Organocatalysis

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

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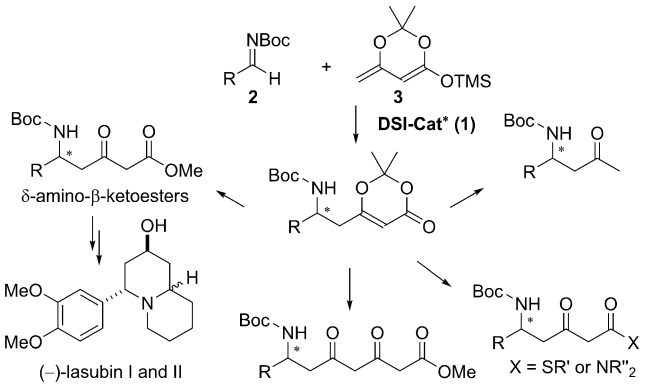
Abstract: *An organocatalytic asymmetric synthesis of δ-amino-β-ketoester derivatives has been developed. A chiral disulfonimide (DSI) serves as a highly efficient precatalyst for a vinylogous Mukaiyama–Mannich reaction of readily available dioxinone-derived silyloxydienes with N-Boc-protected imines, 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).

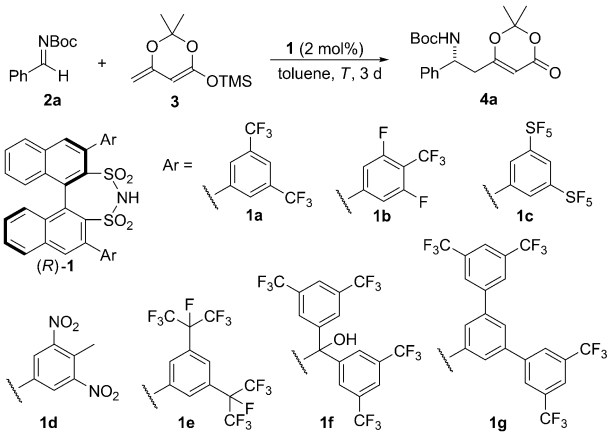
Disulfonimides (DSIs) of the general structure **1** (Table 1) are not only strong Brønsted acids,[7] but also precatalyts, which become strong Lewis acids upon in situ silylation.[8] These silicon Lewis acids emerged as powerful catalysts for the activation of aldehydes in Mukaiyama–aldol reactions[8b] as well as vinylogous and bisvinylogous variants[8c] and in hetero-Diels–Alder reactions,[8d] and in methallylations.[8e] Quite recently it was also found that chiral silylated DSIs activate alkyloxycarbonyl 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 ^{1}H 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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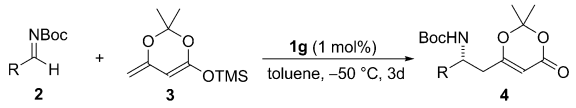
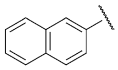
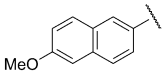
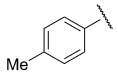
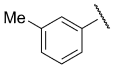
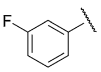
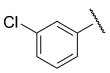
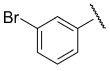
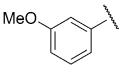
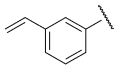
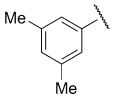
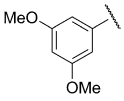
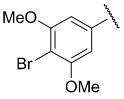
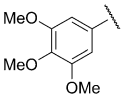
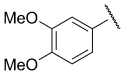
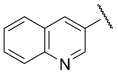
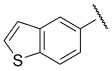
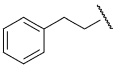
the reaction conditions was carried out to optimize the enantioselectivity (Table 1). A solvent screen revealed that toluene is the optimal solvent.[10] Disulfoniminde **1a** could promote the conversion of **2a** to **4a** at −30 °C, delivering the desired product with >95% conversion and 89:11 e.r. (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 disulfoniminde **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.[c]
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
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	–

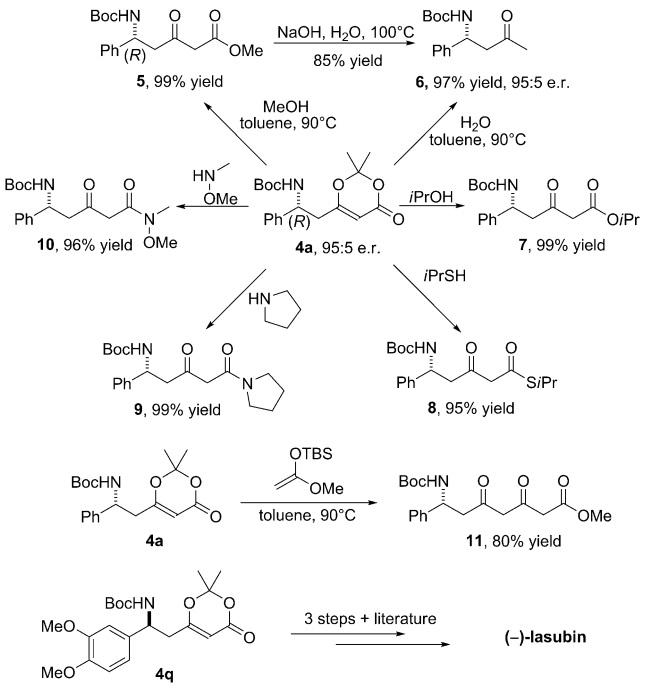
[a] Reactions were carried out with **2** (0.1 mmol) and **3** (0.15 mmol) in toluene (1 mL) for 3 d. [b] The exclusive formation of γ-products was confirmed by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration 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

in 94% yield and with 95:5 e.r. (entry 13). As alkoxy groups are quite common substituents in natural products and their synthesis,[11] several di- and trimethoxy-substituted *N*-Boc imines were tested, and the products **4n–q** were isolated in good yields and with excellent enantioselectivities (entries 14–17). With *N*-Boc imine **2n**, bearing methoxy groups at the 3- and 5-positions, an e.r. as high as 98.5:1.5 could be obtained. 3,4-Dimethoxyimine **2q** reacted to give the enantiomeric product **4q** in 96% yield and with 90:10 e.r. when (*S*)-**1a** served as the catalyst (entry 17). For heterocyclic substrates, the corresponding products were obtained in reasonable to good yields and enantioselectivities. With the quinoline-substituted *N*-Boc imine **2r**, 99% yield and 94:6 e.r. were observed (entry 18). The reaction of the 1-benzothiophene-5-carbaldehyde-derived *N*-Boc imine gave product **4s** in 87% yield and 90:10 e.r. (entry 19). The 2-thiophenyl product **4t** and 3-furyl product **4u** were isolated with lower e.r. (entries 20 and 21). The aliphatic *N*-Boc imines **2v** and **2w** gave disappointingly low yield and e.r. (entries 22 and 23). Further explorations towards the development of a catalytic system suitable for aliphatic substrates are ongoing. The absolute configuration of **4j** was determined to be (*R*) by X-ray crystallographic analysis and all further products were assigned by analogy.

We applied the produced chiral dioxinone derivatives in various versatile transformations giving useful enantiomerically pure building blocks (Scheme 2).[10,12,13] For example, δ-amino-β-ketoester **5** was generated in quantitative yield by treatment of **4a** with MeOH in toluene at 90°C. After extensive experiments, we concluded that no racemization occurred during the process, as the enantiomeric ratio was completely retained even after the further conversion of ester **5** to ketone **6** under basic conditions. β-Aminoketone **6** could also be generated directly from **4a** without any loss of enantiopurity, by utilizing H_2O instead of methanol as nucleophile under the same conditions. Further versatile transformations were conducted, by utilizing similar reaction conditions, but with different nucleophiles including alcohols, amines, and thiols. The corresponding δ-amino-β-ketoester **7**, δ-amino-β-ketothioester **8**, and δ-amino-β-ketoamides **9** and **10** were obtained in excellent yields. Remarkably, when **4a** was treated with a silyl ketene acetal, a C–C bond-forming reaction occurred furnishing ε-amino-δ,β-diketoester **11** in 80% yield. Our methodology was furthermore applied in the formal synthesis of (−)-lasubin starting from **4q** (see the Supporting Information).

In summary, a versatile organocatalytic asymmetric synthesis of δ-amino-β-ketoesters has been developed. Disulfonimide **1g**, which is converted into a strong *Si* Lewis acid under the reaction conditions, serves as a highly efficient precatalyst for the asymmetric vinylogous Mukaiyama–Mannich reaction with silyloxydiene **3**,[14] delivering products in excellent yields and enantioselectivities. Various useful transformations of **4a** have also been developed, thus enabling the synthesis of different enantioenriched amino ketoesters. The methodology has been further applied in a formal synthesis of (−)-lasubin. Our results represent an application of our asymmetric counteranion-directed catalysis (ACDC) strategy to Lewis acid catalysis.[15]



Scheme 2. Versatile transformations providing useful building blocks and the formal synthesis of (−)-lasubin

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