of our method (Scheme 4). We found that the B–H bond insertion reaction of *gem*-difluoroalkyl alkynyl sulfonylhydrazone **1b** and trimethylamine–borane adduct **2a** could be conducted at a gram scale with 0.2 mol% **4d** as the catalyst to afford (*R*)-**3ba** in good yield with excellent enantioselectivity (Scheme 4a). Gold-catalyzed cyclization of **5b** stereoselectively furnished *gem*-difluoroalkyl 2,5-dihydrofuran **6**, which has two chiral centers (Scheme 4b). Hydrogenation of the trisubstituted olefin moiety of **6** over Pd/C afforded chiral *gem*-difluoroalkyl-substituted tetrahydrofuran 7, which has three chiral centers (Scheme 4b). Recently, various compounds containing tetrahydrofuran units bearing chiral *gem*-difluoroalkyl substituents have been proposed for the treatment of cancers and other diseases.¹⁶

Conclusions

In conclusion, we have developed two types of chiral gemdifluoroalkyl reagents: gem-difluoroalkyl propargylic borons and gem-difluoroalkyl α -allenols. First, a wide range of novel, stable chiral gem-difluoroalkyl propargylic borons were synthesized in high yields with high enantioselectivities by means of dirhodium-catalyzed B-H bond insertion reactions. Then, aldehydes (formaldehyde and aromatic and aliphatic aldehydes) were allenylated with chiral gem-difluoroalkyl propargylic boron in the presence of BF₃·Et₂O for rapid access to a wide range of chiral gem-difluoroalkyl α -allenols with two or three contiguous chiral centers, including adjacent axial and central chiralities. Moreover, a gem-difluoroalkyl α -allenol was readily derivatized to afford chiral gem-difluoroalkylated 2,5dihydrofuran and tetrahydrofuran derivatives, demonstrating the considerable potential utility of chiral gem-difluoroalkyl reagents for organic synthesis.

Data availability

All experimental data were provided in ESI.†

Author contributions

S. F. Z. and H. N. Z. conceived and guided the study; H. N. Z., M. L. H., and M. Y. H. designed the experiments and analysed the data; H. N. Z. performed the reactions; Y. X. S. performed the DFT calculations; M. L. H., J. W. Z. and X. Y. Z. made some of the substrates; S. F. Z. and H. N. Z. wrote the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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Notes and references

- 1 (a) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, New York, 2000; (b) P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2013; (c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, Chem. Rev., 2016, 116, 422–518.
- 2 G. M. Dubowchik, V. M. Vrudhula, B. Dasgupta, J. Ditta, T. Chen, S. Sheriff, K. Sipman, M. Witmer, J. Tredup, D. M. Vyas, T. A. Verdoorn, S. Bollini and A. Vinitsky, *Org. Lett.*, 2001, 3, 3987–3990.
- 3 (a) G. L. Grunewald, M. R. Seim, J. Lu, M. Makboul and K. R. Criscione, *J. Med. Chem.*, 2006, 49, 2939–2952; (b)
 M. S. Smyth, H. Ford and T. R. Burke, *Tetrahedron Lett.*, 1992, 33, 4137–4140.
- 4 K. McKeage, G. L. Plosker and M. A. Siddiqui, *Drugs*, 2006, 66, 873-879.
- 5 S. M. Hoy, Drugs, 2022, 82, 1017-1023.
- 6 J. E. Frampton and M. D. Moen, Drugs, 2010, 70, 1283-1293.
- 7 S. Noble and K. L. Goa, Drugs, 1997, 54, 447-472.
- 8 (a) X. Yue, X.-L. Qiu and F.-L. Qing, J. Fluorine Chem., 2008, 129, 866–874; (b) R.-W. Wang and F.-L. Qing, Org. Lett., 2005, 7, 2189–2192; (c) Y.-Y. Wu, X. Zhang, W.-D. Meng and F.-L. Qing, Org. Lett., 2004, 6, 3941–3944; (d) K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya and T. Ohta, Org. Lett., 2000, 2, 977–980; (e) Z. Zhang, Y.-L. Xiao and X. Zhang, Acc. Chem. Res., 2018, 51, 2264–2278.
- 9 (a) C. Ni, F. Wang and J. Hu, Beilstein J. Org. Chem., 2008, 4, 21–27; (b) P. Zhang and C. Wolf, Angew. Chem., Int. Ed., 2013, 52, 7869–7873; (c) Y.-L. Liu, J.-S. Yu and J. Zhou, Asian J. Org. Chem., 2013, 2, 194–206; (d) X. Gao, Y.-L. Xiao, X. Wan and X. Zhang, Angew. Chem., Int. Ed., 2018, 57, 3187–3191; (e) X. Gao, R. Cheng, Y.-L. Xiao, X.-L. Wan and X. Zhang, Chem, 2019, 5, 2987–2999; (f) L. An, F.-F. Tong, S. Zhang and X. Zhang, J. Am. Chem. Soc., 2020, 142, 11884–11892; (g) J. Liu, L. Yu, C. Zheng and G. Zhao, Angew. Chem., Int. Ed., 2021, 60, 23641–23645; (h) H. Uno, K. Kawai, T. Araki, M. Shiro and N. Shibata, Angew. Chem., Int. Ed., 2022, 61, e202117635.
- 10 (a) D. G. Hall, Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, Wiley-VCH, Weinheim, 2nd edn, 2011; (b) E. Fernández, Advances in Organoboron Chemistry towards Organic Synthesis, Georg Thieme Verlag, Stuttgart, 2020.
- 11 (a) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria and A. Simonneau, *Chem. Rev.*, 2011, 111, 1954–1993; (b) J. Ye and S. Ma, *Acc. Chem. Res.*, 2014, 47, 989–1000; (c) S. Yu and S. Ma, *Angew. Chem., Int. Ed.*, 2012, 51, 3074–3112.

- 12 B. Liu, H.-H. Wu and J. Zhang, ACS Catal., 2018, 8, 8318-8323.
- 13 For reviews, see: (a) S.-F. Zhu, Chin. J. Chem., 2021, 39, 3211–3218; (b) M.-Y. Huang and S.-F. Zhu, Chem. Sci., 2021, 12, 15790–15801; (c) M.-Y. Huang and S.-F. Zhu, Chem. J. Chin. Univ., 2020, 41, 1426–1448; For examples, see: (d) Q.-Q. Cheng, S.-F. Zhu, Y.-Z. Zhang, X.-L. Xie and Q.-L. Zhou, J. Am. Chem. Soc., 2013, 135, 14094–14097; (e) Q.-Q. Cheng, H. Xu, S.-F. Zhu and Q.-L. Zhou, Acta Chim. Sin., 2015, 73, 326–329; (f) J.-M. Yang, Z.-Q. Li, M.-L. Li, Q. He, S.-F. Zhu and Q.-L. Zhou, J. Am. Chem. Soc., 2017, 139, 3784–3789; (g) Y. Pang, Q. He, Z.-Q. Li, J.-M. Yang, J.-H. Yu, S.-F. Zhu and Q.-L. Zhou, J. Am. Chem. Soc., 2018, 140, 10663–10668; (h) Y.-T. Zhao, Y.-X. Su, X.-Y. Li, L.-L. Yang, M.-Y. Huang and S.-F. Zhu, Angew. Chem., Int. Ed., 2021, 60, 24214–24219; (i) M.-Y. Huang, Y.-T. Zhao,

C.-D. Zhang and S.-F. Zhu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202203343; (*j*) H.-N. Zou, Y.-T. Zhao, L.-L. Yang, M.-Y. Huang, J.-W. Zhang, M.-L. Huang and S.-F. Zhu, *ACS Catal.*, 2022, **12**, 10654–10660.

- 14 (a) J. M. Alonso and P. Almendros, Chem. Rev., 2021, 121, 4193-4252; (b) X. Fan, Y. He and X. Zhang, Chem. Rec., 2016, 16, 1635-1646; (c) M. Deliaval, R. Jayarajan, L. Eriksson and K. J. Szabó, J. Am. Chem. Soc., 2023, 145, 10001-10006.
- 15 N. Okamoto, T. Sueda, H. Minami and R. Yanada, *Org. Lett.*, 2019, **21**, 8847–8851.
- 16 (a) G. Wang, D. B. Smith, L. Beigelman and C. A. Jekle, US Pat., 0176910A1, 2016; (b) M. Gmachl and M. H. Hofmann, US Pat., 0249492A1, 2022; (c) M. Smith and K. G. Klumpp,US Pat., 10092649B2, 2018; (d) D. J. Mergott and B. A. Willis, US Pat., 0231791A1, 2019.