

Asymmetric Disulfonimide-Catalyzed Synthesis of δ -Amino- β -Ketoester Derivatives by Vinylogous Mukaiyama–Mannich Reactions**

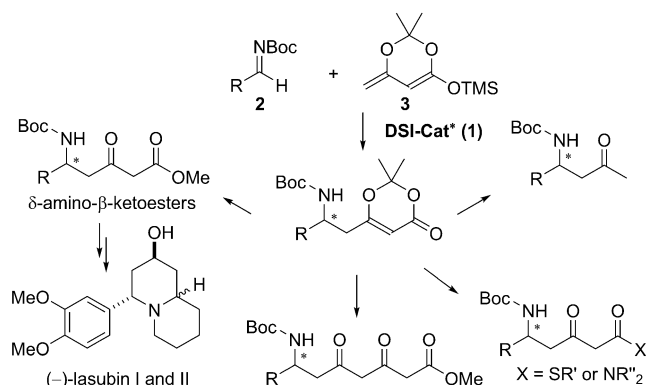
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Abstract: An organocatalytic asymmetric synthesis of δ -amino- β -ketoester derivatives has been developed. A chiral disulfonimide (DSI) serves as a highly efficient precatalyst for a vinylogous Mukaiyama–Mannich reaction of readily available dioxinone-derived silyloxydienes with *N*-Boc-protected imines, delivering products in excellent yields and enantioselectivities. The synthetic utility of this reaction is illustrated in various transformations, including a new C–C bond-forming reaction, which provide useful enantioenriched building blocks. The methodology is applied in a formal synthesis of (–)-lasubin.

δ -Amino- β -ketoesters are useful building blocks, in particular for the synthesis of various piperidine and pyrrolidine alkaloids such as the lasubins.^[1,2] Common methods to access enantiomerically pure δ -amino- β -ketoesters rely on the “chiral pool”^[1,3] or on chiral auxiliaries,^[4] and catalytic asymmetric approaches are very rare.^[5] Here, we report a general and highly enantioselective approach to the synthesis of δ -amino- β -ketoesters by a disulfonimide-catalyzed vinylogous Mukaiyama–Mannich reaction,^[6] utilizing *N*-Boc imines **2** and silyloxydienes **3** as substrates (Scheme 1).

Disulfonimides (DSIs) of the general structure **1** (Table 1) are not only strong Brønsted acids,^[7] but also precatalysts, which become strong Lewis acids upon in situ silylation.^[8] These silicon Lewis acids emerged as powerful catalysts for the activation of aldehydes in Mukaiyama–aldol reactions^[8b] as well as vinylogous and bisvinylogous variants^[8c] and in hetero-Diels–Alder reactions,^[8d] and in methallations.^[8e] Quite recently it was also found that chiral silylated DSIs activate alkoxycarbonyl imines, promoting the corresponding reactions with excellent enantioselectivity.^[9] We therefore hypothesized that our DSIs could potentially catalyze the enantioselective vinylogous Mukaiyama–Mannich reaction, thus offering a general approach for the synthesis of enantiomerically enriched δ -amino- β -ketoesters.

We began our investigations using silyloxydiene **3** and *N*-Boc imine **2a** as model substrates. A systematic screening of



Scheme 1. Approach and synthetic potential of δ -amino- β -ketoesters. Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl.

Table 1: Optimization of the enantioselectivity.

Entry ^[a]	Catalyst	T [°C]	Conv. [%] ^[b]	e.r. ^[c]
1	1a	–30	> 95	89:11
2	1b	–30	> 95	86:14
3	1c	–30	> 95	84:16
4	1d	–30	> 95	86:14
5	1e	–30	> 95	87.5:12.5
6	1f	–30	> 95	73:27
7	1g	–30	> 95	92.5:7.5
8 ^[d]	1g	–30	> 95	89:11
9	1g	–50	> 95	95:5
10 ^[e]	1g	–50	> 95	95:5
11 ^[e]	1g	–78	< 60	95:5

[a] Reactions were carried out with **2a** (0.05 mmol) and **3** (0.075 mmol) in toluene (0.5 mL) for 3 days. [b] Conversions were determined by ¹H NMR analysis by comparing the typical signals of products and hydrolyzed aldehydes. [c] Determined by HPLC analysis on a chiral stationary phase. [d] TBS-protected nucleophile was used. [e] Catalyst loading: 1 mol%.

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the reaction conditions was carried out to optimize the enantioselectivity (Table 1). A solvent screen revealed that toluene is the optimal solvent.^[10] Disulfonimide **1a** could promote the conversion of **2a** to **4a** at -30°C , delivering the desired product with > 95 % conversion and 89:11 e.r. (enantiomeric ratio) in less than three days (entry 1). Of the investigated catalysts **1b–g**, disulfonimide **1g**, with branched 3,3'-substituents, afforded the highest enantioselectivity of 92.5:7.5 e.r. (entries 2–7). The enantioselectivity was slightly lower (89:11 e.r.) when the TBS-protected silyloxydiene was employed (entry 8 versus entry 7). By lowering the temperature to -50°C , the enantioselectivity could be increased to 95:5 e.r. (entry 9). Gratifyingly, when the catalyst loading was lowered to 1 mol%, > 95 % conversion and equally good enantioselectivity could be achieved in less than three days (entry 10). Further cooling to -78°C did not prove useful, as the enantioselectivity remained unchanged, and lower conversion was observed (entry 11).

Under the optimized conditions, the scope of the enantioselective vinylogous Mannich reaction of silyloxydiene **3** catalyzed by disulfonimide **1g** was investigated (Table 2). From benzaldehyde-derived *N*-Boc imine **2a**, product **4a** was obtained with 96 % yield and 95:5 e.r. (entry 1). With naphthyl-substituted *N*-Boc imines, excellent yields and

Table 2: Substrate scope of the vinylogous Mukaiyama–Mannich reaction.

Entry ^[a,b]	R	Product	Yield [%]	e.r. ^[d]
1		4a	96	95:5
2		4b	88	95:5
3		4c	91	99:1
4		4d	98	91:9
5		4e	99	91:9
6		4f	93	95.5:4.5
7		4g	98	89.5:10.5
8		4h	93	95:5
9		4i	90	94:6
10 ^[d]		4j	85	93.5:6.5

Table 2: (Continued)

Entry ^[a,b]	R	Product	Yield [%]	e.r. ^[d]
11		4k	89	98:2
12		4l	96	97.5:2.5
13		4m	94	95:5
14		4n	89	98.5:1.5
15		4o	90	95:5
16		4p	94	94:6
17 ^[e]		4q	96	90:10
18		4r	99	94:6
19		4s	87	90:10
20		4t	80	86.5:13.5
21		4u	89	80:20
22		4v	60	60:40
23		4w	< 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 exclusive formation of γ -products was confirmed by ^1H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration was determined by X-ray crystallographic analysis of **4j** (see the Supporting Information). [e] 1 mol% (*S*)-**1a** was used as catalyst.

enantioselectivities could be obtained (entries 2–4). The influence of the substitution at different positions was investigated next. A *meta*-methyl-substituted substrate reacted with higher enantioselectivity than the *para*-methyl- and *ortho*-methyl-substituted substrates (entry 6 versus entries 5 and 7). The *meta*-methyl product **4f** could be isolated in 93 % yield and with 95.5:4.5 e.r. Substrates bearing halogen substituents provided the corresponding products **4h–j** (entries 8–10) with comparable enantioselectivities. The *meta*-methoxy-substituted *N*-Boc imine proved to be a good substrate, giving **4k** in 89 % yield and with 98:2 e.r. (entry 11). The *meta*-vinyl *N*-Boc imine provided the expected product in 96 % yield and with 97.5:2.5 e.r. (entry 12). With 3,5-dimethyl-substituted *N*-Boc imine, product **4m** was obtained

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