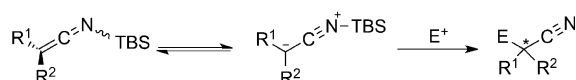


Asymmetric Synthesis of β -Amino Nitriles through a Sc^{III} -Catalyzed Three-Component Mannich Reaction of Silyl Ketene Imines**

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Dedicated to Professor Zhi-Tang Huang on the occasion of his 85th birthday

Chiral β -amino nitriles are versatile synthetic intermediates that are readily transformed into optically active compounds such as β -amino acids, and 1,3-diamines.^[1] The asymmetric addition of alkyl nitriles to imines provides a straightforward route to such compounds.^[2] Although many methods for the asymmetric Mannich reaction have been described,^[3] the use of less nucleophilic alkyl nitriles as the nitrile species is a continuing challenge;^[4–6] one reason for this issue is the poor acidity of the α protons of alkyl nitriles.^[5,6] One strategy to solve this problem is the use of an *N*-metalloketene imine, generated from cyanocarboxylic acid or benzyl nitrile, as an active intermediate; two catalytic asymmetric systems have been reported for such Mannich reactions.^[4b,d] As an alkyl nitrile equivalent, silyl ketene imines^[7] (SKIs) are competent nucleophiles that can react to form C-substituted nitriles (Scheme 1). Moreover, owing to their unique structure and



Scheme 1. The synthesis of nitriles with a quaternary stereogenic center by the addition of silyl ketene imines to electrophiles. TBS = *tert*-butyldimethylsilyl.

ready racemization, SKIs are attractive substrates for the construction of vicinal tertiary and quaternary stereogenic carbon centers,^[8] which are difficult to synthesize.^[9]

Since Fu and co-workers reported the first asymmetric acylation of SKIs,^[10a] they have become attractive nucleophiles for asymmetric catalytic reactions.^[10] The asymmetric aldol-type reaction of SKIs has been reported.^[10b,c,e] However, there is only a limited number of examples of the asymmetric addition of SKIs to aldimines and the addition of SKIs to similar substrates has proven somewhat more difficult to

achieve and is generally characterized by a narrow substrate scope; the only asymmetric system, which uses stoichiometric quantities of a chiral silicon Lewis acid as the promoter, was reported by Leighton and co-workers.^[11] Therefore, the development of a general and efficient asymmetric Mannich reaction of SKIs is particularly desirable. We have recently developed chiral *N,N'*-dioxide/metal catalysts, which we used for a variety of asymmetric transformations,^[12] one of which is the three-component,^[13] one-pot addition of *N*-aryl imines.^[14] Herein, we describe a practical and highly efficient Mannich reaction of SKIs to address the challenges mentioned above. A three-component, one-pot method involving the use of a chiral *N,N'*-dioxide scandium(III) catalyst under mild reaction conditions was developed for the synthesis of β -amino nitriles. The desired products, which contain a quaternary stereogenic center, were generated in excellent yield and stereoselectivity (up to 95% yield, >95:5 d.r., 97% *ee*). The procedure is convenient as no exclusion of air and moisture is required.

In the initial study, the reaction between aldimine **1a**^[15] and SKI **2a** was performed in EtOAc at -20°C with 10 mol % of a Lewis acid catalyst, which was prepared *in situ* from $\text{Sc}(\text{OTf})_3$ and chiral *N,N'*-dioxide ligand **L1**. The desired β -amino nitrile **3a** was obtained in moderate yield and enantioselectivity and extremely low diastereoselectivity (56:44 d.r.; Table 1, entry 1). A change in the chiral backbone of the ligand affected both the enantio- and diastereoselectivity of the reaction. As shown in Table 1, the use of ligand **L3**, derived from *L*-ramipril, gave a superior result (82% yield, 64:36 d.r., and 77% *ee*) than the use of those derived from *L*-pipecolic acid (**L1**) and *L*-proline (**L2**; Table 1, entry 3 versus entries 1 and 2). The unsatisfactory diastereoselectivity prompted us to investigate other *N,N'*-dioxides (see the Supporting Information for details). Pleasingly, the use of bulky ligand **L4**, bearing isopropyl groups at the *ortho* and *para* positions of the aniline moiety, resulted in an enhanced diastereomeric ratio of 72:28 (Table 1, entry 4).

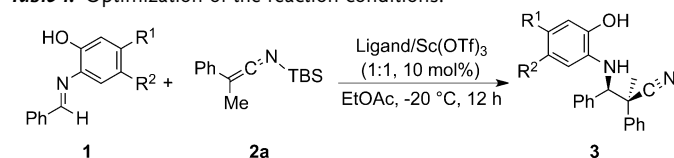
Investigations into the use of an additive showed that bases played an important role in improving both the diastereo- and enantioselectivity (Table 1, entries 5–7). To our delight, the use of 20 mol % of *i*PrNH₂ as the additive resulted in a dramatic improvement in the catalytic efficiency (82:18 d.r. and 91% *ee*; Table 1, entry 7). It was envisioned that bases might facilitate the deprotonation of aldimine **1**, thereby making it easier for it to coordinate with the Sc^{III} center in a bidentate fashion. The substituent on the phenol protecting group of the imine also influenced the diastereoselectivity (Table 1, entries 8–10). When imine **1c** was used

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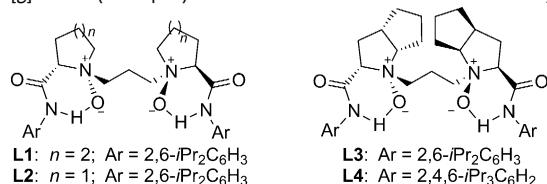
Table 1: Optimization of the reaction conditions.^[a]



- 1a:** R¹ = H, R² = H
1b: R¹ = Me, R² = H
1c: R¹ = H, R² = Me
1d: R¹ = H, R² = Cl

Entry	Ligand	1	Additive	Yield [%] ^[b]	ee [%] ^[c]	d.r. ^[c]
1	L1	1a	—	72	57	56:44
2	L2	1a	—	77	60	62:38
3	L3	1a	—	82	77	64:36
4	L4	1a	—	78	70	72:28
5	L4	1a	Et ₃ N	70	81	77:23
6	L4	1a	<i>i</i> Pr ₂ NH	82	74	71:29
7	L4	1a	<i>i</i> PrNH ₂	83	91	82:18
8	L4	1b	<i>i</i> PrNH ₂	71	87	80:20
9	L4	1c	<i>i</i> PrNH ₂	89	93	92:8
10	L4	1d	<i>i</i> PrNH ₂	67	87	85:15
11 ^[d]	L4	1c	<i>i</i> PrNH ₂	84	93	90:10
12 ^[e]	L4	1c	<i>i</i> PrNH ₂	87	92	92:8
13 ^[e,f]	L4	1c	<i>i</i> PrNH ₂	92	95	92:8
14 ^[e,g]	L4	1c	<i>i</i> PrNH ₂	85	91	91:9

[a] Unless otherwise noted, all reactions were carried out with imine **1** (0.1 mmol), SKI **2a** (0.2 mmol) and additive (none or 20 mol%) in EtOAc (1.0 mL) under nitrogen at −20 °C for 12 h. [b] Yields are of the isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at −40 °C. [e] The reaction was carried out under air. [f] The imine **1c** was generated in situ from benzaldehyde (0.12 mmol) and 2-amino-4-methylphenol (0.10 mmol). [g] Water (1.0 equiv) was added. Tf = trifluoromethanesulfonyl.

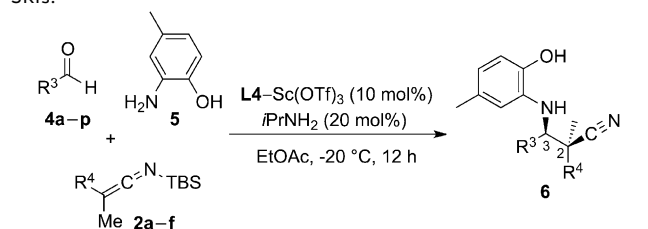


instead of **1a** as the electrophile, the diastereomeric ratio was improved to 92:8 (Table 1, entry 9 versus entry 7). Similar results were obtained when the reaction was performed at lower temperature (Table 1, entry 11). In established methods for reactions involving the use SKI as a nucleophile, an anhydrous atmosphere of inert gas is usually required.^[10,11] However, in this case, we found that the catalytic system was sensitive to neither atmospheric oxygen nor moisture (Table 1, entry 12), thus making the protocol operationally simpler and convenient. Owing to the importance of step economy, the imine **1c** was generated in situ from the corresponding aldehyde and aminophenol. Remarkably, the three-component method was more efficient than the two-step reaction, and gave the desired β-amino nitrile **3c** in 92 % yield with 95 % ee and 92:8 d.r. (Table 1, entry 13). The addition of water to the reaction system resulted in a slight decrease in yield and stereoselectivity (Table 1, entry 14).

With the optimized reaction conditions established, the substrate scope was investigated (Table 2). A wide range of

aldehydes are suitable substrates for the reaction of α-methyl-α-phenyl silyl ketene imine **2a**, and excellent diastereo- and enantioselectivity was achieved in most cases (Table 2, entries 1–16). The reactions of imines derived from elec-

Table 2: Substrate scope for the three-component Mannich reaction of SKIs.^[a]



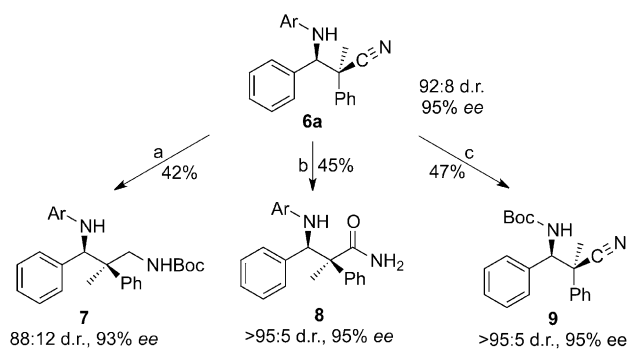
Entry	R ³	R ⁴	Yield (6) [%] ^[b]	ee [%] ^[c]	d.r. ^[c]
1	Ph	Ph	92 (6a)	95	92:8
2	2-MeC ₆ H ₄	Ph	77 (6b)	95	97:3
3	3-MeC ₆ H ₄	Ph	85 (6c)	94	90:10
4	4-MeC ₆ H ₄	Ph	94 (6d)	93	94:6
5 ^[d]	3-MeOC ₆ H ₄	Ph	94 (6e)	89	89:11
6	4-MeOC ₆ H ₄	Ph	79 (6f)	97	95:5
7	2-ClC ₆ H ₄	Ph	95 (6g)	94	95:5
8	3-ClC ₆ H ₄	Ph	82 (6h)	92	90:10
9 ^[d]	4-ClC ₆ H ₄	Ph	95 (6i)	94	90:10
10 ^[d]	2-BrC ₆ H ₄	Ph	96 (6j)	93	95:5
11	3-BrC ₆ H ₄	Ph	93 (6k)	94	90:10
12	4-BrC ₆ H ₄	Ph	91 (6l)	94	94:6
13	1-naphthyl	Ph	91 (6m)	96 ^[e]	98:2
14	2-naphthyl	Ph	88 (6n)	96	97:3
15	3-furyl	Ph	87 (6o)	77	80:20
16 ^[f]	cyclohexyl	Ph	65 (6p)	89	90:10
17 ^[d]	Ph	3-MeC ₆ H ₄	88 (6q)	92	91:9
18 ^[d]	Ph	4-MeOC ₆ H ₄	80 (6r)	90	94:6
19	Ph	4-ClC ₆ H ₄	95 (6s)	92	98:2
20	Ph	2-BrC ₆ H ₄	87 (6t)	93	99:1
21 ^[d]	Ph	4-BrC ₆ H ₄	88 (6u)	92	94:6

[a] Unless otherwise noted, all reactions were carried out under the optimized conditions for 12 h. [b] Yields are of the isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The ee value and d.r. of the β-amino nitriles were determined by HPLC analysis of the corresponding *p*-toluenesulfonyl-protected derivatives. [e] The absolute configuration of **6m** was determined to be 2*S*,3*R* (see the Supporting Information for details). [f] Reaction was carried out for 4 h.

tron-rich and electron-deficient aromatic aldehydes gave the desired products in good yield and enantioselectivity (89–97 % ee; Table 2, entries 2–12). The diastereoselectivity was influenced a little by the position of the substituents on the aromatic ring of the aldehydes. Generally, *ortho*-substituted aromatic aldehydes gave the desired products with better diastereoselectivity (Table 2, entries 2, 7, and 10) than the *meta*-substituted ones (Table 2, entries 3, 5, 8, and 11). Notably, fused-ring aromatic aldehydes successfully participated in the reaction to afford the respective products **6m** and **6n**, in high yields with >95:5 d.r. and 96 % ee (Table 2, entries 13 and 14). A heteroaromatic aldehyde was also tolerated, and the corresponding adduct was obtained in high yield with good diastereo- and enantioselectivity (Table 2, entry 15). The catalyst system was also effective when the

imine was derived from cyclohexylaldehyde (Table 2, entry 16). Linear aliphatic aldehydes were unreactive.^[16] Next, we investigated the scope of the Mannich reaction with respect to the variation of the aryl group of the silyl ketene imine. Electron-rich and electron-poor silyl ketene imines with different substituents on the aromatic ring were prepared and tested in the transformation. Pleasingly, each SKI was found to be a suitable nucleophile in this system, and the corresponding β -amino nitriles were obtained in good yields (80–95 %) with excellent diastereo- and enantioselectivities (90–93 % *ee*, 91:9–99:1 d.r.; Table 2, entries 17–21). In addition, the absolute configuration of the adduct **6m** was unambiguously determined to be 2*S*,3*R* by single-crystal X-ray diffraction analysis of the *p*-toluenesulfonyl-protected β -amino nitrile Ts-**6m** (see the Supporting Information for details).^[17]

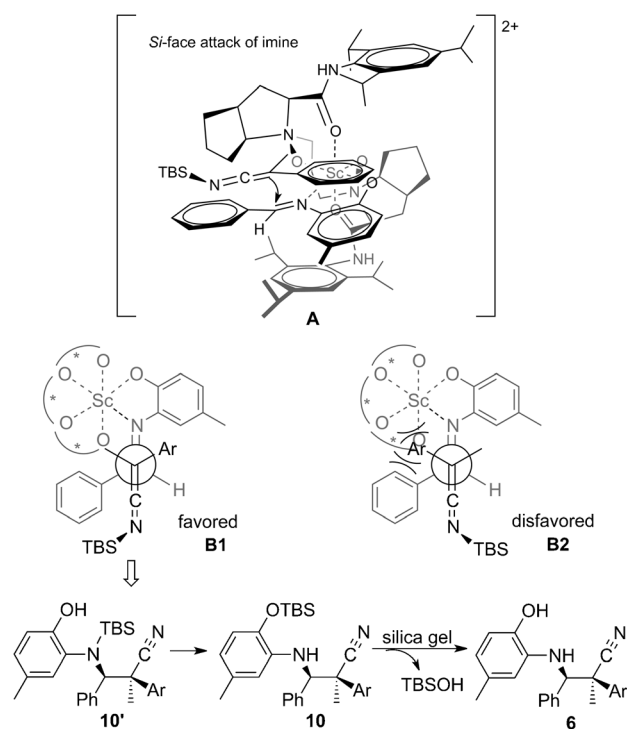
To evaluate the synthetic potential of the products, their conversion into various derivatives was examined (Scheme 2). The reduction of the cyano group in **6a** by



Scheme 2. Transformations of the product **6a** into other derivatives. Reaction conditions: a) 1) AlCl_3 , LiAlH_4 , Et_2O ; 2) Et_3N , Boc_2O ; b) $\text{Pd}(\text{OAc})_2$, PPh_3 , $\text{CH}_3\text{CH}=\text{NOH}$, $\text{EtOH}/\text{H}_2\text{O}$ (4:1), reflux; c) 1) K_2CO_3 , MeI , acetone, 93%; 2) CAN , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, then Et_3N , Boc_2O . Ar = 2-OH-4-MeC₆H₃. Boc = *tert*-butoxycarbonyl.

using LiAlH_4 and subsequent one-pot reaction with $(\text{Boc})_2\text{O}$ afforded the 1,3-diamine **7** in moderate yield.^[18] Hydrolysis of **6a** by using $\text{Pd}(\text{OAc})_2$, PPh_3 , and acetaldehyde oxime in aqueous EtOH heated to reflux gave the β -amino amide **8** without any loss of enantiopurity.^[19] Although β -amino nitriles having an *N*-hydroxyphenyl group are interesting products, deprotection of this group would broaden their utility. The Mannich adduct **6a** was converted into *N*-Boc- β -amino nitrile **9** by methylation of the phenolic OH and deprotection with cerium ammonium nitrate (CAN)^[20] followed by Boc protection of the amino group.

Based on the X-ray crystal structure,^[12] HRMS analysis of the catalyst, as well as the absolute configuration of the product, a possible transition state was proposed (Scheme 3). From this proposed transition state, we can infer that the use of **L4** and $\text{Sc}(\text{OTf})_3$ in the reaction is likely to generate a hexacoordinate $\text{Sc}(\text{OTf})_3$ -derived intermediate, in which not only the oxygen atoms of *N*-oxide but also the carbonyl oxygen atoms coordinate with $\text{Sc}(\text{III})$ in a tetradentate manner. HRMS analysis of a mixture of aldimine **1c** and the catalyst that was prepared in situ from $\text{Sc}(\text{OTf})_3$, **L4**, and



Scheme 3. Proposed catalytic model.

1c (1:1:1) in EtOAc confirms that the aldimine interacts with the catalyst. A peak at m/z 519.8139 is detected and corresponds to the complex $[\text{Sc}^{3+} + \text{L4} + (\text{1c}-\text{H}^+)]^{2+}$ (calc. m/z 519.8167). This result suggests that the aldimine **1c** could be activated upon bidentate coordination to the scandium center. To achieve high enantio- and diastereoselectivity, simultaneous discrimination of the prochiral faces of both the aldimine and SKI is crucial. Intermediate **A** (Scheme 3), in which the *Re* face of the aldimine is shielded by the neighboring 2,4,6-triisopropylphenyl group of the ligand, is believed to be favored. Therefore, the silyl ketene imine is believed to attack from the *Si* face predominantly to afford the corresponding *cis* product. The diastereodiscrimination of SKI in the reaction process can be rationalized according to model **B**. Based on the absolute configuration of product **6m**, we postulate that the steric hindrance between the aryl group of SKI, the Sc^{III} complex, and the aryl substituent of imine makes model **B2** unfavorable. It would thus appear that the *Re*-face of SKI readily attacks the *Si*-face of the aldimine to afford the (2*S*,3*R*)-product (Scheme 3, **B1**). The initial product is believed to be silylated and this was confirmed by HRMS analysis of the reaction system before chromatography on silica gel. The HRMS spectrum contained peaks at m/z 457.2691 and 474.2600, corresponding to $[\text{10a} + \text{H}^+]$ and $[\text{10a} + \text{NH}_4^+]$ respectively. In addition, the *O*-*tert*-butyldimethylsilylated adduct **10a** was observed by ^1H NMR analyses.^[21] After the work-up procedure, the final product **6** was generated.

In summary, we have described a highly enantioselective three-component Mannich reaction of silyl ketene imines (SKIs) catalyzed by a chiral *N,N'*-dioxide scandium(III) complex. The method gives efficient access to a variety of

linear β -amino nitriles containing vicinal tertiary and quaternary stereogenic carbon centers in excellent yield and stereoselectivity (up to 95% yield, >95:5 d.r., and 97% ee). Moreover, the broad substrate scope, a operationally simple procedure, and mild reaction conditions indicate the potential of the catalytic system. Further studies will focus on the enantioselective addition of SKIs to other electrophiles.

Experimental Section

Typical procedure for the asymmetric three-component Mannich reaction of SKI: A mixture of **L4** (7.9 mg, 0.01 mmol), Sc(OTf)₃ (4.9 mg, 0.01 mmol), 2-amino-4-methylphenol **5** (12.3 mg, 0.1 mmol), benzaldehyde **4a** (12.0 μ L, 0.12 mmol), and *i*PrNH₂ (1.72 μ L, 0.02 mmol) was stirred in EtOAc (1.0 mL) at 30°C for 30 min. SKI **2a** (2.0 equiv) was added to the reaction mixture at -20°C. Then the reaction was stirred at -20°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 **6a** (31.5 mg, 92% yield) as a colourless viscous liquid.

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