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 aldimes 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 diastereoselectivities.

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.1 They are useful building blocks for the synthesis of various pharmaceuticals and biologically active natural products.2 It is well known that fluorine-containing compounds are considered as the extraordinarily promising drug candidates because the introduction of the fluorine atom or fluorine-containing groups into organic compounds often significantly improves the chemical, physical, and biological properties of the parent compound.3,4 Especially, the fluoroalkyl-substituted molecules, such as trifluoromethylated and difluoromethylated compounds, have attracted increasing attention.5 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.6 In 1992, Tsukamoto and Kitazume reported the Lewis acid promoted reaction of fluorinated N,O-acetal with trimethylsilyloxyfuran (Scheme 1, a).7 The Lewis acid catalyzed vinylogous Mannich addition of trimethylsilyloxyfuran to fluorinated aldimes was disclosed by Crousse and co-workers in 2004 (Scheme 1, a).8 Shi’s group realized the first enantioselective vinylogous Mannich reaction of fluorinated aldimes bearing a chiral auxiliary [(S)-1-phenylethyl group] and silyloxyfurans under the catalytic environment of silver acetate and axially chiral phosphine-oxazoline ligand (Scheme 1, b).9 Very recently, we developed a tunable and highly regio- and diastereoselective addition reaction of acyclic silyl dienolates to α-fluoroalkyl silylnilimines, in which the Lewis acid TMSOTf was a critical parameter in the control of γ-site regioselectivity (Scheme 1, c).10 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,11 herein we report a regio- and diastereoselective vinylogous Mannich addition of 3-alkenyl-2-oxindoles to α-fluoroalkyl aldimes to afford various chiral α-alkylidene-δ-amino-δ-fluoroalkyl oxindoles (Scheme 1, d).

Initially, the reaction conditions were optimized using (S)-N-tert-butanesulfinyl-3,3,3-trifluoroacetaldimine (1a)12 and N-Boc-protected 3-alkylidene-2-oxindole 2a as the model substrates (Table 1). Treatment of the substrates with TMSOTf and Et3N gave only a silylated intermediate of 2a13d. 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 activity because of its coordination with sulfinylimine substrate,
Among the three typical Lewis acids, Ti(O\text{-Pr})_4, AlMe_3, and BF_3·OEt_2, Ti(O\text{-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, Et_2O, 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.15,16 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 R^3 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 difluoroethylated sulfinylimine 1b. The corresponding difluoroethylated 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).18 Normally, a nonchelated transition-state model was involved in the addition reaction of nucleophiles to fluorinated sulfinylimines.12 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(O\text{-Pr})_4 and sterically shields the Re face of the imine. Thus, the Si attack from metallic enolate intermediates would produce adducts 3 with (C\text{S},S\text{S})-configurations. The high Z/E ratios in compound 3 might be caused by the cyclic structure of nucleophilic enolate intermediates.19 The accurate reaction mechanism still needs further investigation.
Scheme 2  Vinylogous Mannich addition of 3-alkenyl-2-oxindoles to α-fluoroalkyl aldimines
Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>Z/E</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et3N</td>
<td>TMSOTf</td>
<td>CH2Cl2</td>
<td>0 to r.t.</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>–</td>
<td>THF</td>
<td>–78</td>
<td>60</td>
<td>8:1</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>Ti(Oi-Pr)4</td>
<td>THF</td>
<td>–78</td>
<td>98</td>
<td>96:4</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>AlMe3</td>
<td>THF</td>
<td>–78</td>
<td>58</td>
<td>12:1</td>
<td>92:8</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>BF3·OEt2</td>
<td>THF</td>
<td>–78</td>
<td>70</td>
<td>7:1</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS</td>
<td>Ti(Oi-Pr)4</td>
<td>THF</td>
<td>–78</td>
<td>97</td>
<td>16:1</td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td>KHMDS</td>
<td>Ti(Oi-Pr)4</td>
<td>toluene</td>
<td>–78</td>
<td>87</td>
<td>12:1</td>
<td>93:7</td>
</tr>
<tr>
<td>8</td>
<td>KHMDS</td>
<td>Ti(Oi-Pr)4</td>
<td>Et2O</td>
<td>–78</td>
<td>41</td>
<td>2:1</td>
<td>94:6</td>
</tr>
<tr>
<td>9</td>
<td>KHMDS</td>
<td>Ti(Oi-Pr)4</td>
<td>hexane</td>
<td>–78</td>
<td>18</td>
<td>18</td>
<td>–</td>
</tr>
</tbody>
</table>

* Reactions were carried out using 1a (0.3 mmol), 2a (0.36 mmol, 1.2 equiv), base (0.36 mmol, 1.2 equiv), and Lewis acid (0.33 mmol, 1.1 equiv) in dry solvent (2.5 mL) for 12 h.

** Ratios and yields were determined by 19F NMR spectroscopy of the crude reaction mixture using benzotrifluoride as an internal standard.

** Base (0.33 mmol, 1.1 equiv) and Lewis acid (0.36 mmol, 1.2 equiv).

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

(1) For selected reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. Chem. Rev. 2000, 100, 1929.


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).

Figure 1 X-ray crystal structure of 3d and proposed transition-state model.


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).
