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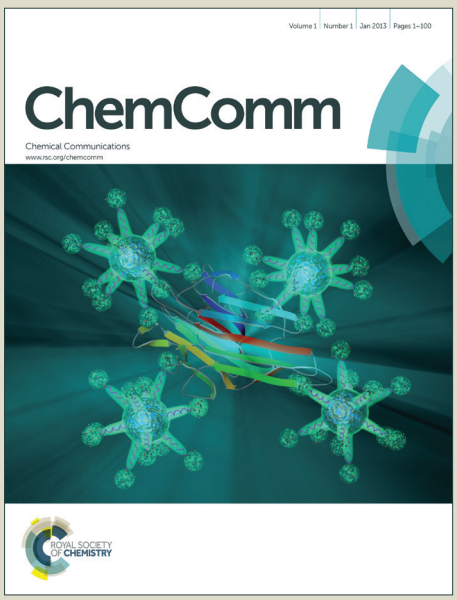

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Asymmetric Michael Addition of α-Fluoro-α-nitroalkanes to Nitroolefins: Facile Preparation of Fluorinated Amines and Tetrahydropyrimidines

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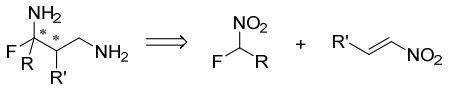
An asymmetric Michael addition of α-fluoro-α-nitroalkanes to nitroolefins was developed, and the products were obtained in good chemical yields and with high stereoselectivities. Highly functionalized adducts provided ready access to fluorinated amines and tetrahydropyrimidines in an optically enriched form.

The small size of the fluorine atom, together with its extreme electronegativity, makes it an excellent substituent for tuning the properties of bioactive compounds, and this is now well recognized in pharmaceutical industry.[1] Asymmetric synthesis of chiral fluorinated molecules has become a hot research area and attracted tremendous attention in recent years.[2] Complementary to the direct asymmetric fluorination methods, an emerging approach is to utilize fluorine-containing prochiral substrates to derive optically enriched fluorine-containing molecules. In the past few years, asymmetric C–C and C–N bond forming processes employing fluorinated substrates were developed, including: Michael additions,[3] Mannich reactions[4] and aminations,[5] among others.

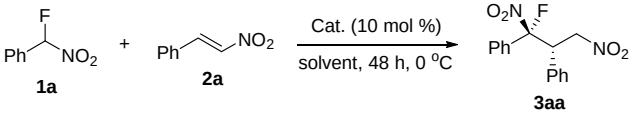
Amino compounds are of extreme importance in organic chemistry, and apparently fluorine-incorporating amines are valuable molecules. However, there are only limited examples describing synthesis of amines fluorinated at the vicinal carbon,[6] and there was no report on asymmetric synthesis of geminally fluorinated amines. Our group has keen interest in constructing quaternary stereogenic centers[7] and we set out to develop a convenient asymmetric synthesis to access molecular structures containing unchallenged α-fluoro-α-amino quaternary centers. As illustrated in Scheme 1, such structural motifs could be readily accessed through a Michael addition of α-fluoro-α-nitroalkanes[8] to nitroolefins. Herein, we describe an asymmetric process for the above reaction, which led to highly enantioselective construction of a novel α-fluoro-α-amino stereogenic center.

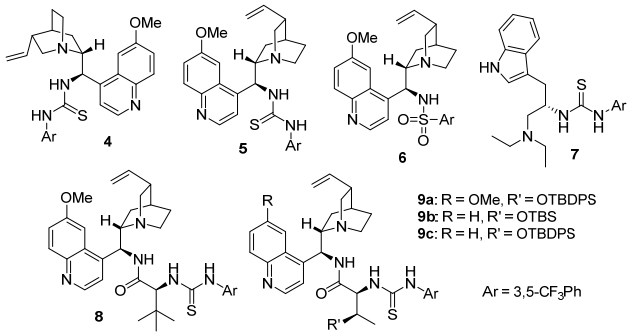


Scheme 1. Synthesis of α-fluoro-α-amino quaternary centers.

We chose Michael addition of α-fluorinated nitroalkane **1a** to nitroolefin **1b** as a model reaction to examine catalytic effects of various tertiary amino catalysts with a Brønsted acid moiety, and the results are summarized in Table 1. Quinidine-derived **4** and quinine-derived **5** afforded desired products in high yields, but with poor enantioselectivity (entries 1 and 2). Sulfonamide **6** and tryptophan-based **7** were ineffective for the reaction (entries 3 and 4). We next turned to amino acid-incorporating multifunctional catalysts which were developed by us earlier.[9] With the employment of catalyst **8** containing a *tert*-leucine moiety, the desired products were obtained in excellent yields, high enantioselectivity, and modest diastereoselectivity (entries 5 and 6). Catalysts **9a-c** with an incorporated threonine moiety were found to be equally effective (entries 7–9). Subsequently, solvent screening was performed, and effects of adding molecular sieves were examined (entries 10–19). Under the optimized reaction conditions, the desired product was obtained in 85% yield, with 90% ee and 5:1 diastereomeric ratio (entry 9), and the reaction could be scaled up with same efficiency (entry 20).

Table 1. Optimization of organocatalyzed Michael addition of 1-fluoro-1-phenylnitromethane (**1a**) to (*E*)-β-nitrostyrene (**2a**).[a]



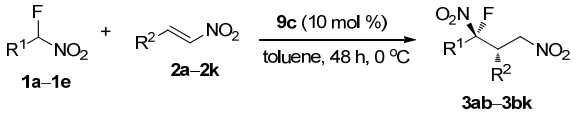


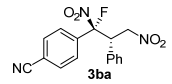
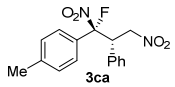
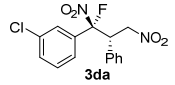
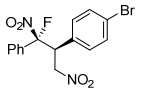
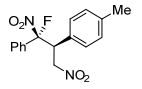
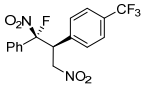
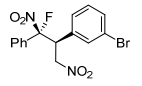
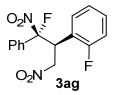
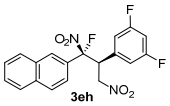
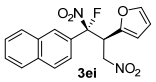
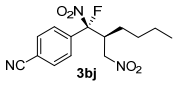
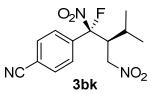
Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]	dr[d]
1[e]	**4**	Toluene	90	9	1:1
2[e]	**5**	Toluene	91	19	1:1
3[e]	**6**	Toluene	<15	-	-
4[e]	**7**	Toluene	88	18	1:1
5[e]	**8**	Toluene	92	86	3:1
6	**8**	Toluene	85	90	7:2
7	**9a**	Toluene	66	86	3:1
8	**9b**	Toluene	87	86	5:1
9	**9c**	Toluene	85	90	5:1
10	**8**	CH_2Cl_2	51	88	2:1
11	**8**	Et_2O	20	87	2:1
12	**8**	THF	90	78	3:2
13	**8**	$CHCl_3$	62	86	5:2
14	**9c**	$CHCl_3$	69	81	3:1
15	**8**	Xylene	72	89	3:1
16[f]	**8**	Toluene	78	86	5:1
17[g]	**8**	Toluene	80	91	3:1
18[h]	**8**	Toluene	86	78	5:2
19[h]	**9c**	Toluene	82	90	5:1
20[i]	**9c**	Toluene	82	90	5:1

[a] Reaction conditions: **1a** (0.1 mmol), the catalyst (0.01 mmol) and nitrostyrene **2a** (0.11 mmol) in the solvent specified (1 mL) at 0 °C. [b] Isolated yield of two diastereomers. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Reaction at room temperature, >3 days. [f] In the presence of 3 Å molecular sieves (10 mg). [g] In the presence of 4 Å molecular sieves (10 mg); [h] In the presence of 5 Å molecular sieves (10 mg); [i] 1.5 mmol of **1a** was used.

With the optimized reaction conditions in hand, we further investigated the reaction scope (Table 2). Different α-aryl-α-fluorine nitromethanes[10] were found to be suitable for the reaction, and substrates containing aryls with substituents of different electronic nature at either *para*- or *meta*- position could be employed (entries 1–3). The structures of nitroolefins could also be varied, and excellent yields, good diastereoselectivity, and high enantioselectivity were attainable (entries 4–7). Moreover, nitroolefin with an *ortho*-fluorine atom could also be tolerated (entry 8). Nitroolefin with a bis-substituted aromatic substituent was especially favourable (entry 9), and nitroolefin containing a 2-furan was found to be suitable substrate (entry 10). When alkyl substituted nitroolefins were used, either reactive donor containing an electron-poor aryl ring was required or higher catalyst loading (20 mol%) was needed, and excellent results were maintained (entries 11 and 12). Unfortunately, fluorinated nitroalkanes with a simple alkyl substituent were unsuitable for the reaction.

Table 2. Scope of organocatalysed Michael addition of 1-fluoro-1arylnitromethane to nitroalkenes.[a]



Entry	3	Yield (%)[b]	dr[c]	ee (%)[d]
1[e]		85	6:1	88
2		79	7:1	91
3		84	7:1	87
4		74	7:1	90
5		71	8:1	88
6		75	5:1	91
7		71	8:1	90
8[f,g]		76	5:1	85
9		87	8:1	96
10		80	7:1	88
11[h]		75	5:1	82
12[e,g]		95	6:1	82

[a] Reaction conditions: **1** (0.1 mmol), **9c** (0.01 mmol) and nitroalkenes **2** (0.11 mmol) in toluene (1 mL) at 0 °C. [b] Isolated yield of the major diastereomer. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase; [e] The reaction time was 12 h; [f] Catalyst **9b** (10 mol%) was used. [g] Isolated yield of two diastereomers. [h] 20 mol% of catalyst was used and the reaction time was 14 h.

Although the diastereoselectivity of the reaction was not very high, different diastereomers of most products could be obtained upon flash chromatographic purification on silica gel.[10b] The absolute configurations of the Michael addition products were assigned based on X-ray analysis of **3ab** (Figure 1). In our proposed stereochemical model, we believe bifunctional activation of the substrates was crucial for observed stereoselectivity (Scheme 2).

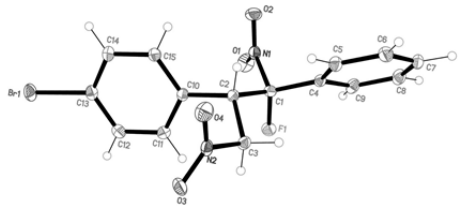
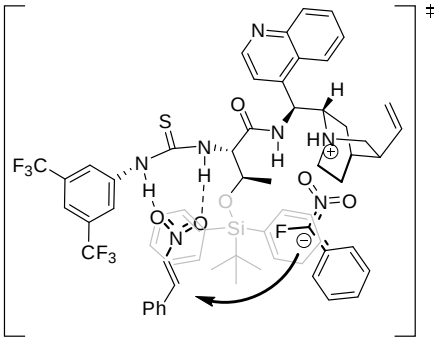
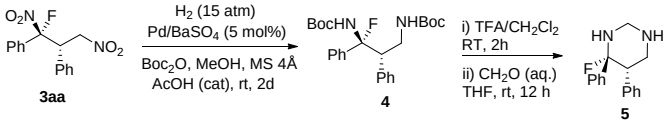


Figure 1. X-ray structure of single crystal of **3ab**.



Scheme. 2. Proposed stereochemical model.

The fluorinated quaternary stereogenic center with a latent amino group created is structurally very unique and interesting. However, we were mindful that potential de-fluorination reaction may occur during the subsequent reduction. After much experimentations,[11] hydrogenation of α-fluoro- α-nitro product **3aa** with a hydrogen pressure of 15 atm using Lindlar's catalyst ($Pd/BaSO_4$) led to smooth reduction of the nitro group, and the de-fluorination was effectively suppressed. The α-fluorinated diamino compound **4** could be converted readily to tetrahydropyrimidine **5**, a fluorinated analogue of potential inhibitors of neurotransmitter reuptake[12] (Scheme 3).



Scheme 3. Synthesis of fluorinated amines and tetrahydropyrimidine.

In summary, we have developed an asymmetric Michael addition of α-fluoro-α-nitroalkanes to nitroolefins, catalysed by amino acid-incorporating multifunctional catalysts. It is noteworthy that this is the first synthesis of quaternary stereogenic centers with an α-fluorine atom and an α-amino function. The reported method open a new route to access optically enriched quaternary carbon-containing fluorinated amines and tetrahydropyrimidines.

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Notes and references

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† Electronic supplementary information (ESI) available: Representative experimental procedures, X-ray crystallographic data, HPLC chromatogram, and NMR spectral data for all the compounds are described. CCDC 975748. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

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