Zinc(II)-Catalyzed Mannich-type Reactions of Hydrazones with Difluoroenoxysilane and Its Application in the Synthesis of Optically Active 2,2-Difluoro-3-oxo-benzohydrazide†

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With the catalysis of $Zn(OTf)_2$, Mannich-type reactions of various aromatic hydrazones **1** with difluoroenoxysilane **2** proceeded smoothly to produce 2,2-difluoro-3-oxo-benzohydrazides in 27%—78% yields in THF or DCM under mild conditions. An unexpected monofluorination of hydrazone **1m** with difluoroenoxysilane **2** was also disclosed in this paper. The first example of the asymmetric Mannich-type reaction of hydrazone **1a** with difluoroenoxysilane **2** using chiral phosphine-oxazoline ligand has been reported, giving the adduct **3a** in good yields and moderate enantioselectivities under mild conditions.

Keywords $Zn(OTf)_2$, Mannich-type reaction, hydrazone, difluoroenoxysilane, asymmetric Mannich-type reaction, chiral phosphine-oxazoline ligand

Introduction

Asymmetric Mannich-type reactions, which have been confirmed as highly efficient routes for the synthesis of many nitrogen-containing biologically interesting compounds, have been developed rapidly in the past several years.[1] Among them, Lewis acids promoted enantioselective additions to carbon-nitrogen double bonds have been demonstrated as one of the most important methods to access nitrogen-containing optically active compounds.[2] Acylhydrazones, which have been widely used as building blocks in organic synthesis, could be synthesized by the condensation of aldehydes or ketones and acylhydrazines.[3] In addition, these interesting compounds are more stable and storable than most of imines and can be easily purified by simple recrystallization under ambient atomsphere.[4] The successful examples of catalytic asymmetric addition of acylhydrazones, however, are limited.[5] On the other hand, a difluoromethylene unit, which plays a significant role in current organofluorine chemistry,[6] was revealed containing in some biologically interesting compounds, such as in phosphotyrosine (pTyr) mimetics,[7] anticancer agent gemcitabine,[8] and HIV-1 protease inhibitors.[9] In order to introduce difluoromethylene units into organic compounds, difluoroenolsilylanes, which could be readily prepared by Mg(0) promoted selective defluorination of trifluoromethyl ketones in the presence of TMSCl,[10] are considered as excellent building blocks for the synthesis of *gem*-difluorinated compounds.

Catalytic asymmetric vinylogous Mannich-type (AVM) reactions of readily available aldimines with trimethylsiloxyfuran promoted by silver salts have been reported by our group recently.[11] We envisioned that the use of difluoroenoxysilanes in the Mannich-type reaction of hydrazones instead of trimethylsiloxyfuran might be a novel method to achieve chiral *gem*-difluorinated compounds. Although asymmetric fluorination reactions are attractive,[12,13] there has been no report on Lewis acids-catalyzed asymmetric difluoromethylation of hydrazones. Herein, we wish to report a novel zinc(II)-promoted Mannich-type reaction of hydrazones **1** with difluoroenoxysilane **2**. Furthermore, this paper will disclose the investigation on the enantioselective addition of difluoroenoxysilane **2** to hydrazone **1a** and this transformation represents the first example of asymmetric difluoromethylation method involving the use of a catalytic amount of zinc(II) to date.

Results and discussion

First, the reaction of hydrazone **1a** (0.2 mmol), which can be easily prepared from benzaldehyde and benzoylhydrazine, with difluoroenoxysilane **2** (0.3 mmol) in THF (2.0 mL) was carried out in the presence

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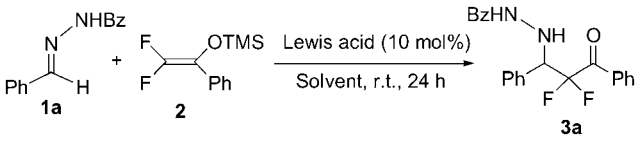
of various Lewis acids (10 mol%) at room temperature (25 ℃) to examine the reaction outcome and the results of these experiments are summarized in Table 1. It was found that neither $Ni(ClO_4)_2$•$6H_2O$ nor copper salts could promote this reaction (Table 1, Entries 1—4). As shown in Table 1, the corresponding Mannich-type adduct **3a** was obtained in 22% yield when catalytic amount of $Sc(OTf)_3$ or $Yb(OTf)_3$ was utilized (Table 1, Entries 5 and 6). Although silver salts were successfully applied into a catalytic asymmetric vinylogous Mannich (AVM) reaction,[11] neither AgOAc nor AgOTf could catalyze the reaction of hydrazone **1a** with difluoroenoxysilane **2** efficiently to give adduct **3a** (Table 1, Entries 7 and 8). Furthermore, the corresponding Mannich-adduct **3a** could not be obtained using $FeCl_3$, $Zr(O\textit{n}\text{-Bu})_4$, $Ti(O\textit{i}\text{-Pr})_4$ and $In(OTf)_3$ as the Lewis acids (Table 1, Entries 13—15 and 17). Only 35% yield of adduct **3a** was achieved when $Bi(OTf)_2Cl$ was employed as a Lewis acid (Table 1, Entry 16). After several examinations, we found that the reaction of hydrazone **1a** with difluoroenoxysilane **2** proceeded smoothly to give **3a** in 72% yield in the presence of 10 mol% of $Zn(OTf)_2$ (Table 1, Entry 9). We next investigated various zinc salts in this reaction. Unfortunately, neither $ZnCl_2$ nor $ZnBr_2$ could catalyze this Mannich-type reaction and the reaction was sluggish to give **3a** in 19% yield in the presence of a catalytic amount of ZnF_2 (Table 1, Entries 10—12). Subsequently, the examination of solvents effects using $Zn(OTf)_2$ (10 mol%) as a catalyst revealed that dichloromethane (CH_2Cl_2) is the solvent of choice, affording adduct **3a** in 79% yield under otherwise identical conditions presumably due to the better solubility of substrate **1a** in CH_2Cl_2 (Table 1, Entries 18—22).

Table 1 Survey of reaction conditions of Lewis acids promoted Mannich-type reaction of hydrazone **1a** and difluoroenoxysilane **2**[a]

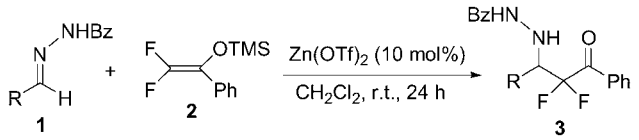


Entry	Lewis acid	Solvent	Yield[b]/%, **3a**
1	$Ni(ClO_4)_2$•$6H_2O$	THF	0
2	$Cu(OTf)_2$	THF	0
3[c]	$(CuOTf)_2$·C_6H_6	THF	0
4	$Cu(CH_3CN)_4ClO_4$	THF	0
5	$Sc(OTf)_3$	THF	20
6	$Yb(OTf)_3$	THF	22
7	AgOAc	THF	0
8	AgOTf	THF	12
9	$Zn(OTf)_2$	THF	72
10	ZnF_2	THF	19
11	$ZnCl_2$	THF	0
12	$ZnBr_2$	THF	0
13	$FeCl_3$	THF	0
14	$Zr(O\textit{n}\text{-Bu})_4$	THF	0
15	$Ti(O\textit{i}\text{-Pr})_4$	THF	0
16	$Bi(OTf)_2Cl$	THF	35
17	$In(OTf)_3$	THF	0
18	$Zn(OTf)_2$	Toluene	Trace
19	$Zn(OTf)_2$	CH_3CN	51
20	$Zn(OTf)_2$	1,4-Dioxane	Trace
21	$Zn(OTf)_2$	Et_2O	39
22	$Zn(OTf)_2$	CH_2Cl_2	79

[a] Reaction conditions: the reaction was carried out with 0.20 mmol of **1a**, 0.30 mmol of **2** and 10 mol% of Lewis acids in solvent (2.0 mL) at room temperature. [b] Isolated yield. [c] 5 mol% of $(CuOTf)_2$•C_6H_6 was used as the catalyst.

With these optimized reaction conditions in hand, we next turned our attention to the reaction scope using a variety of hydrazones **1** with difluoroenoxysilane **2** under the standard conditions and the results are summarized in Table 2 along with the results obtained in THF. As for aromatic substrates **1b**—**1g**, the reactions proceeded smoothly to produce Mannich-type adducts **3b**—**3g** in moderate to good yields (up to 78% yield) in THF or CH_2Cl_2 (Table 2, Entries 1—6). In the case of 2-chlorobenzenealdehyde **1f**, the corresponding product **3f** was achieved in 45% yield (35% yield in THF), presumably due to the steric effect (Table 2, Entry 5). Using hydrazone **1h** bearing a phenolic hydroxy group as the substrate, no reaction occurred (Table 2, Entry 7). It should be noted that in the reaction of hydrazone **1i**

Table 2 Survey of $Zn(OTf)_2$ promoted Mannich-type reactions of hydrazones **1** with difluoroenoxysilane **2**[a]



Entry	Hydrazone **1** (R)	Yield[b]/%, **3**
1	4-ClC_6H_4 **1b**	**3b**, 63/(75[c])
2	4-BrC_6H_4 **1c**	**3c**, 71/(78[c])
3	4-$CH_3C_6H_4$ **1d**	**3d**, 76/(73[c])
4	4-$OCH_3C_6H_4$ **1e**	**3e**, 27/(61[c])
5	2-ClC_6H_4 **1f**	**3f**, 45/(35[c])
6	3-ClC_6H_4 **1g**	**3g**, 78/(67[c])
7	2-OHC_6H_4 **1h**	**3h**, 0/(0[c])
8	1-Naphthyl **1i**	**3i**, 67/(51[c])
9	2-Furan **1j**	**3j**, 57/(63)[c]
10	$C_6H_5(CH_2)_2$ **1k**	**3k**, 0/(0[c])
11	$CH_3(CH_2)_2$ **1l**	**3l**, 0/(0[c])

[a] Experimental conditions: the reaction was carried out with 0.20 mmol of **1**, 0.30 mmol of **2** and 10 mol% of $Zn(OTf)_2$ in CH_2Cl_2 (2.0 mL) at room temperature. [b] Isolated yield. [c] The reaction was carried out in THF (2.0 mL) instead of CH_2Cl_2.

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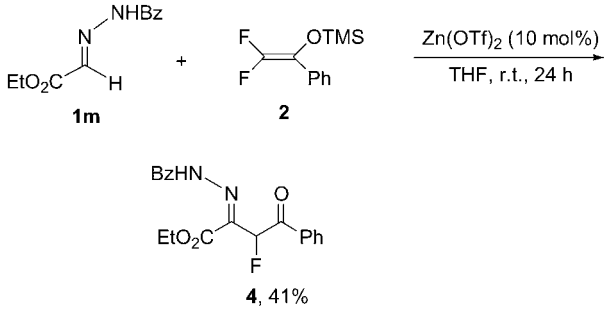
having a 1-naphthyl group and hydrazone **1j** bearing a furan ring with difluoroenoxysilane **2**, the corresponding adducts **3i** and **3j** could also be formed in up to 67% yield (Table 2, Entries 8 and 9). Aliphalic hydrazones, such as **1k** [R＝$C_6H_5(CH_2)_2$] and **1l** [R＝$CH_3(CH_2)_3$], proved to be inefficient in this $Zn(OTf)_2$ promoted Mannich-type reaction (Table 2, Entries 10 and 11). In some cases, the corresponding adducts **3** were achieved in higher yields when THF was utilized as the solvent instead of CH_2Cl_2 (Table 2, Entries 1, 2, 4 and 9), presumably due to the different solubility of different hydrazones **1** in CH_2Cl_2 and THF.

Interestingly, an unexpected monofluoro-adduct **4** was obtained in 41% yield instead of the corresponding Mannich-type adduct in the reaction of hydrazone **1m** with difluoroenoxysilane **2** under the optimized reaction conditions (Scheme 1). We also investigated this unexpected reaction in the presence of various Lewis acids (10 mol%) and the results of these experiments are summarized in Table 3. Conducting the reaction of hydrazone **1m** with difluoroenoxysilane **2** in 2.0 mL of THF in the presence of 10 mol% of $Cu(OTf)_2$, AgOTf or ZnF_2 did not improve the yields of **4** (up to 33%) (Table 3, Entries 2, 5 and 6). Other Lewis acids, for instance $Ni(ClO_4)_2$•$6H_2O$, $Sc(OTf)_3$, $Yb(OTf)_3$, $FeCl_3$ and $Bi(OTf)_2Cl$, did not promote this reaction under identical conditions (Table 3, Entries 1, 3, 4, 7 and 8). Subsequently, the solvent effects have also been examined by using $Zn(OTf)_2$ (10 mol%) as the catalyst (Table 3, Entries 9—12). However, the unexpected adduct **4** was still obtained in low yields (20% in CH_2Cl_2, trace in Et_2O, and no reaction proceeded in CH_3CN and 1,4-dioxane). A plausible mechanism for the formation of unexpected monofluorination is the elimination of a difluorination intermediate. The monofluorination may occur to the difluorination intermediate only when using hydrazone bearing a strong electron-withdrawing group such as an alkoxycarbonyl group (—CO_2R).

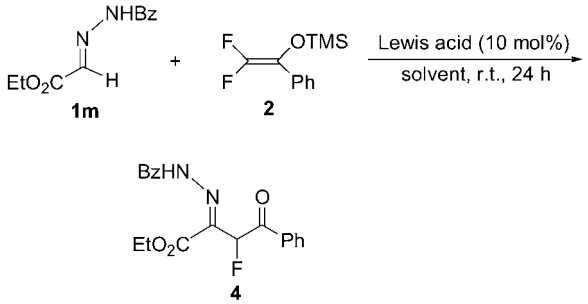
Scheme 1 An unexpected monofluorination of hydrazone **1m** with difluoroenoxysilane **2**



With these optimized reaction conditions in hand, we then attempted to examine $Zn(OTf)_2$-catalyzed asymmetric Mannich-type reaction of aromatic hydrazone **1a** with difluoroenoxysilane **2** in the presence of various chiral ligands **L1**—**L20** (Figure 1).

Initially, we utilized Lewis acid $Zn(OTf)_2$ (10 mol%) combined with **L1** (11 mol%) in THF (2.0 mL) to catalyze the Mannich-type reaction to examine the catalytic ability of this system, and it was found that the corresponding adduct **3a** was obtained in 62% yield and 2% *ee* at ambient temperature (Table 4, Entry 1). As an enantioselective catalytic system, we then utilized the combination of $Zn(OTf)_2$ (10 mol%) with chiral imine ligands **L2** or **L3** (11 mol%), which was effective chiral catalyst for the previous Friedel-Crafts reaction,[14] in the reaction of hydrazone **1a** with difluoroenoxysilane **2** in 2.0 mL of THF, affording **3a** in up to 45% yield with no *ee* value (Table 4, Entries 2 and 3). Chiral oxazoline ligands **L4**—**L6** were also employed in this reaction, but did not give good result either (Table 4, Entries 4—6). Axially chiral ligand **L7**, derived from (*R*)-BINAM could slightly improve the reaction outcome, giving **3a** in 78% yield and 5% *ee* under the standard conditions (Table 4, Entry 7). Unfortunately, chiral phosphine-Schiff base ligand **L8**, which has been successfully applied in a copper(I) catalyzed Henry reaction,[15] and chiral phosphine-Schiff base ligands **L9** and **L10**, which were effective for the previously reported silver catalyzed asymmetric vinylogous Mannich (AVM) reaction[11b]

Table 3 Screening of the reaction conditions in the Lewis acids promoted unexpected monofluorination of hydrazone **1m** with difluoroenoxysilane **2**[a]



Entry	Lewis acid	Solvent	Yield[b]/%, **4**
1	$Ni(ClO_4)_2$•$6H_2O$	THF	0
2	$Cu(OTf)_2$	THF	29
3	$Sc(OTf)_3$	THF	0
4	$Yb(OTf)_3$	THF	0
5	AgOTf	THF	12
6	ZnF_2	THF	33
7	$FeCl_3$	THF	0
8	$Bi(OTf)_2Cl$	THF	0
9	$Zn(OTf)_2$	CH_3CN	0
10	$Zn(OTf)_2$	1,4-Dioxane	0
11	$Zn(OTf)_2$	Et_2O	Trace
12	$Zn(OTf)_2$	CH_2Cl_2	20

[a] Experimental conditions: The reaction was carried out with 0.20 mmol of **1m**, 0.30 mmol of **2** and 10 mol% of Lewis acids in solvent (2.0 mL) at room temperature. [b] Isolated yield.

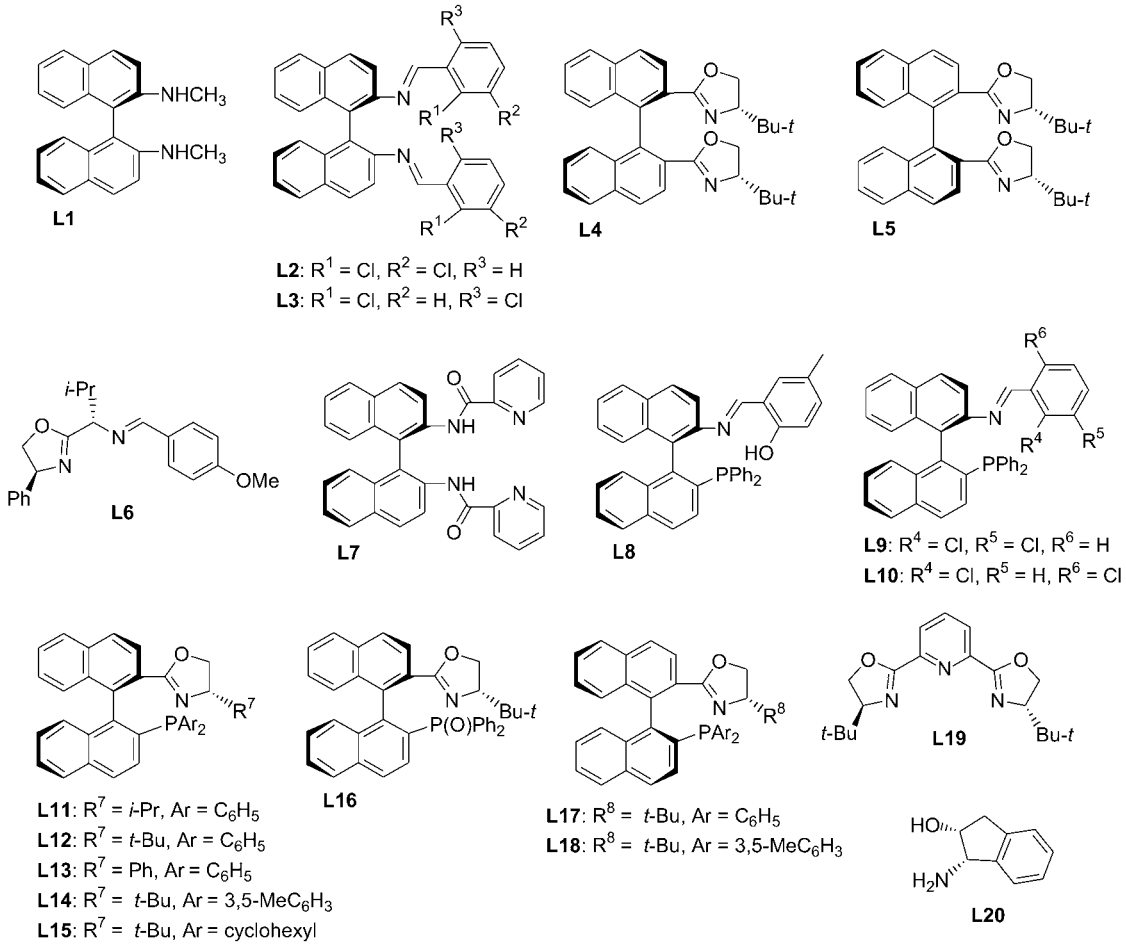


Figure 1 Chiral ligands **L1**—**L20**.

combined with $Zn(OTf)_2$ afforded product **3a** in good yields but with almost no *ee* (Table 4, Entries 8—10).

Occasionally, it was found that when phosphine-oxazoline ligand **L11** [(*R*,*S*)-P-Oxa-*I*-Pr] was employed in this $Zn(OTf)_2$ catalyzed Mannich-type reaction, the corresponding adduct **3a** was obtained in 61% yield along with 15% *ee* (Table 4, Entry 11). Since phosphine-oxazoline ligand **L11** could improve the enantioselectivity of adduct **3a**, we then turned our attention to examine various phosphine-oxazoline ligands **L12**—**L18** in this reaction and the results using these chiral ligands are outlined in Table 4, Entries 12—18. It was found that the desired Mannich-type addition proceeded smoothly to give the desired product **3a** in 69% yield and 39% *ee* when **L12** [(*R*,*S*)-P-Oxa-*t*-Bu] was employed as a ligand in this reaction (Table 4, Entry 12). Using **L13** [(*R*,*S*)-P-Oxa-Ph] as a ligand combined with $Zn(OTf)_2$ afforded **3a** in 71% yield and 15% *ee* (Table 4, Entry 13). Moreover, when a di(3,5-dimethylphenyl)-phosphine group was introduced into the phosphine-oxazoline ligand instead of diphenylphosphine group in **L12**, both the yield and *ee* value of Mannich-type adduct **3a** were improved (77% yield and 40% *ee*) (Table 4, Entry 14). However, the phosphine-oxazoline ligand **L15**, bearing a dicyclohexylphosphine group instead of diphenylphosphine group in **L12**, combined with $Zn(OTf)_2$ gave **3a** in 78% yield with 17% *ee* (Table 4, Entry 15). As shown in Entry 16 of Table 4, **L16** bearing a phosphing oxide group showed similar reactivity as that of **L12** but leading to **3a** in low enantioselectivity. Encouraged by the results of **L12** and **L14**, we then synthesized chiral ligands **L17** [(*S*,*S*)-P-Oxa-*t*-Bu] and **L18** [(*S*,*S*)-DMP-P-Oxa-*t*-Bu], which are the diastereomeric isomers of **L12** and **L14** and applied them in the reaction of hydrazone **1a** with difluoroenoxysilane **2** as well. However, no improvement was observed (Table 4, Entries 17 and 18). In addition, the combination of $Zn(OTf)_2$ and 1,3-bis(oxazolin-2-yl)pyridine **L19** (pybox type ligand) or (1*S*,2*R*)-(−)-1-amino-2-indanol **L20** gave **3a** in low enantiomeric excesses either (up to 13% *ee*) though the yields of adduct **3a** were 77% and 79% (Table 4, Entries 19 and 20).

Previous researches have disclosed that additives often played an important role in the enhancement of the reactivity and enantioselectivity.[16] We next performed the optimization studies on the effects of different additives with the best ligand **L14** being identified. When the reaction was carried out with 1.5 equiv. of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), the desired product **3a** was obtained in 77% yield and 47% *ee* (Table 4, Entry 21). Adding CF_3CH_2OH into this Mannich-type reaction system afforded **3a** in similar yield

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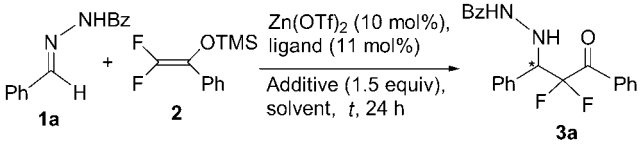
Table 4 Screening of chiral ligands in the $Zn(OTf)_2$-catalyzed asymmetric Mannich-type reaction of aromatic hydrazone **1a** with difluoroenoxysilane **2**[a]



Entry	Ligand	Solvent	Additive	t/℃	Yield[b]/%, **3a**	*ee*[c]/%, **3a**
1	**L1**	THF	—	r.t.	62	2
2	**L2**	THF	—	r.t.	45	0
3	**L3**	THF	—	r.t.	43	0
4	**L4**	THF	—	r.t.	61	0
5	**L5**	THF	—	r.t.	69	0
6	**L6**	THF	—	r.t.	70	0
7	**L7**	THF	—	r.t.	78	5
8	**L8**	THF	—	r.t.	33	0
9	**L9**	THF	—	r.t.	76	0
10	**L10**	THF	—	r.t.	71	3
11	**L11**	THF	—	r.t.	61	15
12	**L12**	THF	—	r.t.	69	39
13	**L13**	THF	—	r.t.	71	15
14	**L14**	THF	—	r.t.	77	40
15	**L15**	THF	—	r.t.	78	17
16	**L16**	THF	—	r.t.	70	15
17	**L17**	THF	—	r.t.	59	2
18	**L18**	THF	—	r.t.	50	0
19	**L19**	THF	—	r.t.	79	3
20	**L20**	THF	—	r.t.	77	13
21	**L14**	THF	HFIP	r.t.	77	47
22	**L14**	THF	CF_3CH_2OH	r.t.	75	23
23	**L12**	THF	HFIP	r.t.	73	20
24	**L12**	THF	CF_3CH_2OH	r.t.	75	43
25	**L14**	CH_2Cl_2	HFIP	r.t.	86	38
26	**L14**	THF	HFIP	0	39	38
27	**L14**	THF	HFIP	−5	20	51
28	**L14**	THF	HFIP	−10	0	—
29[d]	**L14**	THF	HFIP	−5	51	48

[a] Experimental conditions: **1a** (0.20 mmol), **2** (0.30 mmol), additive (0.30 mmol), $Zn(OTf)_2$ (10 mol%), ligand (11 mol%), solvent (2.0 mL), and the reaction was carried out at r.t. for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 20 mol% $Zn(OTf)_2$ and 22 mol% **L14** were used in this reaction.

but less effective in *ee* (Table 4, Entry 22). Interestingly, using **L12** instead of **L14** combined with $Zn(OTf)_2$ produced the corresponding adduct **3a** in only 20% *ee* when HFIP was used as the additive (Table 4, Entry 23). However, the combination of **L12** and $Zn(OTf)_2$ could slightly improve the enantioselectivity of Mannich-type adduct **3a** when CF_3CH_2OH was used as the additive (Table 4, Entry 24). Under the optimized reaction conditions described above, that is, use of 10 mol% of $Zn(OTf)_2$, 11 mol% of **L14**, 1.5 equiv. of HFIP as the additive, we next examine the solvent and temperature effects in this Mannich-type reaction. When the reaction was carried out in CH_2Cl_2, **3a** was attained in 86% yield but lower *ee* (Table 4, Entry 25). The examination of temperature effects revealed that the reaction proceeded inefficiently at 0 ℃, affording adduct **3a** in 39% yield and 38% *ee* (Table 4, Entry 26). Reducing the reaction temperature to −10 ℃ did not give **3a** (Table 4, Entry 28). When the reaction was carried out at −5 ℃, the enantiomeric excess of **3a** could be improved to 51% but only in 20% yield (Table 4, Entry 27). The combination of 20 mol% of $Zn(OTf)_2$ and 22 mol% of **L14** led to **3a** in 51% yield and 48% *ee* at −5 ℃ (Table 4, Entry 29). Product **3a** could be obtained in 51% *ee* along with 20% yield at −5 ℃ and 77% yield along with 40% *ee* at room temperature using **L14** as a chiral ligand combined with $Zn(OTf)_2$.

Conclusion

We have presented a novel catalytic reaction system applicable to the reactions of hydrazones and difluoroenoxysilane using Lewis acid $Zn(OTf)_2$ as a catalyst. Using this new synthetic protocol, we can produce Mannich adducts **3** in moderate to good yields under mild conditions. An unexpected monofluorination adduct **4** could be formed when hydrazone **1m** was utilized as the substrate in this reaction. On the basis of the optimized reaction conditions, we found that the optically active adduct **3a** could be achieved in moderate enantioselectivity and good yield when 10 mol% of $Zn(OTf)_2$ was used as a promoter and **L14** was used as a ligand in the reaction of hyrazone **1a** with difluoroenoxysilane **2**. Current efforts are in progress to improve the enantioselectivity of this novel approach to the chiral 2,2-difluoro-3-oxo-benzohydrazides in our laboratory.

Experimental section

General procedure for the preparation of difluoroenoxysilane **2**.[10] A mixture of chlorotrimethylsilane (TMSCl) (6.0 mmol), Mg (6.0 mmol) and THF (10 mL) was cooled down to 0 ℃ under argon atmosphere. Then trifluoroacetophenone (1.5 mmol) was added dropwise and the resulting mixture was stirred for additional 1.0 h. After the solvent was removed under vacuum, hexane (15 mL) was added to the residue. The resulting salt was filtered and the filtrate was then concentrated to give the crude product of difluoroenoxysilane **2** under reduced pressure. This crude product **2** was used for the Mukaiyama-aldol type reaction without further purification.

Typical procedure for the Zinc(II)-catalyzed Mannich-type reaction of hydrazone 1a with difluoroenoxysilane 2

The solution of hydrazone **1a** (0.20 mmol), $Zn(OTf)_2$

(0.02 mmol) and THF (2.0 mL) was allowed to stir for 5.0 min at ambient temperature. A freshly prepared difluoroenoxysilane **2** (0.30 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir for 24 h at ambient temperature. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (5.0 mL). After stirring for 15 min at room temperature, the mixture was extracted by DCM and washed with brine. The organic layer was dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2) to give the corresponding product **3a**.

***N*-(2,2-Difluoro-3-oxo-1,3-diphenylpropyl)benzohydrazide (3a)** A pale yellow oil (79%, 61 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.01 (t, J=12.6 Hz, 1H, NH), 5.46 (br, 1H, CH), 7.34—7.60 (m, 13H, ArH), 7.69 (s, 1H, BzNH), 7.95 (d, J=7.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 66.5 (dd, J_{C-F}=23.8, 21.1 Hz), 117.3 (t, J_{C-F}=259.1 Hz), 126.8, 128.5, 128.6, 129.1, 129.5, 129.9 (t, J_{C-F}=3.6 Hz), 131.9, 132.1, 132.4 (t, J_{C-F}=1.9 Hz), 132.7 (d, J_{C-F}=2.3 Hz), 134.2, 167.5, 189.6 (t, J_{C-F}=28.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$, TMS) δ: −111.5 (dd, J=276, 12 Hz, 1F), −114.0 (dd, J=276, 14 Hz, 1F); IR (acetone) ν: 3293, 3064, 2374, 1775, 1702, 1697, 1676, 1655, 1598, 1579, 1528, 1450, 1310, 1283, 1211, 1184, 1066, 907 cm^{-1}; MS (ESI) *m/z* (%): 381 (100) [M^++1]; HRMS (MALDI) calcd for $C_{22}H_{18}F_2N_2O_2Na^{+1}$ (M^++1) 403.1234, found 403.1229. Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*-PrOH=70/30, 0.6 mL/min, 230 nm, t_{minor}=34.00 min, t_{majorr}=47.63 min; $[\alpha]_D^{20}$ −12.7 (*c* 0.55, CH_2Cl_2), 51% *ee*).

***N*-(1-(4-Chlorophenyl)-2,2-difluoro-3-oxo-3-phenylpropyl)benzohydrazide (3b)** A pale yellow oil (75%, 62 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.02 (t, J=12.6 Hz, 1H,NH), 5.46 (br, 1H, CH), 7.30—7.51 (m, 9H, ArH), 7.55—7.62 (m, 3H, ArH), 7.76 (d, J=4.8 Hz, 1H, BzNH), 7.98 (d, J=7.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 65.9 (dd, J_{C-F}=23.3, 20.9 Hz), 117.0 (t, J_{C-F}=261.1 Hz), 126.8, 128.6, 128.7, 128.8, 130.0 (t, J_{C-F}=3.5 Hz), 130.9, 131.4, 132.0, 132.1, 132.3, 134.5, 135.2, 167.6, 189.3 (t, J_{C-F}=29.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −111.3 (dd, J=278, 12 Hz, 1F), −114.3 (dd, J=278, 16 Hz, 1F); IR (acetone) ν: 3293, 3064, 2925, 2854, 1777, 1703, 1649, 1598, 1579, 1527, 1492, 1467, 1449, 1310, 1282, 1211, 1184, 1091, 1016, 925, 908 cm^{-1}; MS (ESI) *m/z* (%): 415 (100) [M^++1]; HRMS (MALDI) calcd for $C_{22}H_{17}ClF_2N_2O_2Na^{+1}$ (M^++1) 437.0844, found 437.0839.

***N*-(1-(4-Bromophenyl)-2,2-difluoro-3-oxo-3-phenylpropyl)benzohydrazide (3c)** A yellow oil (78%, 72 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 4.99 (t, J=12.3 Hz, 1H, NH), 5.45 (d, J=3.3 Hz, 1H, CH), 7.36—7.51 (m, 9H, ArH), 7.55—7.63 (m, 3H, ArH), 7.73 (d, J=6.0 Hz, 1H, BzNH), 7.98 (d, J=7.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 65.9 (dd, J_{C-F}=23.6, 20.3 Hz), 116.9 (t, J_{C-F}=260.0 Hz), 123.4, 126.8, 128.6, 128.7, 130.0 (t, J_{C-F}=3.4 Hz), 131.2, 131.7, 131.9, 132.1, 132.3, 134.5, 167.6, 189.2 (t, J_{C-F}=28.7 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −111.1 (dd, J=279, 1F, 12 Hz), −114.5 (dd, J=279, 1F, 14 Hz); IR (acetone) ν: 3292, 3064, 2924, 2853,1778, 1704, 1645, 1597, 1579, 1528, 1488, 1467, 1449, 1309, 1281, 1212, 1182, 1072, 1012, 925, 908 cm^{-1}; MS (ESI) *m/z* (%): 460 (97) [M^++1]; HRMS (MALDI) calcd for $C_{22}H_{17}BrF_2N_2O_2^{+1}$ (M^++1) 459.0518, found 459.0514.

***N*-(2,2-Difluoro-3-oxo-3-phenyl-1-*p*-tolylpropyl)benzohydrazide (3d)** A pale yellow oil (76%, 60 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 2.33 (s, 3H, CH_3), 4.96 (t, J=13.5 Hz, 1H, NH), 5.44 (d, J=5.1 Hz, 1H, CH), 7.15 (d, J=7.8 Hz, 2H, ArH), 7.35—7.51 (m, 7H, ArH), 7.57 (d, J=6.9 Hz, 3H, ArH), 7.63 (d, J=4.8 Hz, 1H, BzNH), 7.97 (d, J=7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 21.2, 66.5 (dd, J_{C-F}=21.3, 2.4 Hz), 118.2 (t, J_{C-F}=302.0 Hz), 126.8, 128.6, 129.3 (d, J_{C-F}=3.2 Hz), 129.7, 130.0 (t, J_{C-F}=3.5 Hz), 132.0, 132.2, 132.6, 134.3, 139.1, 167.3, 189.7 (t, J_{C-F}=29.5 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −111.7 (dd, J=277, 13 Hz, 1F), −114.0 (dd, J=277, 14 Hz, 1F); IR (acetone) ν: 3294, 3061, 3030, 2923, 2860, 1779, 1706, 1648, 1598, 1579, 1515, 1449, 1309, 1283, 1183, 1126, 1068, 1026, 925 cm^{-1}; MS (ESI) *m/z* (%): 395 (100) [M^++1]; HRMS (MALDI) calcd for $C_{23}H_{21}F_2N_2O_2^{+1}$ (M^++1) 395.1574, found 395.1565.

***N*-(2,2-Difluoro-1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)benzohydrazide (3e)** A pale yellow oil (61%, 53 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 3.78 (s, 3H, OCH_3), 4.99 (dt, J=14.4, 1.8 Hz, 1H, NH), 5.41 (d, J=4.5 Hz, 1H, CH), 6.85 (d, J=8.7 Hz, 2H, ArH), 7.35—7.50 (m, 7H, ArH), 7.55—7.60 (m, 3H, ArH), 7.69 (d, J=6.0 Hz, 1H, BzNH), 7.96 (d, J=7.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 55.2, 66.1 (dd, J_{C-F}=22.9, 21.0 Hz), 113.9, 119.2 (t, J_{C-F}=130.2 Hz), 124.6 (d, J_{C-F}=2.7 Hz), 126.8, 128.6, 130.0 (t, J_{C-F}=3.4 Hz), 130.7, 131.9, 132.2, 132.5, 134.2, 160.1, 167.3, 189.7 (t, J_{C-F}=28.3 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −112.0 (dd, J=292, 14 Hz, 1F,), −113.9 (dd, J=292, 13 Hz, 1F); IR (acetone) ν: 3298, 3065, 3003, 2958, 2934, 2838, 1775, 1709, 1642, 1612, 1580, 1514, 1449, 1363, 1306, 1253, 1179, 1125, 1072, 1027, 925 cm^{-1}; MS (ESI) *m/z* (%): 411 (100) [M^++1]; HRMS (MALDI) calcd for $C_{23}H_{21}F_2N_2O_3^{+1}$ (M^++1) 411.1520, found 411.1515.

***N*-(1-(2-Chlorophenyl)-2,2-difluoro-3-oxo-3-phenylpropyl)benzohydrazide (3f)** A pale yellow oil (45%, 37 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.52 (br, 1H, NH), 5.66 (dd, J=18.6, 7.5 Hz, 1H, CH), 7.29—7.48 (m, 8H, ArH), 7.50—7.63 (m, 4H, ArH), 7.77 (d, J=7.5 Hz, 1H, BzNH), 8.07 (d, J=7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 62.1 (dd, J_{C-F}=24.9, 20.6 Hz), 117.1 (t, J_{C-F}=255 Hz), 126.8, 127.0, 128.5, 128.7, 129.7, 130.0 (t, J_{C-F}=3.4 Hz), 130.2, 131.0, 131.9, 132.0, 132.2, 134.4, 135.5, 167.4,

189.2 (t, J_{C-F}=27.9 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −109.3 (dd, J=276, 7.6 Hz, 1F), −116.6 (dd, J=276, 18 Hz, 1F); IR (acetone) v: 3291, 3065, 1968, 1901, 1818, 1780, 1703, 1648, 1598, 1579, 1528, 1475, 1449, 1362, 1308, 1282, 1181, 1128, 1070, 1028, 1001, 926, 901 cm^{-1}; MS (ESI) *m/z* (%): 415 (100) [M^++1]; HRMS (MALDI) calcd for $C_{22}H_{17}ClF_2N_2O_2^{+1}$ (M^++1) 415.1032, found 415.1019.

***N*-(1-(3-Chlorophenyl)-2,2-difluoro-3-oxo-3-phenylpropyl)benzohydrazide (3g)** A pale yellow oil (78%, 65 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.00 (dt, J=11.4, 1.8 Hz, 1H, NH), 5.45 (d, J=3.9 Hz, 1H, CH), 7.26—7.31 (m, 3H, ArH), 7.34—7.41 (m, 3H, ArH), 7.43—7.46 (m, 2H, ArNH), 7.48—7.62 (m, 4H, ArH), 7.77 (d, J=5.7 Hz, 1H, BzNH), 7.98 (d, J=7.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 66.0 (dd, J_{C-F}=23.5, 20.6 Hz), 116.9 (t, J_{C-F}=255 Hz), 126.8, 127.9, 128.6, 128.7, 129.3, 129.6, 129.8, 130.0 (t, J_{C-F}=3.3 Hz), 131.9, 132.0, 132.3 (t, J_{C-F}=2.6 Hz), 134.4, 134.5, 134.9 (d, J_{C-F}=2.6 Hz), 167.6, 189.2 (t, J_{C-F}=28.3 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −110.8 (dd, J=280, 11 Hz, 1F), −114.5 (dd, J=280, 16 Hz, 1F); IR (acetone) v: 3303, 3066, 3003, 2922, 1968, 1908, 1818, 1779, 1715, 1638, 1598, 1579, 1528, 1449, 1361, 1309, 1282, 1220, 1186, 1055, 1027, 1001, 933, 910 cm^{-1}; MS (ESI) *m/z* (%): 415 (100) [M^++1]; HRMS (MALDI) calcd for $C_{22}H_{17}ClF_2N_2O_2^{+1}$ (M^++1) 415.1026, found 415.1019.

***N*-(2,2-Difluoro-1-(naphthalen-1-yl)-3-oxo-3-phenylpropyl)benzohydrazide (3i)** A yellow oil (67%, 58 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.56 (br, 1H, CH), 5.92 (t, J=12.0 Hz, 1H, NH), 7.29—7.36 (m, 4H, ArH), 7.40—7.54 (m, 7H, ArH), 7.82—7.89 (m, 6H, ArNH), 8.15 (br, 1H, BzNH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 60.5 (dd, J_{C-F}=22.9, 21.2 Hz), 117.9 (t, J_{C-F}=258.1 Hz), 124.9, 125.7, 126.7, 126.8, 128.4, 128.5, 128.7, 128.9, 129.8, 129.9 (t, J_{C-F}=3.4 Hz), 131.9, 132.0, 132.2, 132.6, 133.7, 134.2, 167.5, 189.9 (t, J_{C-F}=43.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −109.1 (dd, J=274, 8 Hz, 1F), −113.1 (dd, 1F, J=274, 11 Hz); IR (acetone) v: 3292, 3062, 2925, 1919, 1779, 1704, 1656, 1598, 1579, 1514, 1468, 1449, 1362, 1310, 1277, 1184, 1125, 1069, 1028, 908 cm^{-1}; MS (ESI) *m/z* (%): 431 (100) [M^++1]; HRMS (MALDI) calcd for $C_{26}H_{21}F_2N_2O_2^{+1}$ (M^++1) 431.1570, found 431.1565.

***N*-(2,2-Difluoro-1-(furan-2-yl)-3-oxo-3-phenylpropyl)benzohydrazide (3j)** A yellow oil (63%, 47 mg); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ: 5.15 (dt, J=10.2, 3.0 Hz, 1H, NH), 5.59 (br, 1H, CH), 6.35 (dd, J=3.3, 1.8 Hz, 1H, ArH), 6.50 (d, J=3.3 Hz, 1H, ArH), 7.37—7.52 (m, 6H, ArH), 7.59—7.76 (m, 3H, ArH), 7.77 (d, J=3.6 Hz, 1H, BzNH), 8.03 (d, J=8.1 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ: 60.6 (dd, J_{C-F}=24.2, 22.1 Hz), 110.7, 111.3, 120.1 (t, J_{C-F}=261 Hz), 126.9, 128.7, 130.0 (t, J_{C-F}=3.5 Hz), 132.0, 132.2 (t, J_{C-F}=3.8 Hz), 134.4, 143.4, 146.3 (d, J_{C-F}=3.5 Hz), 167.4, 189.1 (t, J_{C-F}=28.7 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, TMS) δ: −109.6 (dd, 1F, J=282, 10 Hz), −114.5 (dd, J=282, 16 Hz, 1F); IR (acetone) v: 3293, 3063, 2926, 2285, 1969, 1911, 1707, 1648, 1598, 1580, 1534, 1450, 1311, 1279, 1201, 1185, 1128, 1062, 1027, 1001, 917, 809 cm^{-1}; MS (ESI) *m/z* (%): 371 (100) [M^++1]; HRMS (MALDI) calcd for $C_{20}H_{17}F_2N_2O_3^{+1}$ (M^++1) 371.1213, found 371.1202.

***(E)*-Ethyl 2-(2-benzoylhydrazono)-3-fluoro-4-oxo-4-phenylbutanoate (4)** A pale yellow solid, m.p. 99—102 ℃ (33%, 23 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ: 1.34 (t, J=6.8 Hz, 3H, CH_3), 4.38 (q, J=6.8 Hz, 2H, CH_2), 5.13 (br, 1H, NH), 5.60 (d, J_{H-F}=52 Hz, 1H, CH), 7.35—7.40 (m, 3H, ArH), 7.45—7.49 (m, 4H, ArH), 7.55—7.59 (m, 1H, ArH), 7.97 (d, J=7.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ: 14.0, 62.3, 95.5 (d, J_{C-F}=91 Hz), 96.8 (d, J_{C-F}=26 Hz), 124.2, 125.7 (d, J_{C-F}=2.7 Hz), 128.1, 128.2, 128.3, 128.5, 128.8, 129.3, 129.4, 130.4, 130.6, 131.5, 132.8 (d, J_{C-F}=52 Hz), 133.0, 134.3 (d, J_{C-F}=3.8 Hz), 143.2 (d, J_{C-F}=17 Hz), 160.1, 168.8; ^{19}F NMR ($CDCl_3$, 376 MHz, TMS) δ: −177.6 (d, J=52 Hz, 1F); IR (acetone) v: 3448, 3066, 2975, 1741, 1720, 1665, 1578, 1450, 1389, 1365, 1302, 1247, 1192, 1091, 1065, 1013, 905, 855 cm^{-1}; MS (EI) *m/z* (%): 356 [M^+] (0.4), 283 (7.9), 251 (4.3), 232 (2.8), 219 (3.1), 175 (1.5), 130 (1.7), 105 (100), 77 (32.9). 51 (5.4); HRMS (EI) calcd for $C_{19}H_{17}N_2O_4F$ (M+H^+): 356.1172, found 356.1171.

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