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Chiral *gem*-difluoroalkyl reagents: *gem*-difluoroalkyl propargylic borons and *gem*-difluoroalkyl  $\alpha$ -allenols†

Hui-Na Zou, Meng-Lin Huang, Ming-Yao Huang, Yu-Xuan Su, Jing-Wei Zhang, Xin-Yu Zhang and Shou-Fei Zhu \*

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  $\alpha$ -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.

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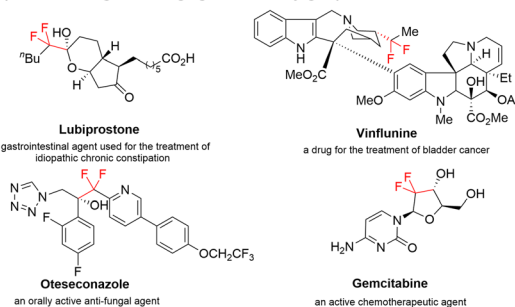
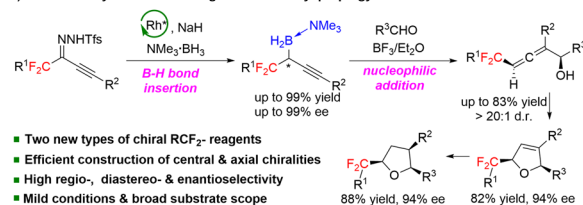
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## Introduction

Fluorine-containing compounds have unusual physicochemical properties and have had a considerable impact on the discovery of new medicines, agrochemicals, catalysts, and functional materials.<sup>1</sup> Thus, the development of fluorine-containing building blocks has recently been receiving increasing attention. The *gem*-difluoromethylene group is considered to be a bioisostere<sup>2</sup> of carbonyl groups and oxygen atoms of ethers and can modulate the  $pK_a$  of neighboring functional groups.<sup>3</sup> *gem*-Difluoroalkyl groups ( $-CF_2-R$ ) are key moieties in many fluorine-containing drugs, including lubiprostone,<sup>4</sup> oteseconazole,<sup>5</sup> vinflunine,<sup>6</sup> and gemcitabine<sup>7</sup> (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.<sup>8</sup>

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

efficient synthetic methods. Since organoboron compounds,<sup>10</sup> alkynes, and allenes<sup>11</sup> are common building blocks in organic synthesis, *gem*-difluoroalkyl-substituted chiral boron

a) Representative drugs containing a *gem*-difluoroalkyl group at a chiral centerb) Previous work: asymmetric catalytic synthesis of a chiral *gem*-difluoroalkyl boratec) This work: synthesis of chiral *gem*-difluoroalkyl propargylic boron and  $\alpha$ -allenol

Scheme 1 Background and strategy.

Frontiers Science Center for New Organic Matter, State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China. E-mail: sfzhu@nankai.edu.cn

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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),<sup>12</sup> while chiral *gem*-difluoroalkyl propargylic borons and chiral *gem*-difluoroalkyl-substituted 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 *N*-triflylhydrazones 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  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -promoted allenylation of aldehydes with a chiral *gem*-difluoroalkyl propargylic boron; this method offers rapid access to a wide range of chiral *gem*-difluoroalkyl  $\alpha$ -allenols with adjacent axial and central chiralities. These two types of chiral *gem*-difluoroalkyl 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  $\alpha$ -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,<sup>13</sup> we hypothesized that *gem*-difluoroalkyl alkynyl *N*-triflylhydrazones 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*-triflylhydrazone **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  $\text{Et}_2\text{O}$  (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*-triflylhydrazones **1** with trimethylamine–borane adduct **2a** (Scheme 2). Reactions of *N*-triflylhydrazones bearing an aryl group attached to the alkynyl moiety (**1b–1t**) gave the corresponding B–H bond insertion products (**3ba–3ta**)

**Table 1** Optimization of conditions for rhodium-catalyzed enantioselective B–H bond insertion of *N*-triflylhydrazone **1a** with trimethylamine–borane adduct **2a**<sup>a</sup>

**4a**, R = H,  $\text{Rh}_2[\text{S-PTTL}]_4$

**4b**, R = 2,3,4,5-tetrafluoro,  $\text{Rh}_2[\text{S-TFPTTL}]_4$

**4c**, R = 2,3,4,5-tetrachloro,  $\text{Rh}_2[\text{S-TCPTTL}]_4$

**4d**, R = 2,3,4,5-tetrabromo,  $\text{Rh}_2[\text{S-TBPTTL}]_4$

**4e**,  $\text{Rh}_2[\text{S-PTPA}]_4$

**4f**,  $\text{Rh}_2[\text{S-PTPA}]_4$

**4g**,  $\text{Rh}_2[\text{S-NTTL}]_4$

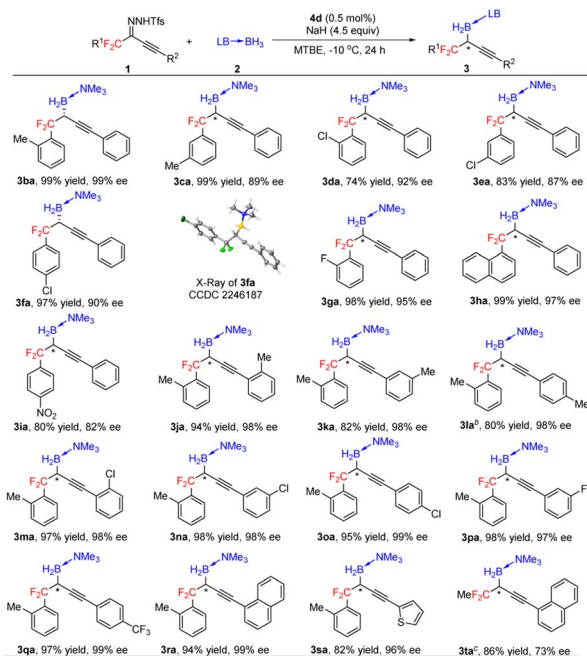
**4h**,  $\text{Rh}_2[\text{R-BTPCP}]_4$

**4i**,  $\text{Rh}_2[\text{S-DOSP}]_4$

Entry	[Rh]	Solvent	Base	Yield (%)	ee (%)
1	<b>4a</b>	$\text{Et}_2\text{O}$	NaH	41	31
2	<b>4b</b>	$\text{Et}_2\text{O}$	NaH	40	70
3	<b>4c</b>	$\text{Et}_2\text{O}$	NaH	71	85
4	<b>4d</b>	$\text{Et}_2\text{O}$	NaH	85	89
5	<b>4e</b>	$\text{Et}_2\text{O}$	NaH	52	11
6	<b>4f</b>	$\text{Et}_2\text{O}$	NaH	34	11
7	<b>4g</b>	$\text{Et}_2\text{O}$	NaH	67	63
8	<b>4h</b>	$\text{Et}_2\text{O}$	NaH	72	12
9	<b>4i</b>	$\text{Et}_2\text{O}$	NaH	15	26
10	<b>4d</b>	$\text{Et}_2\text{O}$	NaOH	64	90
11	<b>4d</b>	$\text{Et}_2\text{O}$	$\text{K}_2\text{CO}_3$	60	89
12	<b>4d</b>	$\text{Et}_2\text{O}$	$\text{K}_3\text{PO}_4$	56	90
13	<b>4d</b>	$\text{Et}_2\text{O}$	LiOtBu	54	86
14	<b>4d</b>	MTBE	NaH	99	89
15	<b>4d</b>	DCM	NaH	28	36
16 <sup>b</sup>	<b>4d</b>	MTBE	NaH	99	93
17 <sup>c</sup>	<b>4d</b>	MTBE	NaH	59	86

<sup>a</sup> 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. <sup>b</sup> Performed at –10 °C. <sup>c</sup> Performed at –20 °C.

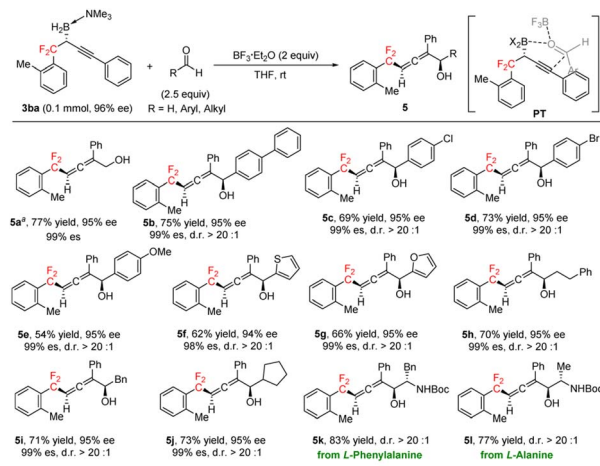
in 74–99% yields with 73–99% ee. The steric properties of the substituent on the aryl group clearly affected the enantioselectivity of the reaction. A substrate with an *ortho*-methyl group gave the expected product **3ba** in high yield with high enantioselectivity, whereas the corresponding *meta*-methyl-substituted 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 1-naphthyl-substituted *N*-triflylhydrazone 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. <sup>a</sup> 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. <sup>b</sup> Performed at room temperature. <sup>c</sup> Catalyst **4b** was used.

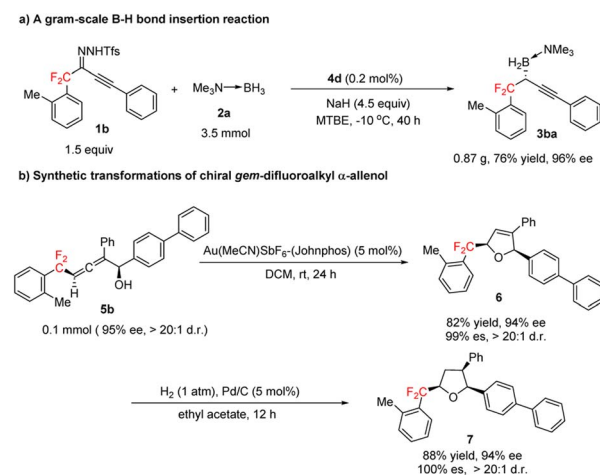
with an electron-donating methyl group or an electron-withdrawing fluorine or chlorine atom or a trifluoromethyl group on the 1-phenyl ring were tolerated (**3ja–3qa**). Compounds with a 1-naphthyl or 1-thienyl group attached to the alkynyl moiety showed high yields and enantioselectivities (**3ra**, **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  $\alpha$ -allenols,<sup>14</sup> 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  $\alpha$ -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 allenols have not been reported. Serendipitously, we found that  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -promoted addition reactions between (*R*)-**3ba** and aldehydes generated chiral *gem*-difluoroalkyl  $\alpha$ -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  $\alpha$ -allenols through addition reactions of *gem*-difluoroalkyl propargylic boron with aldehydes. <sup>a</sup>  $(\text{CH}_2\text{O})_n$  (10 equiv.).

(*R*)-**3ba** gave chiral *gem*-difluoroalkyl  $\alpha$ -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  $\alpha$ -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,  $\alpha$ -chiral amino aldehydes derived from natural amino acids reacted smoothly with (*R*)-**3ba** under the standard conditions, diastereoselectively providing *gem*-difluoroalkyl  $\beta$ -amino  $\alpha$ -allenols **5k** and **5l**, which have three contiguous chiral centers. We propose that this reaction proceeds *via* transition state **PT** (Scheme 3). Coordination of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to the carbonyl group of the aldehyde enhances the electrophilicity of the carbonyl carbon atom,<sup>15</sup> and



**Scheme 4** Gram-scale B–H bond insertion reaction and transformations of *gem*-difluoroalkyl  $\alpha$ -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.<sup>16</sup>

## Conclusions

In conclusion, we have developed two types of chiral *gem*-difluoroalkyl reagents: *gem*-difluoroalkyl propargylic borons and *gem*-difluoroalkyl  $\alpha$ -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  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  for rapid access to a wide range of chiral *gem*-difluoroalkyl  $\alpha$ -allenols with two or three contiguous chiral centers, including adjacent axial and central chiralities. Moreover, a *gem*-difluoroalkyl  $\alpha$ -allenol was readily derivatized to afford chiral *gem*-difluoroalkylated 2,5-dihydrofuran 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.

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