Disulfonimide-Catalyzed Asymmetric Synthesis of δ-Amino-β-Keto Esters

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Abstract A chiral disulfonimide-catalyzed asymmetric synthesis of δ-amino-β-keto esters via a vinylogous Mukaiyama–Mannich reaction of the Chan diene with N-Boc imines has been developed. The desired products were obtained in good to excellent yields and enantioselectivities.

Key words chiral disulfonimides, δ-amino-β-keto esters, Chan diene, N-Boc imines, vinylogous Mukaiyama–Mannich reaction

δ-Amino-β-keto esters are important building blocks1–3 that are frequently accessed via chain extension of enantioselective β-amino esters4 or using chiral auxiliaries.5 To the best of our knowledge, direct catalytic asymmetric approaches to enantioenriched δ-amino-β-keto esters are unknown. Herein, we report an asymmetric synthesis of δ-amino-β-keto esters via a disulfonimide-catalyzed vinylogous Mukaiyama–Mannich reaction6 of the Chan diene 3 with N-Boc imines 2 (Scheme 1).

Disulfonimides (DSI), of the general structure 1 (Table 1), are strong Brønsted acids,6 as well as precatalysts which are converted into highly active Lewis acid catalysts by in situ silylation. These Lewis acids readily activate aldehydes and ketones in various transformations,6 and we recently reported that they are equally suited for the activation of alkoxy carbonyl imines. In this context we have developed disulfonimide-catalyzed asymmetric aminolylations, Mukaiyama–Mannich reactions, and vinylogous Mukaiyama–Mannich reactions.10 In our previous study,10c we reported a two-step sequence for the asymmetric synthesis of δ-amino-β-keto esters via a reaction between a cyclic silyloxydiene and N-Boc imines followed by thermal esterification. We envisaged that our DSIs might also enable the enantioselective vinylogous Mukaiyama–Mannich reaction of the acyclic Chan diene (3) with N-Boc imines 2, thus offering a direct catalytic asymmetric approach to enantioenriched δ-amino-β-keto esters.

Utilizing similar conditions as in our previous report, we could indeed realize the target reaction. The substrate scope of the DSI-catalyzed vinylogous Mukaiyama–Mannich reaction of Chan’s diene is shown in Table 1. From phenyl N-Boc imine (2a), product 4a was obtained in 91% yield and with 93.5:6.5 enantiomeric ratio (Table 1, entry 1). With the corresponding 1-naphthyl N-Boc imine (2b), 85% yield and 96.5:3.5 enantiomeric ratio were obtained (Table 1, entry 2). In this case, a single recrystallization improved the enantiomeric ratio to 99.6:0.4. For the 2-naphthyl and meta-methyl-substituted substrates gave 79% yield and 92.5:7.5 enantiomeric ratio (Table 1, entry 3). For the meta-methyl-substituted N-Boc imine product 4f was isolated in 81% yield and with 94:6 enantiomeric ratio (Table 1, entry 6). With the meta-vinyl-substituted substrate, 95% yield and 95:5 enantiomeric ratio were obtained (Table 1, entry 7). From halogen-substituted substrates, products 4h and 4i were obtained with similarly good yields and enantioselectivities (Table 1, entry 8 and 9). For the 3,5-dimethyl-substituted N-Boc imine 2j, 94% yield and

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Table 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>er b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Me</td>
<td>4e</td>
<td>79</td>
<td>92.5:7.5</td>
</tr>
<tr>
<td>6</td>
<td>MeO</td>
<td>4f</td>
<td>81</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>4g</td>
<td>95</td>
<td>95:5</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>4h</td>
<td>88</td>
<td>91.5:8.5</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>4i</td>
<td>89</td>
<td>92:8</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>4j</td>
<td>94</td>
<td>90:10</td>
</tr>
<tr>
<td>11</td>
<td>MeO</td>
<td>4k</td>
<td>83</td>
<td>93.5:6.5</td>
</tr>
</tbody>
</table>

* Reactions were carried out with 2 (0.1 mmol) and 3 (0.15 mmol) in toluene (1 mL) for 3 d.

** The er was determined by HPLC analysis on a chiral stationary phase using the corresponding ketone.

The absolute configuration was determined by comparing the \([\alpha]_D\) with the reported data.

After a single crystallization from hexane–MTBE (1:1).

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Supporting Information

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References and Notes


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(11) A septum-capped vial with a stirring bar was charged with the corresponding N-Boc imine 2 (0.1 mmol), catalyst 1 (2.8 mg, 2 mol%), and dry toluene (1 mL). The resulting mixture was cooled to -30 °C, before the Chan diene 3 (0.15 mmol) was added via syringe. The reaction mixture was stirred for 3 d. The reaction mixture was quenched by addition of 10% TFA in CH2Cl2 (0.3 mL) at the reaction temperature and diluted with CH2Cl2 (20 mL). The organic phase was washed with sat. NaHCO3 (20 mL) and brine (20 mL). After removing the solvent, the residue was adsorbed onto silica gel and purified by column chromatography (isohexanes–EtOAc, 3:1 to 0:1).