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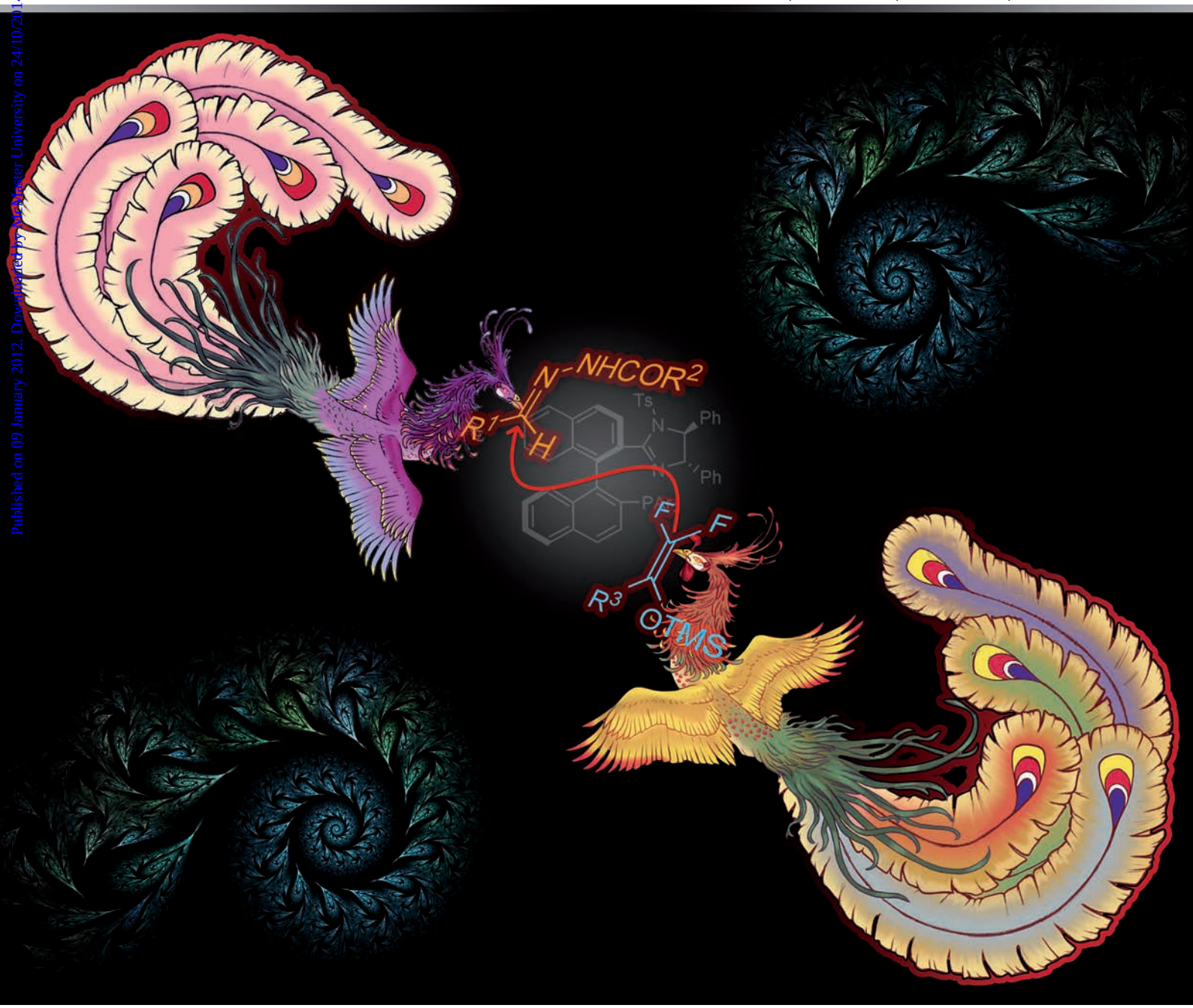

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PAPER

G. Li, M. Shi *et al.*,

Asymmetric catalytic Mannich-type reaction of hydrazones with difluoroenoxysilanes using imidazoline-anchored phosphine ligand–zinc(II) complexes

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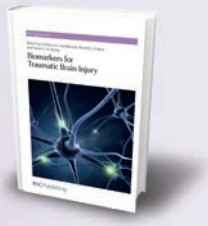

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COMMUNICATION

Asymmetric catalytic Mannich-type reaction of hydrazones with difluoroenoxysilanes using imidazoline-anchored phosphine ligand–zinc(II) complexes†

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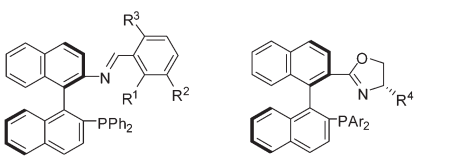
Asymmetric Mannich-type reaction of hydrazones with difluoroenoxysilanes using chiral zinc(II)–imidazoline–phosphine complexes as catalysts have been established, giving the corresponding adducts in good to excellent enantioselectivity and chemical yields under mild conditions.

Organofluorine chemistry has attracted a considerable interest in the past several decades because, the introduction of fluorine atoms onto target molecules can cause significant enhancement in their chemical, physical, and pharmacological properties.[1,2] In fact, the development of more efficient approaches to optically active fluorinated compounds has become one of the most challenging topics in modern organic chemistry.[3,4] Several methodologies and reagents have been established for the asymmetric fluorination, trifluoromethylation, and perfluoroalkylation reactions.[5] However, the progress on assembling chiral difluoromethylene structural scaffolds *via* asymmetric catalytic difluorination has been slow.[6] The enantioselective Reformatsky reaction of bromodifluoroacetate with aldehydes was disclosed by Braun[7] and co-workers in 1995, affording the corresponding α, α-difluoro-β-hydroxy esters in up to 84% ee and moderate yields in the presence of an excess amount of (*1R*,*2S*)-*N*-methylephedrine. The asymmetric Mukaiyama aldol reaction of difluoroketene silyl with various aldehydes afforded the corresponding products in good enantioselectivities (up to 97% ee) and excellent yields by using Masamune's[8a] or Kiyooka's catalysts.[8b] Very recently, Akiyama and his co-workers have established a successful catalytic enantioselective synthesis of β-amino-α,α-difluoro carbonyl compounds *via* the reaction of *N*-Boc-protected imines with difluoroenoxysilanes in the presence of chiral phosphoric acid.[8c] We also reported the zinc-catalyzed asymmetric difluorination reaction of readily available hydrazones with difluoroenoxysilane, providing the corresponding adducts in moderate yields and enantioselectivities.[9] Herein, we would like to disclose the enantioselective Mannich-type reaction of difluoroenoxysilanes with hydrazones by using the catalytic complexes formed from zinc salt and novel chiral imidazoline–phosphine ligands. Our previous study revealed the use of $Zn(OTf)_2$–oxazoline–phosphine ligand complexes (**L5–L8**, Fig. 1) as catalysts for the asymmetric difluorination of hydrazones with difluoroenoxysilane can lead to the formation of corresponding difluorination adducts in low yields and enantioselectivities (up to 51% ee with 23% isolated yield),[9] while their chiral phosphine-anchored Schiff's base counterparts (**L1–L4**, Fig. 1) do nor show any effectiveness. Recently, we switched our strategy to the design and synthesis of *N*-containing heterocycle–phosphine ligands for Mannich-type difluorination reaction. Since the five-membered imidazoline ring can easily coordinate onto metal cations, which is similar to its oxazoline-based situation.[10] We envisioned that they would offer an opportunity to render the asymmetric catalytic Mannich-type reaction of difluoroenoxysilanes with hydrazones. Following an efficient route developed by You and Kelly,[11] we prepared a series of novel chiral imidazoline–phosphine ligands, **L9–L14**, based on a binaphthyl scaffold (Fig. 2). In addition, the structure of **L9** has been unambiguously determined by X-ray diffraction analysis (see ESI†).



L1: R^1 = OH, R^2 = H, R^3 = H
L2: R^1 = OH, R^2 = ^{t}Bu, R^3 = ^{t}Bu
L3: R^1 = Cl, R^2 = Cl, R^3 = H
L4: R^1 = Cl, R^2 = H, R^3 = Cl

L5: R^4 = ^{i}Pr, Ar = C_6H_5
L6: R^4 = ^{t}Bu, Ar = C_6H_5
L7: R^4 = Ph, Ar = C_6H_5
L8: R^4 = ^{t}Bu, Ar = 3,5-MeC_6H_3

Fig. 1 Selected chiral ligands for Mannich-type difluorinations.

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† Electronic supplementary information (ESI) available: Spectroscopic data and chiral HPLC traces of the compounds shown in Tables 1–4, the detailed descriptions of experimental procedures and the crystal structures of **L9** and **5c**. CCDC 785244 and 798183. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07022g

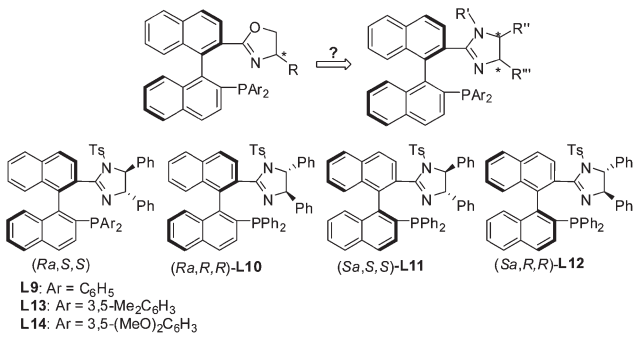
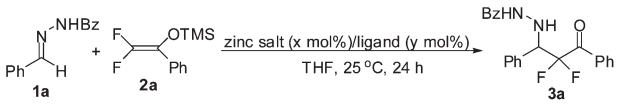


Fig. 2 Novel imidazoline–phosphine ligands **L9–L14**.

Our study was started with the use of hydrazone **1a**.[12,13] The initial reaction of hydrazone **1a** with difluoroenoxysilane **2a**[14] was conducted in 1.0 mL of THF in the presence of Lewis acid, $Zn(OTf)_2$ (10 mol%) together with imidazoline–phosphine ligand (R_a,*S*,*S*)-**L9** (10 mol%) as the catalytic combination. We found that the reaction proceeded smoothly to give the desired product **3a** in 76% yield and 62% ee (Table 1, entry 1), which was greater than the results of using $Zn(OTf)_2$–oxazoline–phosphine ligand as reported previously.[9] The use of $Zn(NTf_2)_2$ together with **L9** showed no improvement in enantioselectivity (Table 1, entry 2). Inspired by the work performed by Mikami's group,[15] the use of $Zn(OTf)_2$ and the chiral imidazoline–phosphine ligand **L9** in a 1 : 2 ratio led to 78% ee with a slightly

Table 1 Screening of ligands in the asymmetric catalytic Mannich-type reaction of hydrazone **1a** with difluoroenoxysilane

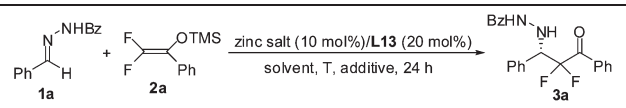


1a + **2a** → **3a**

Entry[a]	Zinc salt (x mol%)	Ligand (y mol%)	Yield[b] (%) **3a**	ee[c] (%) **3a**	Absolute configuration[d]
1	$Zn(OTf)_2$ (10)	(R_a,*S*,*S*)-**L9** (10)	76	62	*S*
2	$Zn(NTf_2)_2$ (10)	(R_a,*S*,*S*)-**L9** (10)	79	61	*S*
3	$Zn(OTf)_2$ (10)	(R_a,*S*,*S*)-**L9** (20)	82	78	*S*
4	$Zn(OTf)_2$ (5)	(R_a,*S*,*S*)-**L9** (10)	59	65	*S*
5	$Zn(OTf)_2$ (10)	(R_a,*R*,*R*)-**L10** (20)	81	13	*S*
6	$Zn(OTf)_2$ (10)	(S_a,*S*,*S*)-**L11** (20)	74	9	*R*
7	$Zn(OTf)_2$ (10)	(S_a,*R*,*R*)-**L12** (20)	71	77	*R*
8	$Zn(OTf)_2$ (10)	(R_a,*S*,*S*)-**L13** (20)	78	87	*S*
9	$Zn(OTf)_2$ (10)	(R_a,*S*,*S*)-**L14** (20)	67	82	*S*

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), zinc salt (x mol%), ligand (y mol%), THF (1.0 mL), and the reaction was carried out at 25 °C for 24 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by X-ray diffraction.

Table 2 Optimization of conditions of the zinc(II)-catalyzed asymmetric Mannich-type reaction



1a + **2a** → **3a**

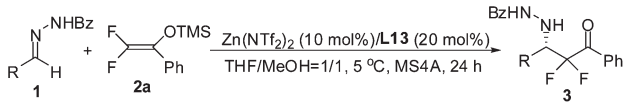
Entry[a]	Zinc salt	Solvent	T (°C)	Additive	Yield[b] (%) **3a**	ee[c] (%) **3a**	Absolute configuration[d]
1	$Zn(OTf)_2$	MTBE/THF = 1/1	25	—	23	82	*S*
2	$Zn(OTf)_2$	MeOH/THF = 1/1	25	—	88	89	*S*
3	$Zn(OTf)_2$	EtOH/THF = 1/1	25	—	92	59	*S*
4	$Zn(OTf)_2$	^{i}PrOH/THF = 1/1	25	—	84	53	*S*
5	$Zn(OTf)_2$	^{t}BuOH/THF = 1/1	25	—	49	90	*S*
6	$Zn(OTf)_2$	CF_3CH_2OH/THF = 1/1	25	—	81	80	*S*
7	$Zn(OTf)_2$	HFIP/THF = 1/1	25	—	60	71	*S*
8	$Zn(OTf)_2$	*t*-amyl-OH/THF = 1/1	25	—	trace	n.d.[e]	—
9	$Zn(OTf)_2$	^{t}BuOH/THF = 1/5	25	—	23	86	*S*
10	$Zn(OTf)_2$	^{t}BuOH/THF = 1/10	25	—	31	83	*S*
11	$Zn(OTf)_2$	MeOH/THF = 1/5	25	—	70	80	*S*
12	$Zn(OTf)_2$	MeOH/THF = 1/10	25	—	71	81	*S*
13	$Zn(OTf)_2$	MeOH/THF = 2/1	25	—	80	87	*S*
14	$Zn(OTf)_2$	MeOH/THF = 1/1	5	—	57	93	*S*
15	$Zn(OTf)_2$	MeOH/THF = 1/1	−5	—	trace	n.d.	—
16	$Zn(NTf_2)_2$	MeOH/THF = 1/1	5	—	71	92	*S*
17	$Zn(NTf_2)_2$	MeOH/THF = 1/1	5	MS4A	79	93	*S*

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), zinc salt (10 mol%), **L13** (20 mol%), solvent (1.0 mL) and MS4A (50 mg), the reaction was carried out for 24 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by X-ray diffraction. [e] n.d. = not determined.

improved yield (Table 1, entry 3). However, 5 mol% of Zn $(OTf)_2$ with 10 mol% of **L9** did not show effectiveness in both the yield and enantioselectivity (Table 1, entry 4). Next, we examined different imidazoline–phosphine ligands, **L10–L14**. We found that ligands (R_a,*R*,*R*)-**L10** and (S_a,*S*,*S*)-**L11** afforded the desired Mannich-type adduct **3a** in up to 81% yield and low enantioselectivities (Table 1, entries 5 and 6). Ligand (S_a,*R*,*R*)-**L12** produced the opposite enantiomer of **3a** in a similar yield and enantioselectivity, which was observed in the reaction of hydrazone **1a** with difluoroenoxysilane **2a** catalyzed by (R_a,*S*,*S*)-**L9**/$Zn(OTf)_2$ (Table 1, entry 7). As compared to ligand (R_a,*S*,*S*)-**L14**, (R_a,*S*,*S*)-**L13**, bearing a di(3,5-dimethylphenyl)phosphine group, led to the corresponding product **3a** in 78% yield and 87% ee (Table 1, entries 8 and 9). With the effective chiral ligand (R_a,*S*,*S*)-**L13** in hand, we further optimized the condition by changing solvents, temperatures, additives, and zinc salts (Table 2). Since the ligand **L13** and hydrazone **1a** have low solubility in MTBE (*tert*-butyl methyl ether) and various alcohols, we combined THF with these solvents in 1 : 1 ratio. Interestingly, we found that when MeOH–THF (1 : 1) was employed, the corresponding adduct **3a** was obtained in 88% yield along with 89% ee (Table 2, entry 2). However, the combination of MeOH with other solvents, such as MeCN, CH_2Cl_2 and toluene gave poor yield and enantioselectivity.[9] Screening of the alcohols revealed that both MeOH–THF (1 : 1) and ^{t}BuOH–THF (1 : 1) resulted in higher enantioselectivity than the combinations of other alcohols (Table 2, entries 2–8). The ratios of MeOH–THF and ^{t}BuOH–THF were also examined, but lower ee was obtained, albeit a similar chemical yield was retained (Table 2, entries 9–13). When the reaction was performed at 5 °C, adduct **3a** was obtained in 57% yield and 93% ee (Table 2, entry 14). Whereas, only a trace amount of **3a** was formed when the reaction was performed at −5 °C (Table 2, entry 15). To further activate the hydrazone **1a** at lower temperature, we utilized Zn $(NTf_2)_2$ instead of $Zn(OTf)_2$ as Lewis activator. Pleasantly, product **3a** was generated in 71% yield and 92% ee when the reaction was carried out at 5 °C in the presence of $Zn(NTf_2)_2$ (Table 2, entry 16). With the addition of 4 Å MS (50 mg), a higher enantioselectivity of 93% ee and yield (93%) were achieved (Table 2, entry 17).

Having established the above optimal conditions, we next investigated the substrate scope of this reaction with the results summarized in Table 3 and Table 4. As for substrates **1b–1i**, the reactions proceeded smoothly to afford the corresponding Mannich-type adducts **3b–3i** in moderate to good yields (up to 87% yield) and good to excellent enantioselectivities (from 87% ee to 96% ee), regardless of electronic nature of the substituents on the aromatic rings (Table 3, entries 1–8). Using hydrazone

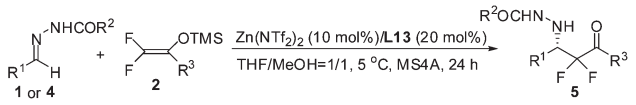
Table 3 Substrate scope of the $Zn(NTf_2)_2$-catalyzed asymmetric Mannich-type reaction of hydrazone with difluoroenoxysilane **2a**



Entry[a]	Hydrazone **1** (R)	Yield[b] (%) **3**	ee[c] (%) **3**	Absolute configuration[d]
1	**1b** (4-ClC_6H_4)	**3b**, 75	95	*S*
2	**1c** (4-BrC_6H_4)	**3c**, 79	96	*S*
3	**1d** (4-FC_6H_4)	**3d**, 83/67[e]	87/93[e]	*S*
4	**1e** (4-MeC_6H_4)	**3e**, 73	92	*S*
5	**1f** (4-$MeOC_6H_4$)	**3f**, 87	94	*S*
6[f]	**1g** (4-$NO_2C_6H_4$)	**3g**, 79	90	*S*
7	**1h** (4-CNC_6H_4)	**3h**, 67	91	*S*
8	**1i** (4-$CF_3C_6H_4$)	**3i**, 69	90	*S*
9	**1j** (3-ClC_6H_4)	**3j**, 71	94	*S*
10	**1k** (1-Naphthyl)	**3k**, 69	91	*S*
11	**1l** (2-Naphthyl)	**3l**, 72	94	*S*
12	**1m** (2-Furyl)	**3m**, 77	57	*S*
13	**1n** (2-Thienyl)	**3n**, 59/51[e]	83/90[e]	*S*
14	**1o** (3-Thienyl)	**3o**, 79/69[e]	87/94[e]	*S*
15	**1p** [$CH_3(CH_2)_6$]	**3p**, 53	60	*S*
16	**1q** (Cyclohexyl)	**3q**, 52	78	*S*

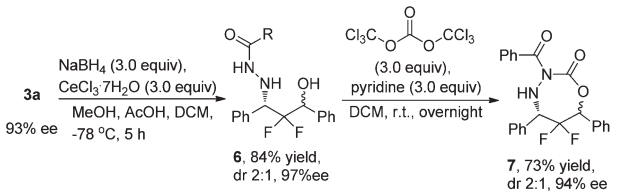
[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.30 mmol), $Zn(NTf_2)_2$ (10 mol%), **L13** (20 mol%), THF (0.50 mL), MeOH (0.50 mL) and MS4A (50 mg), the reaction was carried out at 5 °C for 24 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by the X-ray diffraction. [e] The reaction was carried out at 0 °C. [f] The reaction was carried out at 25 °C.

Table 4 The scope of $Zn(NTf_2)_2$-catalyzed asymmetric Mannich-type reaction of aromatic hydrazones with difluoroenoxysilane



Entry[a]	Hydrazone **1** or **4** (R^1/R^2)	Difluoroenoxysilane **2** (R^3)	Yield[b] (%) **3**	ee[c] (%) **3**	Absolute configuration[d]
1	**4a** (C_6H_5/4-$MeOC_6H_4$)	**2a** (C_6H_5)	**5a**, 81	94	*S*
2	**4b** (C_6H_5/4-$NO_2C_6H_4$)	**2a** (C_6H_5)	**5b**, 59[e]/54[f]	86/92[f]	*S*
3	**4c** (4-BrC_6H_4/4-BrC_6H_4)	**2a** (C_6H_5)	**5c**, 71[e]/52[f]	82/95[f]	*S*
4	**4d** (C_6H_5/4-$C_6H_5C_6H_4$)	**2a** (C_6H_5)	**5d**, 72[e]/52[f]	89/96[f]	*S*
5	**1b** (4-ClC_6H_4/C_6H_5)	**2b** (4-MeC_6H_4)	**5e**, 88/59[g]	88/92[g]	*S*
6	**1b** (4-ClC_6H_4/C_6H_5)	**2c** (2-Thienyl)	**5f**, 81/50[g]	51/76[g]	*S*

[a] Reaction conditions: **1** or **4** (0.10 mmol), **2** (0.30 mmol), $Zn(NTf_2)_2$ (10 mol%), **L13** (20 mol%), THF (0.50 mL), MeOH (0.50 mL) and MS 4A (50 mg), the reaction was carried out at 5 °C for 24 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by the X-ray diffraction. [e] The reaction was carried out at 25 °C. [f] The reaction was carried out at 10 °C and 5.0 equiv of **2a** was utilized. [g] The reaction was carried out at −5 °C and 5.0 equiv of **2b** or **2c** was utilized.



Scheme 1 Transformation of **3a**

bearing a 3-chlorobenzene group gave the corresponding product **3j** in 71% yield and 94% ee (Table 3, entry 9). The naphthyl, furyl or thienyl-containing hydrazones **1k–1o** afforded difluorination adducts **3k–3o** in moderate to good yields and excellent enantioselectivities (up to 77% yield and 94% ee, Table 3, entries 10–14). It should be noted that the enantioselectivities of **3d**, **3n** and **3o** were slightly improved when the reactions were carried out at 0 °C, but chemical yields were diminished due to the lower solubility of hydrazones at this temperature (Table 3, entries 3, 13 and 14).

Previous research showed that aliphatic hydrazones, such as **1t** [R = $CH_3(CH_2)_3$], was inefficient in the $Zn(OTf)_2$-promoted Mannich-type reaction of hydrazones with difluoroenoxysilanes.[8c,9] However, under this new $Zn(NTf_2)_2$/**L13**-based catalytic system, aliphatic hydrazones showed effectiveness leading to moderate yields and enantioselectivities (Table 3, entries 15 and 16). More examples are provided in the Supporting Information (Table S1).†

Hydrazones having a different R^2 group were subjected to the reaction with several difluoroenoxysilanes **2** under the optimized conditions. When R^2 is a 4-methoxyphenyl group, the reaction proceeded smoothly leading to the corresponding adduct **5a** in 81% yield and 94% ee (Table 4, entry 1). As revealed in Table 4, when hydrazones **4b–4d** were used as substrates, the corresponding adducts were obtained in moderate to good yields (59–72%) and enantioselectivity (up to 89% ee) regardless of the electronic nature of R^2 group (Table 4, entries 2–4). Lowering the reaction temperature from r.t. to 10 °C resulted in the corresponding products **5b–5d** in 92–96% ee but in lower yields due to the low solubility of hydrazones (Table 4, entries 2–4). Adduct **5c** was obtained in 95% ee, which enabled successful formation of single crystals for the X-ray diffraction analysis which has proven to be (*S*)-absolute configuration (Fig. SI-1 in the ESI†). In addition, the reaction of hydrazone **1b** with difluoroenoxysilane **2b** or **2c** occurred smoothly to give the corresponding adducts **5e** and **5f** in good yields (up to 88%) and moderate to good enantioselectivities (up to 88% ee) (Table 4, entries 5 and 6). Furthermore, when the reaction was carried out at –5 °C, **5e** and **5f** were formed in 59% yield/92% ee and 50% yield/76% ee, respectively (Table 4, entries 5 and 6). The reaction of **4c** with **2a** was also performed on a 1.0 mmol scale (536 mg), giving **5c** in 63% yield and 95% ee.

To obtain direct evidence of the coordination pattern between the imidazoline–phosphine ligand and Zn(II) salt, we conducted ^1H NMR and ^{31}P NMR spectroscopic studies of (R_a,*S*,*S*)-**L13** by using a 1 : 1 mixture of **L13** : $Zn(OTf)_2$ and 2 : 1 mixture of **L13**/$Zn(OTf)_2$ in $CDCl_3$ at ambient temperature (Fig. SI-2†). The phosphorus signal of **L13** appeared at δ −14.87 ppm. For a 1 : 1 mixture of **L13** : $Zn(OTf)_2$, the phosphorus signal of **L13** appeared at δ −14.84 ppm along with an additional signal at δ −1.88 ppm. The signal at δ −1.88 ppm was strengthened in the 2 : 1 mixture of **L13** and $Zn(OTf)_2$, as compared to that of the 1 : 1 mixture of **L13** and $Zn(OTf)_2$. These results indicate that the 2 : 1 mixture of imidazoline–phosphine ligands and zinc(II) would be able to generate the active species for the present catalytic system.

Finally, it should be noted that adduct **3a** has been easily transformed to the heterocyclic compound **7** upon treatment with $NaBH_4$ and triphosgene in a good yield of 73% (Scheme 1, see ESI†).

In conclusion, we have established a novel catalytic system of using chiral zinc(II)–imidazoline–phosphine complexes as catalysts for the asymmetric Mannich-type difluorinations of hydrazones with difluoroenoxysilanes. The reaction can smoothly occur under mild conditions, affording the corresponding Mannich-type adducts in moderate to good yields and excellent enantioselectivities. The catalytic complexes was studied by direct NMR observations, which indicated that the ratio 2 : 1 of imidazoline–phosphine ligand with zinc(II) salt was sufficient to give the active species for this asymmetric difluorination reaction.

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