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

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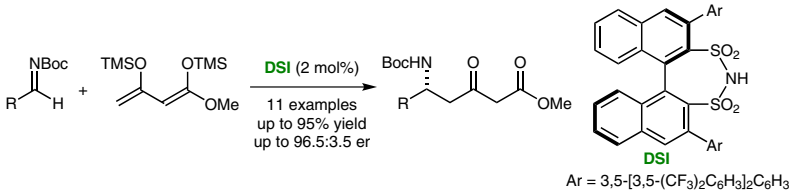

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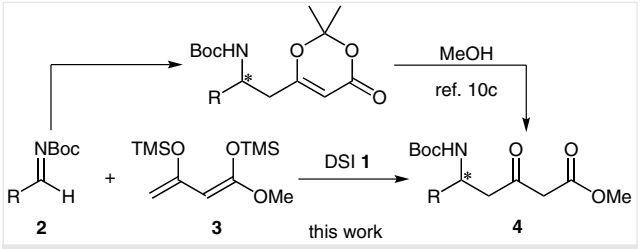
Abstract A chiral disulfonimide-catalyzed asymmetric synthesis of δ-amino-β-keto esters via a vinylogous Mukaiyama–Mannich reaction of the Chan diene with *N*-Boc imines has been developed. The desired products were obtained in good to excellent yields and enantioselectivities.

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



Scheme 1 Direct synthesis of enantioenriched δ-amino-β-keto esters

δ-Amino-β-keto esters are important building blocks[1–3] that are frequently accessed via chain extension of enantiopure β-amino esters[4] 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 reaction[6] of the Chan diene **3**[7] with *N*-Boc imines **2** (Scheme 1).

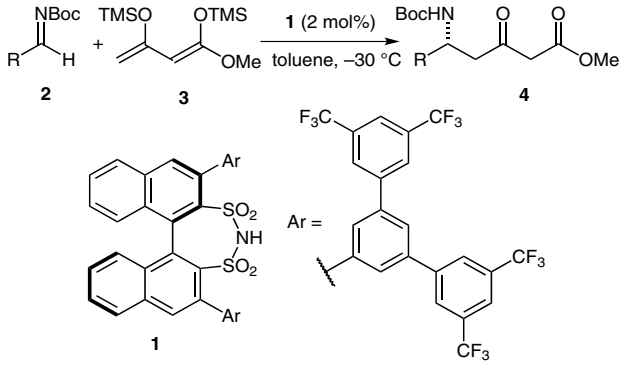
Disulfonimides (DSI), of the general structure **1** (Table 1), are strong Brønsted acids,[8] as well as precatalysts which are converted into highly active Lewis acid catalysts by in situ silylation. These Lewis acids readily activate aldehydes and ketones in various transformations,[9] and we recently reported that they are equally suited for the activation of alkyloxycarbonyl imines. In this context we have developed disulfonimide-catalyzed asymmetric aminoallylations, 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.

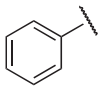
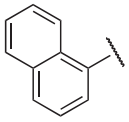
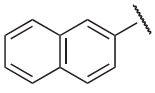
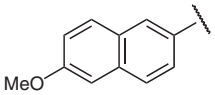
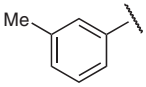
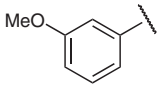
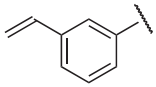
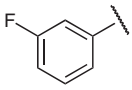
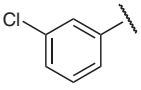
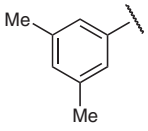
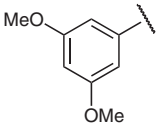
Utilizing similar conditions as in our previous report, we could indeed realize the target reaction. The substrate scope of the DSI-catalyzed vinylogous Mukaiyama–Mannich reaction of Chan's diene is shown in Table 1. From phenyl *N*-Boc imine (**2a**), product **4a** was obtained in 91% yield and with 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 substituted 2-naphthyl *N*-Boc imines, comparably good yields and enantioselectivities were observed (Table 1, entries 3 and 4). The *meta*-methyl-substituted substrate gave 79% yield and 92.5:7.5 enantiomeric ratio (Table 1, entry 5). For the *meta*-methoxy-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

90:10 enantiomeric ratio were observed (Table 1, entry 10). Finally, using 3,5-dimethoxy-substituted *N*-Boc imine, product **4k** was isolated in 83% yield and 93.5:6.5 enantiomeric ratio (Table 1, entry 11). In all cases, the enantioselectivity of the reaction was determined by derivatization as the corresponding ketone, which was obtained via decarboxylation under basic conditions. We have already shown that this procedure does not lead to any loss of enantiopurity.[10c] The absolute configuration was determined by comparing the $[\alpha]_D$ of **4a** with the reported data.[3a]

In summary, a direct organocatalytic asymmetric synthesis of δ-amino-β-keto esters has been developed.[11] Disulfonimide **1** serves as a highly efficient precatalyst of the asymmetric vinylogous Mukaiyama–Mannich reaction of the Chan diene with *N*-Boc imines, giving the δ-amino-β-keto esters with good to excellent yields and enantioselectivities. These results represent a further application of our asymmetric counteranion-directed catalysis (ACDC) strategy applied to Lewis acid catalysis.[12] Further explorations of disulfonimide-catalyzed reactions are currently in progress in our laboratories.

Table 1 DSI-Catalyzed Vinylogous Mannich Reaction[a]



Entry	R	Product	Yield (%)	er[b,c]
1		**4a**	91	93.5:6.5
2		**4b**	85	96.5:3.5 (99.6:0.4)[d]
3		**4c**	84	94:6
4		**4d**	79	92.5:7.5
5		**4e**	79	92.5:7.5
6		**4f**	81	94:6
7		**4g**	95	95:5
8		**4h**	88	91.5:8.5
9		**4i**	89	92:8
10		**4j**	94	90:10
11		**4k**	83	93.5:6.5

[a] Reactions were carried out with **2** (0.1 mmol) and **3** (0.15 mmol) in toluene (1 mL) for 3 d.
[b] The er was determined by HPLC analysis on a chiral stationary phase using the corresponding ketone.
[c] The absolute configuration was determined by comparing the $[\alpha]_D$ with the reported data.
[d] After a single crystallization from hexane–MTBE (1:1).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379999.

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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 resulting reaction mixture was stirred for 3 d. The reaction mixture was quenched by addition of 10% TFA in CH_2Cl_2 (0.3 mL) at the reaction temperature and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with sat. $NaHCO_3$ (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).
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