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Disulfonimide-Catalyzed Asymmetric Synthesis of β^3-Amino Esters Directly from *N*-Boc-Amino Sulfones

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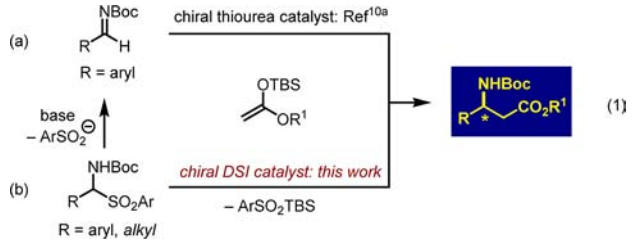
Supporting Information

ABSTRACT: An asymmetric Mannich reaction of silyl ketene acetals with *N*-Boc-amino sulfones has been developed. A chiral disulfonimide efficiently catalyzes both the in situ generation of the corresponding *N*-Boc imines and the asymmetric Mannich reaction with excellent yields and enantioselectivities. Kinetic studies confirm a proposed stepwise mechanism.

β^3-Amino acids have attracted recent attention as constituents of natural products,[1] pharmaceuticals,[2] and peptides with unique properties.[3] Their relevance has stimulated the development of catalytic enantioselective methodologies leading to the β^3-amino acid scaffold, such as additions of acetate enolate equivalents to imines,[4] conjugate additions of amines to unsaturated carbonyls,[5] reductions,[6] and others.[7] Among these methods, the Mannich reaction of imines with silyl ketene acetals is considered particularly attractive, as C−C-bond formation and stereocenter creation coincide.[8,9] An elegant version of this reaction, employing preformed aryl *N*-Boc imines, a synthetic silyl ketene acetal, and a chiral thiourea catalyst was recently reported by Jacobsen et al. (eq 1a).[10] We



report here a complementary approach that directly utilizes *N*-Boc-amino sulfones as electrophiles, a commercially available ketene acetal as the nucleophile, and a new member of our chiral disulfonimide (DSI) catalyst class to deliver high yields of protected aryl and alkyl β^3-amino esters in excellent enantioselectivity (eq 1b).

Disulfonimides of the general structure **1** (Figure 1) have emerged as powerful catalysts for the activation of aldehydes in asymmetric Mukaiyama Aldol reactions,[11a] as well as vinylogous and bisvinylogous variants,[11b] in hetero-Diels−Alder reactions,[11c] and in methallylations.[11d] Kinetic, spectroscopic, and other mechanistic studies have shown that our chiral DSIs are precatalysts that only upon *in situ* silylation become powerful silicon Lewis acid catalysts. We wondered whether or not our DSIs would also catalyze the Mukaiyama−Mannich reaction.

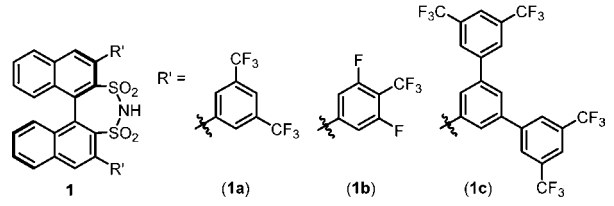
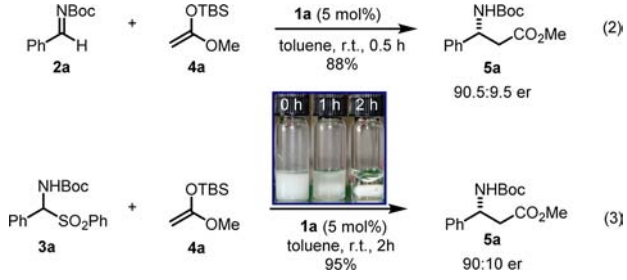


Figure 1. Disulfonimide (DSI) catalysts **1**.

Particularly, we were curious if such Lewis acids could also catalyze the *in situ* formation of *N*-Boc imines from the corresponding amino sulfones, a reaction that is normally mediated by a base.[12]

Our strategy could (1) circumvent this stoichiometric base-mediated process avoiding an entire step and (2) allow for the utilization of *alkyl N*-Boc imines, which are even less stable than the corresponding aryl derivatives. Encouragement came from our recent finding that chiral DSIs catalyze the synthesis of Fmoc-protected homoallylamines from allyl trimethylsilane, the Fmoc carbamate, and an aldehyde via *in situ* imine formation.[13]

Indeed, the Mannich reaction of silyl ketene acetal **4a** with preformed *N*-Boc imine **2a** was readily catalyzed by DSI **1a**, providing product **5a** in 88% yield and 90.5:9.5 er (eq 2).



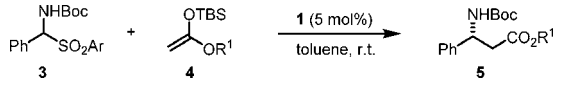
Remarkably, the reaction proceeded equally well and with similar enantioselectivity when we used amino sulfone **3a** directly. The reaction can easily be followed by visual inspection since the almost insoluble amino sulfone disappears upon full conversion (eq 3).

Encouraged by these preliminary results, a systematic exploration of different reaction conditions was conducted to optimize the enantioselectivity (Table 1). A solvent screening revealed toluene to be optimal.[14] Of the investigated catalysts **1a−c**, the new disulfonimide **1c**, bearing a branched 3,3′-substituent, afforded the highest enantioselectivity of 92.5:7.5 er

Received: August 29, 2013
Published: October 3, 2013

   dx.doi.org/10.1021/ja408747m | J. Am. Chem. Soc. 2013, 135, 15334−15337

Table 1. Optimization of the Enantioselectivity



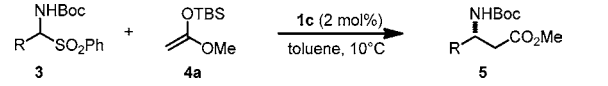
entry[a]	cat.	Ar	R^1	conv. (%)[b]	er[c]
1	**1a**	Ph	Me	>95	90:10
2	**1b**	Ph	Me	>95	85.5:14.5
3	**1c**	Ph	Me	>95	92.5:7.5
4	**1c**	*p*-Me-C_6H_4	Me	>95	91:9
5	**1c**	*p*-OMe-C_6H_4	Me	>95	92:8
6	**1c**	*p*-Cl-C_6H_4	Me	>95	92:8
7	**1c**	Ph	Et	>95	89:11
8	**1c**	Ph	*i*-Pr	>95	81.5:18.5
9	**1c**	Ph	*t*-Bu	>95	89:11
10[d]	**1c**	Ph	Me	>95	94.5:5.5
11[d,e]	**1c**	Ph	Me	>95	94.5:5.5
12[e,f]	**1c**	Ph	Me	>95	95:5

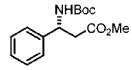
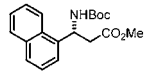
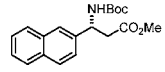
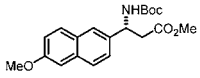
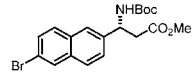
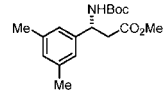
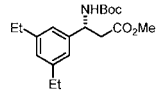
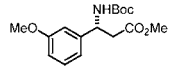
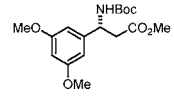
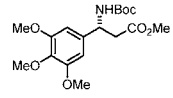
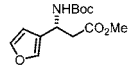
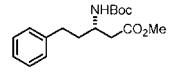
[a]Reactions were carried out with amino sulfone (0.05 mmol) and silyl ketene acetal (0.15 mmol) in toluene (0.5 mL) for 2−72 h. [b]Easily detectable once full homogeneity of the reaction mixture is observed. [c]Determined by HPLC with a chiral stationary phase. [d]The reaction was conducted at 10 °C. [e]2 mol % catalyst. [f]The reaction was conducted at 8 °C; full conversion after 144 h.

(entry 3). We also investigated different sulfone groups (entries 4−6). As anticipated, the effect on the enantioselectivity was marginal, suggesting this group not to be involved in the enantiodiscriminating step. However, in contrast to sulfone **3a** and its electron-poor *p*-Cl-variant, the reaction with the electron-rich *p*-methoxy-substituted sulfone proceeded much faster. Various alkoxy substituents of the silyl ketene acetals were investigated, revealing lower enantioselectivities with increasing bulkiness of the alkoxy group (entry 3 vs entries 7−9). Conveniently, the commercially available silyl ketene acetal **4a** provided the highest enantioselectivity. We also varied the temperature and found that full conversion and 94.5:5.5 er could be achieved at 10 °C in less than 72 h (entry 10). Again full conversion and 95:5 er were obtained at 8 °C after a reaction time of 6 days (entry 12). Lowering the catalyst loading to 2 mol % had no influence on yield and enantioselectivity (entry 11).

The scope of the enantioselective Mannich reaction of the *N*-Boc-amino sulfones catalyzed by disulfonimide **1c** was next investigated under optimized conditions (Table 2). With naphthyl substituted Boc-amino sulfones, excellent yields and enantioselectivities could be obtained, although the 2-naphthyl Boc-amino sulfone requires room temperature (entries 2−3). Electron-donating groups accelerate the reaction while retaining the high enantioselectivity (entries 4 and 6−10). Conversely, the electron-withdrawing 6-Br-2-naphthyl substituent again required room temperature to reach full conversion in 72 h (entry 5). As alkoxy groups are common substituents in natural substances that can possibly be accessed from our products,[15] several different methoxy-substituted substrates were tested. In all cases, the reaction proceeded very well giving the desired products in excellent yields and enantioselectivities (entries 8−10). With heterocyclic substrate **3k**, a 3-furanaldehyde derived Boc-amino sulfone, product **5k** was obtained in 96% yield and with 86:14 er (entry 11). Finally when applying our optimal conditions to an aliphatic substrate, excellent yield and 75.5:24.5 er, was obtained. To the best of our knowledge, this is the first example of a catalytic

Table 2. Substrate Scope of the Asymmetric Mannich Reaction



entry[a]	Product **5**		Yield (%)	er[b]
1[c,d]		**5a**	99	95:5 (>99.5:0.5)[f]
2		**5b**	97	97:3
3[c]		**5c**	95	95.5:4.5
4		**5d**	92	95:5
5[e]		**5e**	94	95.5:4.5
6[c]		**5f**	97	95:5
7[c]		**5g**	98	95:5
8		**5h**	99	96.5:3.5
9		**5i**	92	96.5:3.5
10		**5j**	94	95.5:4.5
11		**5k**	96	86:14
12[d]		**5l**	91	75.5:24.5

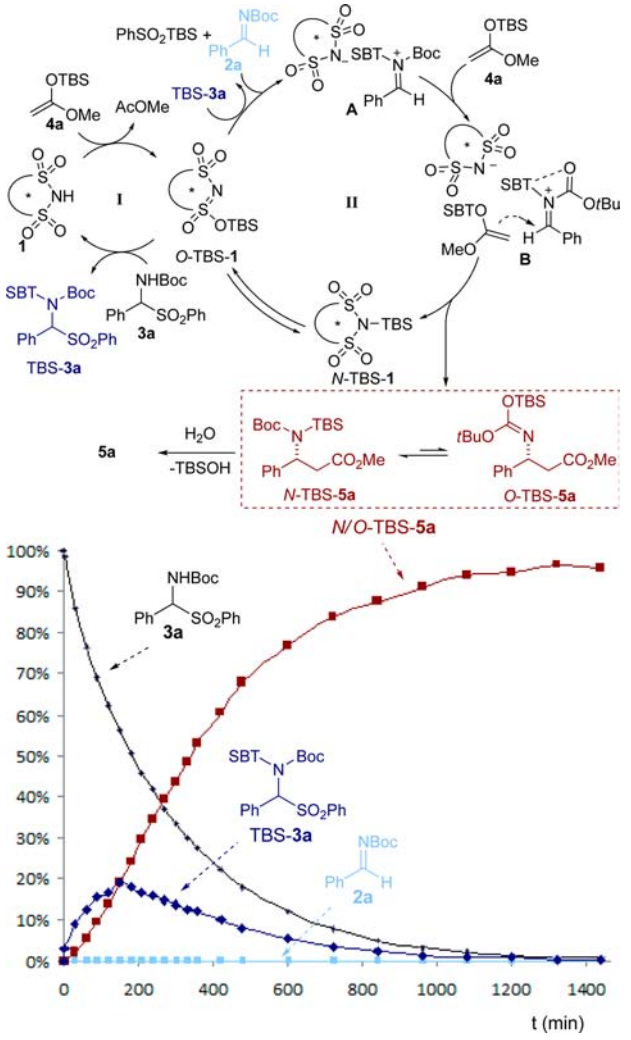
[a]Reactions were carried out with amino sulfone (0.1 mmol) and silyl ketene acetal (0.3 mmol) in toluene (1 mL) for 36−72 h. [b]Determined by HPLC with a chiral stationary phase; the absolute configuration was determined by comparison with literature results. [c]The reaction was conducted at 8 °C. [d]Full conversion after 144 h. [e]The reaction was conducted at rt. [f]After single crystallization from MTBE.

asymmetric Mannich reaction with a silyl ketene acetal, which affords aliphatic Boc-protected β^3-amino acid derivatives (entry 12). Nonetheless, further catalyst explorations are expected to lead to an optimized protocol for aliphatic substrates.

A mechanism that is consistent with our experimental data and careful NMR spectroscopic studies is proposed in Scheme 1. Accordingly, disulfonimide **1** is initially silylated from ketene acetal **4a** predominantly on oxygen to generate the corresponding Lewis acid *O*-TBS-**1**. Interestingly, this catalyst

dx.doi.org/10.1021/ja408747m | J. Am. Chem. Soc. 2013, 135, 15334−15337

Scheme 1. Proposed Catalytic Cycle and ^{1}H NMR Kinetic Study



rapidly silylates sulfone **3a** to the corresponding *N*-silyl derivative TBS-**3a** (cycle **I**). A small but detectable quantity of *N*-Boc-imine **2a** is then generated via a slow and apparently rate determining elimination of $PhSO_2TBS$ from silylated sulfone **3a**, initiating catalytic cycle II. Expectedly, the rate of this slow step is influenced by the electronic properties of the sulfones (entries 3 and 4−6, Table 1). The elimination should predominantly lead to ion pair equivalent **A**, which together with the ketene acetal then assembles transition state **B**. A 4.5:1 mixture of the two silylated Mannich products *N*-TBS-**5a** and *O*-TBS-**5a** results from this reaction at 0 °C in $CDCl_3$. Under these conditions, no obvious equilibration between the two isomers takes place, but after two days at room temperature their ratio will change to >20:1 in $CDCl_3$ and d_8-toluene, suggesting intermediate *N*-TBS-**5a** to be thermodynamically favored.[16] A similar product mixture is generated in a 5.7:1 ratio when product **5a** was treated with TBSOTf and NEt_3 in $CDCl_3$ at room temperature. The formation of both product isomers TBS-**5a** occurred in parallel with the consumption of starting material **3a**. Both intermediate TBS-**3a** and trace amounts of imine **2a** are only observable while the reaction is in progress. They completely disappear upon full conversion.[14]

In summary, the first asymmetric Mannich reaction with silyl ketene acetals, directly from *N*-Boc-amino sulfones, has been developed in our laboratories. Disulfonimide **1c**, which is transformed into a powerful *Si*-Lewis acid, serves as an efficient precatalyst for the asymmetric Mannich reaction with silyl ketene acetals, giving excellent yields and enantioselectivities. Our methodology represents an application of asymmetric counteranion-directed catalysis (ACDC) in Lewis acid catalysis.[17] A stepwise mechanism is proposed based on experimental observations and a ^{1}H NMR kinetic study. Attractive features of our approach include (1) use of a commercially available ketene acetal, (2) easier handling of stable *N*-Boc-amino sulfones (including an aliphatic one) in comparison to the corresponding imines, (3) saving one normally required step, (4) convenient reaction monitoring by visually following homogenization with conversion, (5) a low catalyst loading, and (6) easy to crystallize products. Further exploration of chiral DSI-catalyzed reactions is currently in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all compounds, and detailed information on our mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support by the Max-Planck-Society, and the Fonds der Chemischen Industrie (fellowship to M.v.G.) before is greatfully acknowledged. The project "Sustainable Chemical Synthesis" (SusChemSys) (co-financed by the European Regional Development Fund (ERDF) and the state of North Rhine-Westphalia, Germany, under the Operational Programme "Regional Competitiveness and Employment" 2007 - 2013). The European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT") is gratefully acknowledged.

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