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Highly Diastereoselective Zn/$SnCl_2$-Mediated *gem*-Difluoroallylation of Chiral Hydrazones

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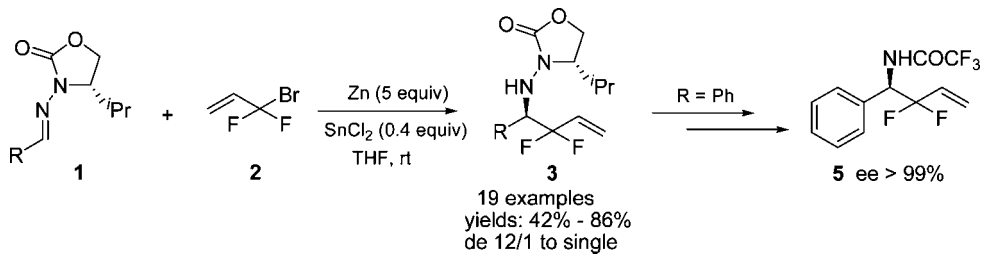
ABSTRACT



***gem*-Difuoroallylic zinc reacts with chiral hydrazones 1 in the presence of $SnCl_2$ to afford the versatile and chiral fluorinated building blocks, *gem*-difluorohomoallylic amines, in good yields and high diastereoselectivities.**

Fluorinated compounds play a very important role in life sciences due to the introduction of one or a few fluorine atoms into an organic molecule showing profound changes in its chemical and biological nature.[1] Among them, *gem*-difluorinated molecules constitute a distinct class of fluorinated compounds.[2] Incorporation of a *gem*-difluoromethylene group (CF_2) into an organic molecule can not only enhance its neighboring group stability or acidity but also act as an isopolar−isosteric substitute for oxygen.[3] It has been used as one strategy for modification of biologically active compounds, such as enzyme inhibitors,[4] and anticancer agents (e.g., Gemcitabine[5] and Vinflunine[6] have been extensively used for treatment of lung, ovarian, renal, pancreatic, head and, neck cancers). Therefore, many efforts have been focused on the synthesis of *gem*-difluorinated compounds.[2,7] The most commonly used methods thus far are direct difluorination of

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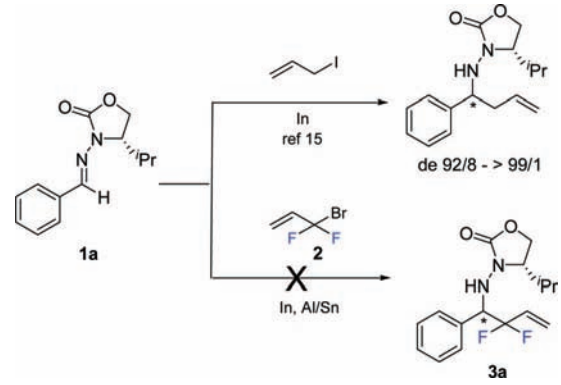
carbonyl with DAST[8] and the Reformatsky reaction using bromodifluoroacetate.[9] However, to incorporate a *gem*-difluoromethylene group to an organic molecule in a *chemo*-, *regio*-, and *stereo*-manner is still a great challenge.[10]

Optically pure *gem*-difluorohomoallylic amines are very important compounds. They can not only be transformed into various new chiral fluorinated building blocks by functionization of alkene moiety, such as substituted alkenes, amino acids, δ-lactams, and pyrrolidines, but also be applied to biologically interesting compounds. In addition, allylic fluorides are potent active-site-directed irreversible inhibitors of isopentenyl−diphosphate isomerase.[11] Surprisingly, only two examples of preparation of *gem*-difluorohomoallylic amines have been reported,[12] despite that impressive progress has been made on the development of asymmetric synthesis of nonfluorinated homoallylic amines.[13,14] One of these two methods is through direct difluorination of allylic ketone with DAST. But the yield was poor, intricate transformations were required, and many functional groups were incompatible under the harsh reaction conditions.[12a] The other one was developed by our group. However, it required the conversion of a chiral *gem*-difluorohomoallylic alcohol into an amine.[12b,c] On the basis of a great demand for difluorinated structures as well as the importance of optically pure *gem*-difluorohomoallylic amines in biological chemistry and natural product modification, a direct and efficient method would thus facilitate their accessibility. Herein, we disclose the first successful, efficient, highly stereoselective synthesis of *gem*-difluorohomoallylic amines through the coupling of the *gem*-difluoroallylic zinc with chiral hydrazones in the presence of $SnCl_2$ in good yields with high diastereoselectivities (in many of the cases, only a single diastereoisomer was obtained). Enantioselectivities up to >99% ee could be achieved after removal of the chiral auxiliary.

Inspired by Cook's indium-mediated diastereoselective allylation of chiral hydrazones,[15] initially we started the selective synthesis of chiral *gem*-difluorohomoallylic amine by coupling of *gem*-difluoroallylic indium with chiral hydrazone **1a** in which the valinol-derived oxazolidinone was employed as a chiral auxiliary. To our surprise, the reaction between **1a** and the 3-bromo-3,3-difluoropropene **2** in the presence of indium powder did not afford any product, which is in strong contrast to Cook's nonfluorinated results[15] (Scheme 1). Investigation of different solvent systems

Scheme 1. Metal-Mediated Non- and Difluorianted Allylation of Chiral Valinol Hydrazone **1a**



(DMSO, THF, or THF/H_2O), metals (In, Al/Sn), or elevating the reaction temperature did not give the desired product either.

We surmised that there might be two reasons for this negative result. First, the strong electron-withdrawing effect of fluorine dramatically reduces the nucleophilicity of *gem*-difluoroallylic metal species toward electrophiles. Second, compared to imines, the oxazolidinone-substituted hydrazones are weak electrophiles. Thus, we assumed that using a Lewis acid to activate the chiral hydrazones or a bifunctional catalyst[16] to activate both a nucleophile and an electrophile would promote this coupling reaction. On the basis of these considerations, we then examined the indium-mediated *gem*-difluoroallylation of **1a** in DMF in the presence of $In(OTf)_3$ or $InCl_3$ (Table 1, entries 1 and 2). However, no desired product was formed. Switching solvent to THF did not afford **3a** (Table 1, entry 3). Since the *gem*-difluoroallylic zinc generated in situ is more reactive than its corresponding indium species, the zinc-mediated addition of **2** to **1a** in the presence of different Lewis acids was screened. We discovered that when the reaction was performed with zinc powder in THF at room temperature in the presence of TMSCl trace **3a** was provided (Table 1, entry 5). Encouraged by this result, other Lewis acids $BiCl_3$, $CeCl_3$, and $SnCl_2$ were tested, where $SnCl_2$ was supposed to be a bifunctional catalyst for the addition of allylic zinc to imines, Sn (Lewis acid) toward imines, and Cl (Lewis base) toward Zn of allylic zinc halide[17] (Table 1, entries 6−8, Figure 1). To our delight, when 2.0 equiv of $SnCl_2$ was investigated, 41% yield of desired product **3a** was afforded. More gratifyingly, ^{19}F NMR of the crude product showed that only

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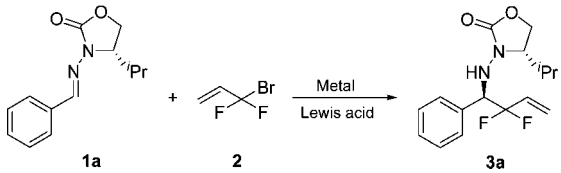
Table 1. Metal-Mediated Addition of 3-Bromo-3,3-difluoropropene **2** to Chiral Hydrazone **1a** in the Presence of Lewis Acid



1a **2** **3a**

entry	metal	solvent	Lewis acid	yield [%][a]
1	In	DMF	$In(OTf)_3$	NR[b]
2	In	DMF	$InCl_3$	NR[b]
3	In	THF	$In(OTf)_3$	NR[b]
4	In	THF	$SnCl_2$	NR[b]
5	Zn	THF	TMSCl	trace[c]
6	Zn	THF	$BiCl_3$	trace[c]
7	Zn	THF	$CeCl_3$	trace[c]
8	Zn	THF	$SnCl_2$ (2.0equiv)	41%
9	Zn	THF	$SnCl_2$ (0.4equiv)	92%

[a] Determined by gas chromatography. [b] No reaction. [c] Determined by ^{19}F NMR.

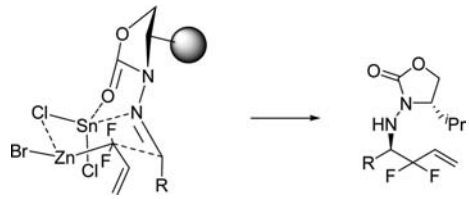


Figure 1. Mechanistic proposal on stereocontrol.

a single diastereoisomer of **3a** was formed. Further optimizing reaction conditions, we found that using 0.4 equiv of $SnCl_2$ and 5 equiv of zinc powder the reaction could be conducted in 92% yield without erosion of the diastereoselectivity (Table 1, entry 9). The amount of $SnCl_2$ has a notable effect on the reaction. Overloading or reducing the amount of $SnCl_2$ would lead to decreased yield, but high stereoselectivities remained (for details, see Supporting Information Table 1, S10). On the contrary, when $SnCl_2$ was used for the indium-mediated addition of **2** to **1a**, no desired product was detected (Table 1, entry 4).

Under the optimized condition, the scope of *gem*-difluorohomoallylation of chiral hydrazones **1** with *gem*-difluoroallylic zinc in the presence of $SnCl_2$ was investigated (Table 2), and the hydrazones included those bearing electron-withdrawing and electron-donating substituents on the aryl ring and aliphatic and functional hydrazones. High diastereoselectivities (de 12/1 to single, determined by ^{19}F NMR) and yields ranging from 42% to 86% were observed for all the hydrazones tested. For all the aryl substituted hydrazones, the yields depend on the electronic

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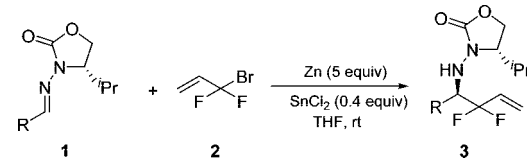
Table 2. Zinc-Mediated Addition of 3-Bromo-3,3-difluoropropene **2** to Chiral Hydrazones **1** in the Presence of $SnCl_2$[a]



1 **2** **3**

entry	substrate	R	yield[b] [%] (conversion)[c] [%]	de[e]
1	**1a**	Ph	76 (84)[d]	single[f]
2	**1b**	*p*-Me-C_6H_4	71 (90)[d]	single[f]
3	**1c**	*p*-MeO-C_6H_4	61 (83)[d]	47/1
4	**1d**	*o*-MeO-C_6H_4	42 (68)[d]	57/1
5	**1e**	*p*-F-C_6H_4	70 (82)[d]	26/1
6	**1f**	*p*-Cl-C_6H_4	70 (81)[d]	18/1
7	**1g**	*m*-Cl-C_6H_4	72 (83)[d]	single[f]
8	**1h**	*p*-Br-C_6H_4	73 (81)[d]	single[f]
9	**1i**	*p*-CF_3-C_6H_4	79 (89)[d]	single[f]
10	**1j**	2-naphthyl	86 (88)[d]	52/1
11	**1k**	2-furyl	77	15/1
12	**1l**	2-thienyl	72 (87)[d]	45/1
13	**1m**	(*E*)-PhCH=CH	74	15/1
14	**1n**	*c*-hex	73	single[f]
15	**1o**	*i*-Pr	76	single[f]
16	**1p**	*n*-heptyl	67	single[f]
17	**1q**		77	single[f]
18	**1r**	EtO_2C	59[d]	22/1
19	**1s**	$BnOCH_2$	63	12/1

[a] Reaction conditions: **1** (1 equiv), **2** (7 equiv), Zn (5 equiv), $SnCl_2$ (0.25 M in THF, 0.4 equiv), room temperature, 0.1 M in THF. [b] Yield of isolated product. [c] Yield based on the conversion. [d] 300 mg of 4 Å molecular sieves/mmol substrate was added. [e] Determined by ^{19}F NMR before column chromatography. [f] ^{19}F NMR showed only a single diastereoisomer was detected.

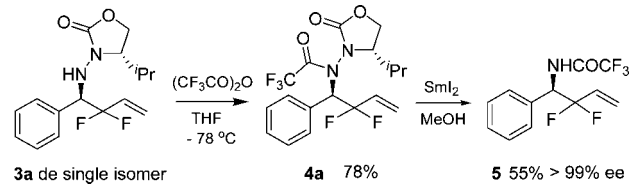
features of the substituents, and 4 Å molecular sieves were required to facilitate the reaction (Table 2, entries 1−9). Generally, moderate to good yields could be achieved for the aromatic hydrazones, despite that the starting materials could not be consumed completely. Electron-rich aryl hydrazones provided moderate yields with high de values (Table 2, entries 3 and 4), while electron-deficient aryl substituents afforded good yields with good to excellent diastereoselectivities (Table 2, entries 5−9). Hydrazones bearing a naphthyl, furyl, or thienyl group also furnished **3j**−**3l** in good yields with high diastereoselectivity (Table 2, entries 10−12), but a slightly decreased selectivity for substrate **1k** (Table 2, entry 11). Notably, all alkyl-substituted hydrazones underwent complete reaction in good yields, and only a single diastereoisomer of desired product was detected by ^{19}F NMR (Table 2, entries 14−16). Functional hydrazones **1q**−**1s** also tolerated the reaction with de 12/1 to single (Table 2, entries 17−19), and only the 1,2-addition product was obtained for cinnamyl-substituted hydrazone **1m**

(Table 2, entry 13). It should be mentioned that the optically pure **3r** resulting from **1r** is a very important building block to access many bioactive β-fluorinated amino acids[18] via the transformation of an alkene moiety (Table 2, entry 18).

The absolute configurations of the hydrazines were assigned by X-ray crystallographic analysis of optically pure **3e** (for details see Supporting Information S27), which indicated that the selectivity of the addition of hydrazones with *gem*-difluoroallylic zinc should be induced from the less hindered *Si* face of the hydrazones to generate the *R* configuration. The greater reactivity of the substrates and high stereoselectivity of the reaction probably could be explained by the coordination of $SnCl_2$ with substrates in a highly restricted chair transition state in which Sn coordinates C=N of hydrazone, and carbonyl group of oxazolidinone to activate the hydrazone and Cl of $SnCl_2$ chelates with Zn to activate the *gem*-difluoroallylic zinc, which allows higher reactivity of both the electrophile and nucleophile and induces the *gem*-difluoroallylic zinc to attack the steric less hindered *Si* face of hydrazone in a high stereoselective manner (Figure 1).

The optical pure primary *gem*-difluorohomoallylic amines could be efficiently obtained by Friestad's procedure for cleavage of the N−N bond of hydrazides.[19] As shown in Scheme 2, compound **3a** was trifluoroacylated with trifluoroacetic anhydride (TFAA), and the resulting *N*-trifluoroacylated hydrazine **4a** was exposed to SmI_2[20] to afford *gem*-difluorohomoallylic amide **5** in 55% yield with up to >99% ee.

Scheme 2. Cleavage of the Hydrazine N−N Bond



3a de single isomer **4a** 78% **5** 55% > 99% ee

In conclusion, we have developed a highly diastereoselective Zn/$SnCl_2$ mediated *gem*-difluoroallylation of chiral hydrazones. The bifunctional catalyst $SnCl_2$ plays an important role in the reaction. The reaction scope can be extended to a series of aromatic, heteroaromatic, aliphatic, and functional hydrazines in good yields with high diastereoselectivities. In many of the cases (both aromatic and aliphatic hydrazones), only a single diastereoisomer could be detected by ^{19}F NMR. To the best of our knowledge, this represents the first example of highly asymmetric *gem*-difluoroallylation of stable, isolable imine equivalents. The potential synthetic utility of this highly stereoselective *gem*-difluoroallylation reaction is in progress.

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Supporting Information Available: Detailed experimental procedures and analytical data for all new compounds and crystallographic data for compound **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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