Regio- and Diastereoselective Vinylogous Mannich Addition of 3-Alkenyl-2-oxindoles to α-Fluoroalkyl Aldimines

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Abstract An efficient asymmetric vinylogous Mannich (AVM) addition reaction of 3-alkenyl-2-oxindoles to α-fluoroalkyl aldimines has been developed. This reaction provided various optical active α-alkylidene-δ-amino-δ-fluoroalkyl oxindoles in excellent yields, complete γ-site regioselectivity, and excellent diastereoselectivites.

Key words fluoroalkylated compounds, oxindole, asymmetric, Mannich addition

The δ-amino-α,β-unsaturated carbonyl compounds represent an important class of units in modern organic and medicinal chemistry. They are useful building blocks for the synthesis of various pharmaceuticals and biologically active natural products. It is well known that fluorine-containing compounds are considered as the extraordinarily promising drug candidates because the introduction of fluorine atom or fluorine-containing groups into organic compounds often significantly improves the chemical, physical, and biological properties of the parent compound. Especially, the fluoroalkyl-substituted molecules, such as trifluoromethylated and difluoromethylated compounds, have attracted increasing attention. Thus, the incorporation of fluoroalkyl into δ-amino-α,β-unsaturated carbonyl compounds will provide novel fluorinated moieties, which might be applied in various research fields. Among them, δ-amino-δ-fluoroalkyl-α,β-unsaturated carbonyl compounds are particularly interesting, because the neighboring electron-withdrawing fluoroalkyl groups would change the basicity of imine groups, thus affecting their bioactivities. Normally, these compounds were prepared by vinylogous Mannich reactions. In 1992, Tsukamoto and Kitazume reported the Lewis acid promoted reaction of fluorinated N.O-acetal with trimethylsilyloyfuran (Scheme 1, a). The Lewis acid catalyzed vinylogous Mannich addition of trimethylsilyloyfuran to fluorinated aldmines was disclosed by Crousse and co-workers in 2004 (Scheme 1, a). Shi’s group realized the first enantioselective vinylogous Mannich reaction of fluorinated aldmines bearing a chiral auxiliary ([S]-1-phenylethyl group) and siloxyfurans under the catalytic environment of silver acetate and axially chiral phosphine-oxazoline ligand (Scheme 1, b). Very recently, we developed a tunable and highly regio- and diastereoselective addition reaction of acyclic silyl dienolates to α-fluoroalkyl sulfinylimines, in which the Lewis acid TMSOTf was a critical parameter in the control of γ-site regioselectivity (Scheme 1, c). All the previous works need silylated substrates as the nucleophiles. From the point of atom and step economy, it is worthy to investigate the addition reactions directly using α,β-unsaturated carbonyl compounds as the nucleophiles. In light of the important pharmaceutical implications of the privileged structural motif oxindole, herein we report a regio- and diastereoselective vinylogous Mannich addition of 3-alkenyl-2-oxindoles to α-fluoroalkyl aldmines to afford various chiral α-alkylidene-δ-amino-δ-fluoroalkyl oxindoles (Scheme 1, d).

Initially, the reaction conditions were optimized using (S)-N-tert-butenesulfanyl-3,3,3-trifluoroacetaldimine (1a)\(^b\) and N-Boc-protected 3-alkylidene-2-oxindole 2a\(^c\) as the model substrates (Table 1). Treatment of the substrates with TMSOTf and Et\(_3\)N gave only a silylated intermediate of 2a\(^d\). The desired product 3a was not obtained (Table 1, entry 1). In view of the better nucleophilic properties of the metallic enolate intermediate in comparison to silyl enolate, LDA was chosen as the base. To our delight, the addition reaction happened in the presence of LDA, and 3a was obtained in moderate yield, with virtually complete γ-site selectivity (>99:1 γ/α) and good diastereoselectivity (94:6 dr, Z/E = 8:1; Table 1, entry 2). Considering the fact that the addition of Lewis acid might improve the yield and diastereoselec-
Cluster Synlett 2015, 26, 67–72

Y. Liu et al.

Activity because of its coordination with sulfinylimine substrate, different Lewis acids were then investigated. Among the three typical Lewis acids, Ti(Oi-Pr)₄, AlMe₃, and BF₃·OEt₂, Ti(Oi-Pr)₄ showed the highest efficiency and sharply increased the yield of 3a from 60% to 98% (Table 1, entries 3–5). When the base was changed from LDA to KHMDS, 3a was obtained in similar yield with much higher Z/E ratio (Table 1, entry 6). Finally, different solvents including toluene, Et₂O, and hexane were screened (Table 1, entries 7–9). However, no better result was obtained.

With the optimized conditions in hand, the substrate scope of direct asymmetric vinylogous Mannich (AVM) reaction was surveyed. The results are summarized in Scheme 2. Firstly, 3-alkylidene-2-oxindoles 2a–d bearing diverse nitrogen protecting groups, Boc, Moc, Bn, and Me, reacted smoothly with 1a under identical conditions, affording the corresponding products 3a–d in moderate to good yields and excellent stereoselectivities. Additionally, the reaction conditions displayed good compatibility with the substituent pattern on the phenyl ring of the 2-oxindole. The substrates 2e–g, bearing electron-donating and electron-withdrawing groups, can be efficiently transformed to the corresponding products in excellent yields and stereoselectivities. Subsequently, the patterns of R³ in 3-alkylidene-2-oxindole 2h–j having aromatic groups were tested as the substrates. The reactions proceeded well affording products 3h–j in good yields and diastereoselectivities, although the Z/E ratios were comparably low. It was noteworthy that this protocol could be applied to difluoromethylated sulfinylimine 1b. The corresponding difluoromethylated products 3k–n were conveniently obtained under the optimal reaction conditions. The 3-(propan-2-ylidene)benzofuran-2(3H)-one 2o was also a suitable substrate for this reaction to furnish the product 3o in modest yield and good stereoselectivity.

The absolute configuration of these α-alkylidene-δ-amino-δ-fluoroalkyl oxindoles 3 was confirmed by X-ray crystallographic analysis of compounds 3d (Figure 1). Normally, a nonchelated transition-state model was involved in the addition reaction of nucleophiles to fluorinated sulfinylimines. The stereochemical outcome observed in the present study could also be explained by the nonchelated transition-state model, in which the sulfinyl oxygen coordinates to Ti(Oi-Pr)₄ and sterically shields the Re face of the imine. Thus, the Si attack from metallic enolate intermediates would produce adducts 3 with (C₆S₂)-configurations. The high Z/E ratios in compound 3 might be caused by the cyclic structure of nucleophilic enolate intermediates. The accurate reaction mechanism still needs further investigation.

Scheme 1 Synthesis of δ-amino-α,β-unsaturated carbonyl compounds by vinylogous Mannich reactions
Y. Liu et al.

Scheme 2  Vinylogous Mannich addition of 3-alkenyl-2-oxindoles to α-fluoroalkyl aldimines

1a: $R_1 = \text{CF}_3$
1b: $R_1 = \text{CHF}_2$

$$\text{KHMDI (1.2 equiv)} \quad \text{Ti(O-i-Pr)}_4 \text{ (1.1 equiv)}$$

THF, $-78^\circ \text{C} \quad 12 \text{ h}$

3a: 89% yield
93:7 dr, 94:6 Z/E

3b: 62% yield
90:10 dr, 99:1 Z/E

3c: 85% yield
95:5 dr, 91:9 Z/E

3d: 80% yield
93:7 dr, 94:6 Z/E

3e: 92% yield
94:6 dr, 91:9 Z/E

3f: 92% yield
93:7 dr, 97:3 Z/E

3g: 91% yield
95:5 dr, 95:5 Z/E

3h: 62% yield
92:8 dr, 80:20 E/Z

3i: 57% yield
98:2 dr, 73:27 E/Z

3j: 55% yield
94:6 dr, 73:27 E/Z

3k: 83% yield
93:7 dr, >99:1 Z/E

3l: 84% yield
90:10 dr, 93:7 Z/E

3m: 78% yield
93:7 dr, 91:9 Z/E

3n: 62% yield
84:16 dr, 90:10 Z/E

3o: 73% yield
84:16 dr, 98:2 Z/E
It should be mentioned that the N-tert-butylsulfinyl group can serve not only as an efficient chiral auxiliary, but also as an amine protecting group. It could be readily cleaved under mild acidic conditions. After deprotection, the trifluoromethylated free amines 4 can be easily obtained in high yield (Scheme 3).

In summary, we have demonstrated a practical and efficient approach to synthesize α-alkylidene-δ-amino-δ-fluoroalkyl oxindoles via a regio- and stereoselective vinylogous Mannich-type reaction of fluorinated N-tert-butanesulfinyl aldimines with 3-alkenyl-2-oxindoles. This protocol displayed broad substrate scope, good functional-group compatibility, and satisfactory stereocontrol. Further applications of this method for the preparation of new fluorinated bioactive molecules are in progress.

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**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379600.

**References and Notes**


General Procedure for the Synthesis of α-Alkylidene-δ-amino-δ-fluoroalkyl Oxindoles

A solution of KHMD (0.36 mL, 1 M solution in THF) was slowly added to a dried Scheck flask containing 3-alkenyl-2-oxindoles (2) (0.36 mmol) in THF (2.0 mL) at –78 °C under N₂ atmosphere. After stirring at –78 °C for 1 h, the mixture of (1) and (2) (0.33 mmol) in THF (1.0 mL) was added dropwise, and the mixture was stirred for 12 h at –78 °C. Then sat. aq NH₄Cl solution and H₂O was added at –78 °C. The mixture was brought to r.t. After 5 min, the mixture was filtered through Celite, and the filtrate was extracted with EtOAc. The combined organic layer was dried over MgSO₄. After the removal of volatile solvents under vacuum, the crude product was purified by silica gel column chromatography to give the required product.

Analytical Data for Compound 3a

Mp 60–61 °C. [α]D +187.7 (c 0.41, CHCl₃). [H] NMR (400 MHz, CDCl₃); δ = 7.88 (d, J = 8.2 Hz, 1 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.35 (t, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.7 Hz, 1 H), 4.35 (dd, J = 24.4, 11.2 Hz, 2 H), 4.19–3.96 (m, 1 H), 2.62 (dd, J = 12.7, 3.8 Hz, 1 H), 2.43 (s, 3 H), 1.87 (s, 9 H), 1.06 (s, 9 H). [13C] NMR (101 MHz, CDCl₃); δ = 166.5, 152.0, 149.1, 138.3, 128.9, 125.6, 125.2, (q, J = 284.8 Hz), 124.1, 123.9, 122.3, 114.6, 84.6, 57.2, 56.4 (q, J = 30.2 Hz), 35.3, 28.1, 24.2, 22.2. IR (KBr): νmax = 3261, 3020, 2975, 1731, 1613, 1462, 1535, 1300, 1258, 1157, 1090, 841, 748 cm⁻¹. MS (EI): m/z = 497.2 [M + Na]⁺. ESI-HRMS: m/z [M + Na]⁺ calcd for C₂₂H₂₇F₃N₂O₄SNa: 497.1692; found: 497.1712.


Further details of the crystal data can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition No. 1011207).
