

Asymmetric aza-Henry reaction of chiral fluoroalkyl α,β -unsaturated *N*-*tert*-butanesulfinyl ketoimines: an efficient approach to enantiopure fluoroalkylated α,β -diamines and α,β -diamino acids†

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The aza-Henry reaction of chiral fluoroalkyl α,β -unsaturated *N*-*tert*-butanesulfinyl ketoimines and nitromethane was achieved in the presence of 0.2 equivalent of anhydrous potassium carbonate to give the corresponding adducts diastereoselectively in high yields. Transformations which highlighted the synthetic potential of these aza-Henry adducts were also performed.

1. Introduction

Aza-Henry reaction (nitro-Mannich reaction), which involves the nucleophilic addition of nitroalkanes to imines and related compounds, is a powerful synthetic method that allows the creation of a carbon-carbon bond with concomitant generation of two vicinal stereogenic centers bearing nitro and amino functional groups.¹ The resulting β -nitroamines are attractive targets in asymmetric synthesis mainly due to their easy conversions to α -amino acids or vicinal diamines *via* Nef-reaction² or the reduction of nitro group.³ Additionally, the two nitrogenated functions are present in different oxidation states, thus giving access to further transformations with complete chemoselectivity.¹

Although catalytic asymmetric synthesis has undergone tremendous growth in the last decade, chiral auxiliary-aided asymmetric synthesis continues to attract considerable attention. Chiral *N*-sulfinamides are undoubtedly of the most efficient auxiliaries to date.⁴ In 2005, García Ruano *et al.* reported their research on asymmetric aza-Henry reaction of *N*-*p*-tolylsulfinylimines, in which excellent yield and selectivity were achieved.⁵ Two years later, Terada reported organic base catalyzed aza-Henry reaction of the very same imines, but poor diastereoselectivity was obtained.⁶ However, to our best knowledge, there is no report on the chiral *N*-*tert*-butanesulfinamide aided aza-Henry reaction until now, despite *tert*-butanesulfinamide is another well developed chiral auxiliary except for *p*-tolylsulfinylamide.⁷

Owing to the unique properties of fluorine, the introduction of a fluoroalkyl group into organic compounds could bring profound changes to their physical, chemical and biological properties.⁸ Accordingly, the development of methods for the asymmetric synthesis of chiral fluoroalkylated diamines is of great significance, and the aza-Henry reaction of fluoroalkylated imines might be a simple and convenient approach. However, this attempt met with a big challenge because most fluoroalkylated imines are unstable at room temperature or suffer from easily hydrolyzing or decomposing during work-up. Recently, it was found in our group that different from usual fluoroalkylated *N*-sulfinyl imines, fluoroalkyl α,β -unsaturated *N*-*tert*-butanesulfinyl ketoimines, derived from fluoroalkyl α,β -unsaturated ketones, were quite stable at room temperature and could be converted to the corresponding allylic amines diastereoselectively by asymmetric reduction with DIBAL-H or L-Selectride.⁹ Further studies showed that the aza-Henry reaction of these stable fluoroalkylated imines occurred readily in the presence of catalytic amount of anhydrous potassium carbonate under mild conditions, giving the corresponding adducts diastereoselectively in good to excellent yields. This is the first example of aza-Henry reaction of fluoroalkylated imines and the first systematic investigation on aza-Henry reaction of *N*-*tert*-butanesulfinyl ketoimine. The results are reported in this paper.

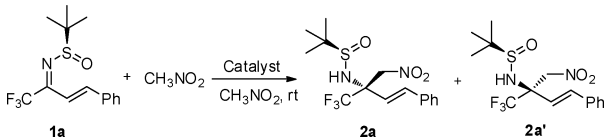
2. Results and discussion

We embarked on our investigation by searching appropriate catalyst for the reaction of chiral (*R*)-*N*-*tert*-butanesulfinyl tri-fluoromethyl vinylketoimine (**1a**) with nitromethane. As shown in Table 1, the catalyst had a crucial effect on both diastereoselectivity and yield. Organic bases were not suitable for this reaction. When strong guanidine base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), was used, aza-Henry adduct **2a** was obtained in moderate yield with low diastereoselectivity (entries 1–2). In the presence of 0.2 equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO), which is less basic than DBU and TBD and was expected to decrease side reactions, the reaction was sluggish and low conversion was observed with low diastereoselectivity and yield (entry 3).

Both as fluoride ionic compounds, tetra-*n*-butylammonium fluoride (TBAF) and potassium fluoride (KF) gave contrasting results. While 95% de value and 59% yield were obtained in the

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Table 1 The aza-Henry reaction of **1a** under various catalysts


Entry	Catalyst (eq)	Time (h)	Conversion (%) ^a	Yield (%) ^b	2a:2a' ^a
1	DBU (0.4)	3	100	45	53 : 47
2	TBD (0.2)	3	100	69	71 : 29
3	DABCO (0.2)	12	47	34 ^a	79 : 21
4	Bu ₄ NF (0.2)	48	0	—	—
5	KF (0.2)	12	100	59	>95 : 5
6	KOH (0.2)	6	100	86	95 : 5
7	K ₂ CO ₃ (0.2)	3	100	98	>95 : 5
8	Cs ₂ CO ₃ (0.2)	3	100	55	87 : 13
9	Na ₂ CO ₃ (0.2)	48	35	28	>95 : 5

^a Determined by ¹⁹F NMR of the reaction mixture; ^b Isolated yield of **2a** and **2a'**.

presence of KF (entry 5), no aza-Henry product was obtained with TBAF (entry 4). Comparing these results, we speculated that potassium ion might play an important role in the reaction. Therefore several inorganic bases were tried next (entries 6–9). It was found that potassium carbonate was the best catalyst for the reaction among all bases tested (entry 7).

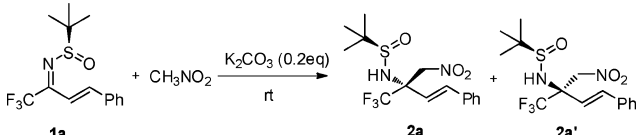
To further improve the reaction, solvents with different polarity were further screened. It was found that the polarity of solvent held a significant impact on the reaction. As shown in Table 2, no conversion of **1a** was observed after stirring in non-polar solvent toluene for 3 days (entry 1). Good yield and diastereoselectivity were obtained in both dichloromethane and nitromethane, but the reaction in nitromethane proceeded much faster than in dichloromethane (entries 2–3). Using acetonitrile as solvent led to full conversion and excellent diastereoselectivity but moderate yield (entry 4). In high polar dimethylsulfoxide (DMSO), more by-products were formed and **2a** was obtained in low yield (entry 5).

Under the optimized conditions (0.2 equiv. anhydrous potassium carbonate in nitromethane at room temperature), the reaction of various fluoroalkyl α,β -unsaturated (*R*)-*N*-tert-butanesulfinyl ketoimines was investigated to probe the generality of this reaction.¹⁰ The results are summarized in Table 3. In most cases, the (*R*_S,*S*)-diastereoisomer of the corresponding aza-Henry adduct was obtained in high yields with high diastereoselectivities.

The absolute configuration of **2** was confirmed by X-ray crystallographic analysis of **2a**.¹⁰ Ketoimines with aromatic substitutions at the β -position were proved to be excellent substrates for this reaction (entries 1–4). The reaction also tolerated alkyl substituent at the β -position, giving excellent diastereoselectivity albeit moderate yield (entry 5). The fluoroalkyl group in ketoimines had a profound effect on the reaction. While chlorodifluoromethylated ketoimine **1f** afforded the corresponding aza-Henry adduct in good yield with excellent diastereoselectivity, hydrodifluoromethylated ketoimine **1g** exhibited decreases both in yield and diastereoselectivity (entries 6–7). Furthermore, it is noteworthy that perfluoropropylated ketoimine **1h** gave 1,4-adducts **2h-1** and **2h-2** in a ratio of about 40 : 60 (Scheme 1). Only one diastereoisomer was observed for either **2h-1** or **2h-2**. The reason is still unknown.

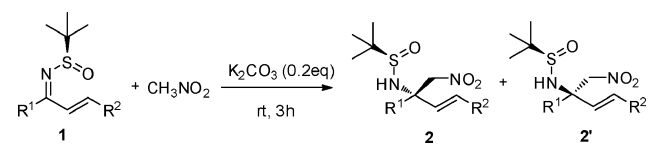
To further demonstrate the effect of the fluoroalkyl substituent on the reaction, the aza-Henry reaction of non-fluoro ketoimine **1i** and **1j** were also investigated under similar conditions (Scheme 2). In the presence of 1.0 equivalent of potassium carbonate, no reaction occurred after 3 days in both cases, indicating that the presence of strong electron-withdrawing fluoroalkyl group is crucial for the success of this reaction.

Fluoroalkylated β -nitroamines **2** obtained in the above reaction are versatile multifunctional fluorine-containing building blocks. To demonstrate their synthetic potentials, **2a** was further

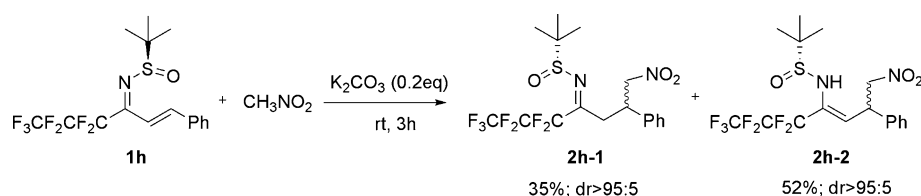
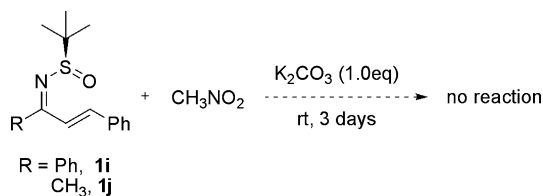
Table 2 The aza-Henry reaction of **1a** catalyzed by potassium carbonate in various solvents


Entry	Solvent	Dielectric constant ^a	Time (h)	Conversion (%) ^b	Yield (%) ^c	2a:2a' ^b
1	Toluene	2.4	72	0	—	—
2	CH ₂ Cl ₂	9.1	12	100	>95	>95 : 5
3	CH ₃ NO ₂	39.4	3	100	>95	>95 : 5
4	CH ₃ CN	37.5	3	100	59	>95 : 5
5	DMSO	55.0	3	100	47	n.d. ^d

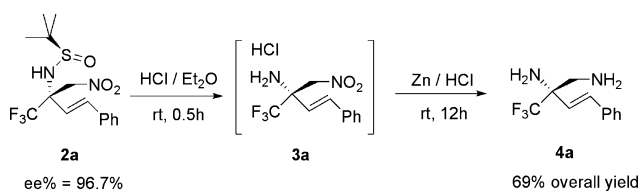
^a Dielectric constants under 20 °C; ^b Determined by ¹⁹F NMR of the reaction mixture; ^c Isolated yield of **2a** and **2a'**; ^d Not determined.

Table 3 The aza-Henry reaction of **1** catalyzed by potassium carbonate in nitromethane


Entry	1	R ¹	R ²	2	Dr ^a	Yield (%) ^b
1	1a	CF ₃	C ₆ H ₅	2a	> 95 : 5	85
2	1b	CF ₃	4-CH ₃ OC ₆ H ₄	2b	> 95 : 5	95
3	1c	CF ₃	4-ClC ₆ H ₄	2c	95 : 5	91
4	1d	CF ₃	1-Naphthyl	2d	> 95 : 5	91
5	1e	CF ₃	<i>n</i> -C ₈ H ₁₇	2e	> 95 : 5	68
6	1f	CF ₂ Cl	C ₆ H ₅	2f	> 95 : 5	80
7	1g	CF ₂ H	C ₆ H ₅	2g	72 : 28	54

^a Determined by ¹⁹F NMR; ^b Isolated yield of **2**.**Scheme 1****Scheme 2**

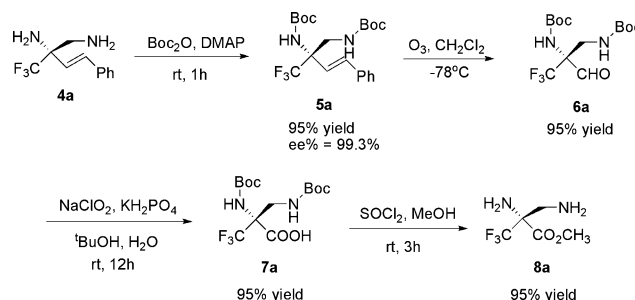
transformed to its corresponding trifluoromethyl diamine **4a** (Scheme 3). Treatment of **2a** with ethereal solution of hydrogen chloride, followed by reduction with zinc powder, gave enantiopure diamine **4a** in 69% overall yield with 99.3% *ee* (determined by HPLC).

**Scheme 3**

α -Fluoroalkyl α,β -diamino acids are extremely interesting analogues of natural α -amino acids owing to the unique properties of fluoroalkyl group, such as high electronegativity, electron density, steric hindrance and hydrophobic character.⁸ However, the relatively difficult availability of most α -fluoroalkyl amino acids in enantiopure form, whose asymmetric synthesis often requires complex experimental protocols and hard to handle starting materials, obstructs a systematic investigation on the biomedical and structural features of α -fluoroalkyl amino acids and their peptidic derivatives. Although a number of procedures which give

access to α -fluoroalkyl amino acids have been developed, there are few reports on the asymmetric synthesis of α -trifluoromethylated diamino acid derivatives.¹¹ To our best knowledge, the only report about the synthesis of chiral fluoroalkylated α,β -diamino acid was contributed by Uneyama in 2003 in which aziridinyl anion was utilized as a precursor.¹²

With optically pure **4a** in hand, we next performed the synthesis of **8a** (Scheme 4). Through a four-step procedure involving the protection of amino groups, the oxidation of double bond with ozone, the oxidation of aldehyde with sodium chlorite, and the removal of protecting group, **8a** was obtained in high overall yield. This provided an efficient and practical access to either enantiomer of α -fluoroalkyl- α,β -diamino acids since the other enantiomer could potentially be obtained by utilizing (*S*)-*tert*-butanesulfinamide as auxiliary rather than (*R*)-*tert*-butanesulfinamide.

**Scheme 4**

3. Conclusion

In summary, the aza-Henry reaction of chiral fluoroalkylated α,β -unsaturated *N-tert*-butanesulfinyl ketoimines was achieved

for the first time under mild conditions, providing a highly efficient method for the asymmetric synthesis of fluoroalkylated β -nitroamines with high diastereoselectivities. Further conversions of these fluoroalkylated β -nitroamines to both fluoroalkylated diamines and fluoroalkylated diamino acids were also illustrated. Given the abundance of biologically active compounds, valuable building blocks, chiral auxiliaries and metal ligands that contain the fluoroalkylated diamine moiety, this method should find wide application in the asymmetric synthesis of a range of substituted derivatives.

Acknowledgements

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References

- 1 E. Marqués-López, P. Merino, T. Tejero and R. P. Herrera, *Eur. J. Org. Chem.*, 2009, 2401 and references therein.
- 2 (a) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017; (b) E. Foresti, G. Palmieri, M. Petrini and R. Profeta, *Org. Biomol. Chem.*, 2003, **1**, 4275.
- 3 (a) M. A. Sturgess and D. J. Yarberry, *Tetrahedron Lett.*, 1993, **34**, 4743; (b) A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, 1991, **32**, 1699.
- 4 For reviews, see: (a) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han and I. Gallou, *Aldrichimica Acta*, 2005, **38**, 93; (b) F. A. Davis, *J. Org. Chem.*, 2006, **71**, 8993; (c) P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003; (d) J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984; (e) J. A. Ellman, *Pure Appl. Chem.*, 2003, **75**, 39; (f) F. A. Davis, P. Zhou and B.-C. Chen, *Chem. Soc. Rev.*, 1998, **27**, 13.
- 5 (a) J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuñán and M. B. Cid, *Org. Lett.*, 2005, **7**, 4407; (b) J. L. García Ruano, J. López-Cantarero, T. De Haro, J. Alemán and M. B. Cid, *Tetrahedron*, 2006, **62**, 12197.
- 6 N. K. Pahadi, H. Ube and M. Terada, *Tetrahedron Lett.*, 2007, **48**, 8700.
- 7 There is only one report involving the aza-Henry reaction of *N*-tert-butanesulfinyl aldimine: J. Weng, Y.-B. Li, R.-B. Wang, F.-Q. Li, C. Liu, A. S. C. Chan and G. Lu, *J. Org. Chem.*, 2010, **75**, 3125.
- 8 (a) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3; (b) *Biomedical Frontiers of Fluorine Chemistry* (ed., I. Ojima, J. R. McCarthy and J. T. Welch), ACS, Washington, 1996; (c) P. N. Edwards, in *Organofluorine Chemistry: Principles and Commercial Applications* (ed., R. E. Banks and J. C. Tatlow), Plenum Press, New York, 1994; (d) *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications* (ed., R. Filler, Y. Kobayashi and L. Agupolskii, Elsevier, Amsterdam, 1993.
- 9 Z.-J. Liu and J.-T. Liu, *Chem. Commun.*, 2008, 5233.
- 10 Typical procedure for the synthesis of **2a**: Potassium carbonate anhydrous (2.8 mg, 0.02 mmol) was added to a solution of **1a** (30.0 mg, 0.1 mmol) in nitromethane (0.5 mL) at room temperature. The reaction mixture was stirred for 3 h. After removal of the volatile solvent under vacuum, **2a** was obtained *via* silica gel chromatography (Petroleum Ether/EtOAc = 5/1) in 85% yield (31.0 mg). (*E*)-2-methyl-*N*-(1,1,1-trifluoro-2-(nitromethyl)-4-phenylbut-3-en-2-yl)propane-2-sulfonamide (**2a**) Colorless crystal, yield 85%; mp: 72–74 °C; IR (film): ν 3306, 3285, 2962, 1560, 1471, 1368, 1397, 1185, 1124, 1081, 1054 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.48–7.36 (m, 5 H), 6.91 (d, J = 16.2 Hz, 1 H), 6.30 (d, J = 16.2 Hz, 1 H), 5.45 (s, 1 H), 5.08–4.99 (m, 2 H), 1.32 (s, 9 H); ^{19}F NMR (282 MHz, CDCl_3): δ –76.4 (s, 3 F); MS (ESI, m/z , %): 365 [$\text{M}+1$] $^+$; Anal. Calcd. For $\text{C}_{15}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{S}$: C, 49.44; H, 5.26; N, 7.69. Found: C, 49.24; H, 5.37; N, 7.56. The chiral HPLC analytical data: chiralpak IC column, detected at 214 nm, eluent: *n*-hexane/*iso*-propanol = 60/40, 0.7 mL min^{-1} , retention times: *tr* (minor) = 5.85 min, *tr* (major) = 6.19 min; ee% = 96.7%; Crystal data: for **2a**, $\text{C}_{15}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{S}$; M = 364.38; Triclinic, $P\bar{1}$; a = 9.1431(10) Å, b = 9.1984(11) Å, c = 21.398(3) Å; α = 98.890(2), β = 92.687(2), γ = 95.661(2), V = 1765.8(4) Å 3 ; Z = 4; 9748 reflections; R_{int} = 0.0668; R_1 = 0.0562 and wR_2 = 0.1244.
- 11 For review about synthesis of α -trifluoromethyl substituted α -amino acid, see: R. Smits, C. D. Cadicamo, K. Burger and B. Koksche, *Chem. Soc. Rev.*, 2008, **37**, 1727.
- 12 (a) Y. Yamauchi, T. Kawate, T. Katagiri and K. Uneyama, *Tetrahedron*, 2003, **59**, 9839; (b) Y. Yamauchi, T. Kawate, H. Itahashi, T. Katagiri and K. Uneyama, *Tetrahedron Lett.*, 2003, **44**, 6319; (c) T. Katagiri, M. Takahashi, Y. Fujiwara, H. Ihara and K. Uneyama, *J. Org. Chem.*, 1999, **64**, 7323.