

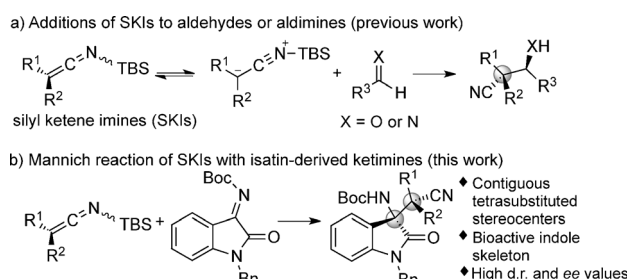
Enantioselective Construction of Vicinal Tetrasubstituted Stereocenters by the Mannich Reaction of Silyl Ketene Imines with Isatin-Derived Ketimines*

Jiannan Zhao, Bing Fang, Weiwei Luo, Xiaoyu Hao, Xiaohua Liu, Lili Lin, and Xiaoming Feng*

Abstract: A highly enantioselective Mannich reaction of silyl ketene imines with isatin-derived ketimines has been realized by using a chiral N,N' -dioxide/ Zn^{II} catalyst. A variety of β -amino nitriles containing congested vicinal tetrasubstituted stereocenters were obtained with excellent outcomes (up to 98 % yield, > 19:1 d.r. and 99 % ee). Based on the experimental investigations, a possible transition state has been proposed to explain the origin of the asymmetric induction.

The catalytic asymmetric construction of vicinal tetrasubstituted stereogenic centers is of great interest to synthetic chemists because of the prevalence of such structural motifs in natural products and bioactive compounds.^[1–3] However, the rapid and selective assembly of them is difficult because the steric congestion affects the formation of the C–C bond. Only a few methods, such as alkylation^[2] and cycloaddition reactions,^[3] have been reported to provide reliable approaches towards the construction of vicinal tetrasubstituted stereocenters in a catalytic asymmetric manner. In recent years, a series of α,α -disubstituted enolates and their synthetic equivalents have been developed, and remarkable advances were made in the area of constructing tetrasubstituted stereogenic carbon atoms.^[4–6] Among them, it is noteworthy that the groups of Shibasaki and Yuan found the additions of α -substituted α -isothiocyanato esters to ketones and ketimines to be a promising way for the construction of contiguous tetrasubstituted stereocenters.^[4d–f]

Silyl ketene imines (SKIs),^[5] which are a class of α,α -disubstituted nucleophiles, have been recognized as highly useful reactants since Fu et al. reported the asymmetric acylation of SKIs for the first time (Scheme 1a).^[6] The resulting nitriles are versatile synthetic intermediates, which enable facile transformations into a range of functional scaffolds. In the past decade, the group of Denmark demon-



Scheme 1. Construction of tetrasubstituted stereogenic centers in the addition of silyl ketene imines to electrophiles. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

strated the synthetic potential of SKIs in chiral Lewis base catalyzed asymmetric aldol reactions of aldehydes.^[6c–e] Recently, the additions of SKIs to aldimines were described by both the group of Leighton and our group.^[6g–i] Nevertheless, daunting challenges remain in the asymmetric additions of SKIs to ketones and ketimines (Scheme 1b). The corresponding processes become more complicated when a second vicinal tetrasubstituted center is present in the synthetic target. Thus, to develop a suitable catalyst with efficient enantiotopic face selectivity is essential for achieving high levels of diastereo- and enantioselectivity for the non-hydrogen substituted reactant. In light of the high synthetic value of enantioenriched β -amino nitriles with vicinal tetrasubstituted stereogenic centers,^[7] we decided to further investigate the unprecedented Mannich reactions^[8] of SKIs with isatin-derived ketimines catalyzed by chiral N,N' -dioxide/metal complexes.^[9]

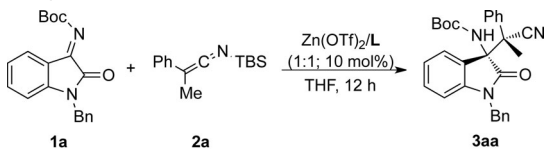
We chose the isatin-derived *N*-Boc ketimine **1a**^[10] as the model substrate (Table 1), considering that 3-aminooxindoles have been treated as the core structure in a variety of bioactive molecules.^[11] Initially, the Mannich reaction of SKI **2a** was performed in THF at 30 °C with 10 mol % catalyst prepared in situ from the N,N' -dioxide ligand L-PrPr₂ and Zn(OTf)₂. Pleasingly, the desired β -amino nitrile **3aa** was obtained in good yield with 43 % ee (entry 1). Decreasing the steric hindrance of the amide substituents improved the diastereoselectivity (entry 2 versus entry 1). As for the chiral backbone moiety, the N,N' -dioxide L-PrPh, derived from L-proline, exhibited a better result than L-PiPh and L-RiPh (entries 3 and 4). In addition, lowering the temperature to –45 °C led to a significant improvement in the diastereo- and enantioselectivity of **3aa** (entry 5). Importantly, the catalyst loading could be reduced to 2.5 mol % without any loss in the stereoselectivity and yield (entry 6).

[*] J. N. Zhao, B. Fang, W. W. Luo, X. Y. Hao, Prof. Dr. X. H. Liu, Dr. L. L. Lin, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry, Sichuan University
Chengdu 610064 (China)
E-mail: xmfeng@scu.edu.cn
Prof. Dr. X. M. Feng
Collaborative Innovation Center of Chemical Science
and Engineering, Tianjin (China)

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Table 1: Optimization of the reaction conditions.



1a + 2a $\xrightarrow{\text{Zn(OTf)}_2/\text{L} (1:1, 10 \text{ mol\%})}$ 3aa

THF, 12 h

L-PrPr₂: *n* = 1; Ar = 2,6-*i*-Pr₂C₆H₃
 L-PrPh: *n* = 1; Ar = C₆H₅
 L-PiPh: *n* = 2; Ar = C₆H₅

Entry ^[a]	L	T [°C]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	L-PrPr ₂	30	98	3:1	43
2	L-PrPh	30	98	11:1	46
3	L-PiPh	30	98	2.5:1	24
4	L-RiPh	30	98	5.5:1	8
5	L-PrPh	−45	98	> 19:1	99
6 ^[e]	L-PrPh	−45	98	> 19:1	99

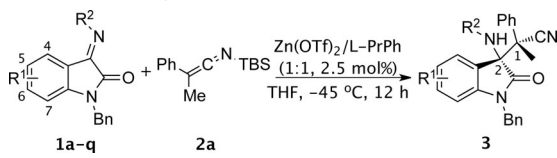
[a] Unless otherwise noted, the reactions were performed with Zn(OTf)₂/L (10 mol%), **1a** (0.10 mmol), **2a** (0.20 mmol) in 1.0 mL THF. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy and HPLC analysis using a chiral stationary phase. [d] Determined by HPLC analysis using a chiral stationary phase. [e] 2.5 mol% catalyst, 0.5 mL THF. Tf = trifluoromethanesulfonyl.

With the optimized reaction conditions in hand, we firstly investigated the reactions between various isatin-derived ketimines and **2a** (Table 2). To our delight, other *N*-alkoxy-carbonyl ketimines gave the products **3ba** and **3ca** with excellent results when the reaction temperature was lowered to −78 °C (entries 2 and 3). Further exploration of the reaction scope was focused on varying the substituents on the isatin-derived ketimines. The electronic nature and the position of the substituents on isatin backbones had little influence on both the yields and the stereoselectivities (93–98% yield, > 19:1 d.r., and 97–99% ee; entries 4–17). Additionally, the absolute configuration of the product **3fa** was determined to be (1*S*, 2*R*) by X-ray crystallography.^[12]

To further elaborate on the scope of this reaction, this approach was extended to the reactions of multiple kinds of silyl ketene imines in the presence of 10 mol% catalyst (Table 3).^[13] Delightfully, SKIs with ethyl or allyl substituents were found to be suitable nucleophiles in this system (entries 2 and 3). The electronic properties and positions of the substituents on the aryl group of the SKIs had a slight influence on the reaction outcomes (entries 4–13). Notably, fused-ring and thiophene-substituted SKIs successfully participated in the reaction to afford the corresponding adducts in good yields with excellent stereoselectivities (entries 14–17). It is worth pointing out that the catalyst system was also efficient when the cyclohexane-derived SKI **2r** was used as the nucleophile (entry 18).

Furthermore, when the reaction of **1a** was carried out on a gram scale, a 98% yield (1.37 g), greater than 19:1 d.r., and 98% ee was still obtained (Table 3, entry 19). In contrast, manipulations of the cyano group offers opportunities to generate other functionalized 3-amino oxindole derivatives.

Table 2: Substrate scope for ketimines.



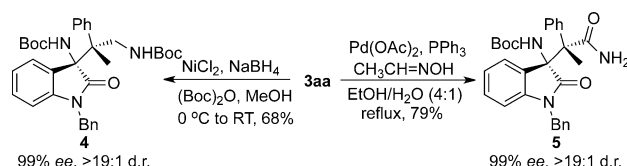
1a-q + 2a $\xrightarrow{\text{Zn(OTf)}_2/\text{L-PrPh} (1:1, 2.5 \text{ mol\%})}$ 3

THF, −45 °C, 12 h

Entry ^[a]	R ¹	R ²	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	H	Boc	98 (3aa)	> 19:1	99
2 ^[e,f]	H	EtO ₂ C	93 (3ba)	> 19:1	91
3 ^[e,f]	H	Cbz	96 (3ca)	> 19:1	97
4	5-F	Boc	93 (3da)	> 19:1	99
5	5-Cl	Boc	98 (3ea)	> 19:1	99
6	5-Br	Boc	96 (3fa)	> 19:1	99 (1 <i>S</i> , 2 <i>R</i>) ^[g]
7	5-I	Boc	98 (3ga)	> 19:1	98
8	5-Me	Boc	98 (3ha)	> 19:1	99
9	5-MeO	Boc	97 (3ia)	> 19:1	99
10 ^[e]	5-F ₃ CO	Boc	93 (3ja)	> 19:1	97
11	6-Cl	Boc	97 (3ka)	> 19:1	99
12	6-Br	Boc	95 (3la)	> 19:1	98
13	7-F	Boc	98 (3ma)	> 19:1	99
14	7-Cl	Boc	97 (3na)	> 19:1	99
15	7-Br	Boc	98 (3oa)	> 19:1	99
16	7-F ₃ C	Boc	93 (3pa)	> 19:1	98
17	5,7-Me ₂	Boc	97 (3qa)	> 19:1	98

[a] Unless otherwise noted, the reactions were performed with Zn(OTf)₂/L-PrPh (2.5 mol%), **1** (0.10 mmol), **2a** (0.20 mmol) in 0.5 mL THF. [b] Yield of isolated product. [c] Determined by ¹H NMR analysis. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Using 10 mol% catalyst in 1.0 mL THF. [f] The reaction was performed at −78 °C for 24 h. [g] The absolute configuration was determined by X-Ray analysis. Cbz = carbobenzyloxy.

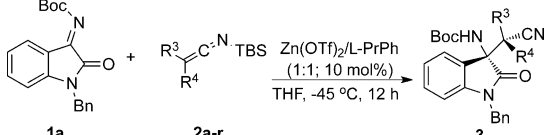
As shown in Scheme 2, the product **3aa** could be efficiently converted into the useful 1,3-diamine **4** through reduction using NaBH₄.^[14] And hydrolysis of the cyano group using Pd(OAc)₂, PPh₃, and acetaldehyde oxime in refluxing aqueous EtOH gave the β-amino amide **5**,^[15] which is the analogous structure of AG-041R.^[11b]



Scheme 2. Further transformations of the products.

To gain insight into the mechanism, the relationship between the ee value of the ligand L-PrPh and that of **3aa** was studied under the optimal reaction conditions.^[16] A linear effect^[17] was observed, thus suggesting that a monomeric catalyst may be the main catalytic active species. In light of the X-ray structure of **3fa** and our previous work,^[9] a proposed stereochemical model was illustrated in Figure 1. The isatin-derived ketimine **1a** could be activated after coordinating to the zinc atom in a bidentate fashion. Based on the absolute configuration of the product **3**, we postulate that the steric hindrance between the *N*-Boc group of the ketimine and one azacycle of the ligand makes intermediate **A2**

Table 3: Substrate scope for silyl ketene imines.



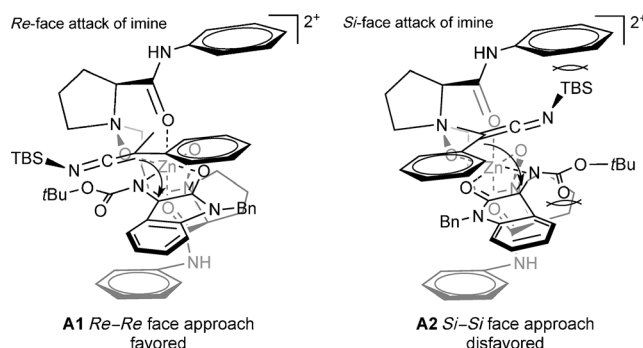
Entry ^[a]	R ³	R ⁴	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	Ph	Me	98 (3aa)	> 19:1	99
2	Ph	Et	92 (3ab)	> 19:1	97
3	Ph	allyl	95 (3ac)	> 19:1	99
4 ^[e]	2-MeC ₆ H ₄	Me	90 (3ad)	> 19:1	94
5	3-MeC ₆ H ₄	Me	98 (3ae)	> 19:1	99
6	4-MeC ₆ H ₄	Me	98 (3af)	> 19:1	99
7	2-MeOC ₆ H ₄	Me	98 (3ag)	> 19:1	98
8	3-MeOC ₆ H ₄	Me	95 (3ah)	> 19:1	98
9	4-MeOC ₆ H ₄	Me	97 (3ai)	> 19:1	99
10	3-ClC ₆ H ₄	Me	98 (3aj)	> 19:1	98
11	4-ClC ₆ H ₄	Me	96 (3ak)	> 19:1	95
12	3-BrC ₆ H ₄	Me	98 (3al)	> 19:1	98
13	4-BrC ₆ H ₄	Me	97 (3am)	> 19:1	96
14 ^[e]	1-naphthyl	Me	78 (3an)	> 19:1	93
15	2-naphthyl	Me	98 (3ao)	> 19:1	98
16	2-thienyl	Me	93 (3ap)	> 19:1	99
17	3-thienyl	Me	98 (3aq)	> 19:1	99
18 ^[f]	-(CH ₂) ₅ -		93 (3ar)	–	95
19 ^[g]	Ph	Me	98 (3aa)	> 19:1	98

[a] Unless otherwise noted, the reactions were performed with Zn(OTf)₂/L-PrPh (10 mol %), **1a** (0.10 mmol), **2** (0.20 mmol) in 1.0 mL THF.

[b] Yield of isolated product. [c] Determined by ¹H NMR analysis.

[d] Determined by HPLC analysis using a chiral stationary phase.

[e] Reaction time was 36 h. [f] The reaction was performed at –78 °C for 24 h. [g] The reaction was carried out on a gram scale with 3.00 mmol **1a**.


Figure 1. Proposed stereochemical model.

unfavorable. The SKI would attack from the *Re* face of the ketimine, because the *Si* face is shielded by the neighboring amide group of the ligand (model **A1**). The prochiral face of **2a**^[18] is probably differentiated by the repulsive interaction between the TBS group of the SKI and the aryl group of the ligand (Figure 1; **A1** versus **A2**). It would thus appear that the *Re* face of the SKI readily attacks the *Re* face of the ketimine to afford the (1*S*,2*R*)-product.

In summary, a highly diastereo- and enantioselective method for the synthesis of vicinal tetrasubstituted stereocenters was realized through the Mannich reaction of SKIs with isatin-derived ketimines. In the presence of a chiral *N,N'*-

dioxide/Zn^{II} complex, the desired functionalized 3-amino oxindoles were obtained in excellent yields (up to 98 %) and extremely high stereoselectivities (up to >19:1 d.r. and 99 % ee). In particular, this new process proceeds under mild reaction conditions and exhibits broad substrate scope and functional-group tolerance. Ongoing studies are focused on the reaction of SKIs with other classes of electrophiles such as ketones and α,β -unsaturated carbonyl compounds.

Experimental Section

Preparation of the chiral catalyst solution: L-PrPh (9.0 mg, 0.02 mmol) and Zn(OTf)₂ (7.2 mg, 0.02 mmol) were stirred in 4.0 mL of THF at 30 °C for 30 min.

Mannich reaction of SKI **2a** with ketimine **1a**: The reaction was performed with **1a** (33.6 mg, 0.1 mmol) and the chiral catalyst solution prepared beforehand (0.0025 mmol Zn(OTf)₂/L-PrPh in 0.5 mL of THF, 2.5 mol % catalyst loading) under nitrogen in a dry reaction tube. **2a** (2.0 equiv) was added to the reaction mixture at –45 °C. Then the reaction was stirred at –45 °C for 12 h. After complete consumption of the starting materials, the mixture was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate 7:1) to afford **3aa** (45.8 mg, 98 % yield) as a white solid.

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