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Highly Enantioselective One-Pot, Three-Component Mannich-type Reaction Catalyzed by an *N*,*N*′-Dioxide–Scandium(III) Complex

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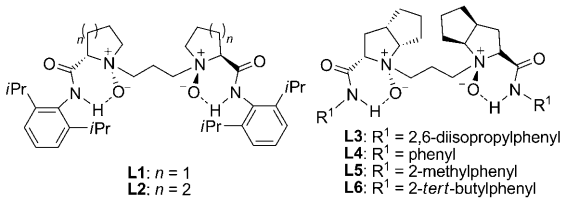
Optically active β-amino esters are important precursors for the preparation of natural products, pharmaceutical agents, and mimics of protein structural motifs.[1] The catalytic asymmetric Mannich reaction is one of the most powerful and direct methods to obtain such chiral building blocks.[2] Since 1997 when Kobayashi's group reported the first example of Mannich-type reaction of aldimines using a BINOL-derived Zr^{IV} complex (BINOL = 2,2′-binaphthol),[3] a couple of efficient catalysts, such as Wulff's VAPOL-Zr^{IV} complex (VAPOL = vaulted 3,3′-biphenanthrol)[4] and Akiyama's TADDOL-[5a] and BINOL-based phosphoric acids (TADDOL = α,α′-(dimethyl-1,3-dioxolane-4,5-diyl)-bis(diphenylmethanol)),[5b–d] have been developed. The first example of catalytic asymmetric Mannich-type reaction of simple ketoimines was published by Shibasaki's group using a Cu^{I} complex with P ligands.[6] Subsequently, Hoveyda's group disclosed an efficient diastereo- and enantioselective Ag-catalyzed method for the vinylogous Mannich reaction of α-ketoimine esters.[7] Nevertheless, the catalytic asymmetric Mannich-type reaction of aldimines with ketene silyl acetals in a one-pot, three-component method has scarcely been reported. The one-pot, multicomponent reaction has many advantages such as the simplified operation, mild reaction conditions, high atom economy, and environmental friendliness.[8] On the other hand, our previous studies showed that *N*,*N*′-dioxides and their complexes were useful for many asymmetric reactions.[9,10] Herein, we reported the use of a novel *N*,*N*′-dioxide scandium(III) triflate (2:1) complex in the asymmetric one-pot, three-component Mannich-type reaction of ketene silyl acetal. Excellent enantioselectivities (up to 98% *ee*) were obtained for a series of substrates with 5 mol% of catalyst.

At the beginning of our research, L-proline-derived *N*,*N*′-dioxide **L1** scandium(III) triflate complexes were examined in the asymmetric three-component Mannich-type reaction



between benzaldehyde (**1a**), 2-aminophenol (**2**), and ketene silyl acetal (**3**; Table 1, entries 1 and 2).[12] As expected, this sort of *N*,*N*′-dioxide–scandium complex could promote the reaction with the promising results (Table 1, entries 1 and 2), and increasing the **L1**/$Sc(OTf)_3$ molar ratio from 1:1 to 2:1, the enantioselectivity was significantly enhanced (Table 1, entry 2 vs. 1). The effect of the structure of *N*,*N*′-dioxide ligands was then examined (Table 1, entries 3–7). The *N*,*N*′-dioxide **L3**, based on L-ramipril acid, was superior to L-proline-derived *N*,*N*′-dioxide **L1** and (*S*)-pipecolic acid-based **L2** (Table 1, entry 4 vs. 2 and 3). Furthermore, the enantioselectivity was greatly dependent on the steric hindrance of amide moiety of the ligand. *N*,*N*′-Dioxide **L3**, which contains bulky 2,6-diisopropyl-substituted aniline groups, displayed the best results (38% yield, and 89% *ee*, Table 1, entry 4). In contrast, while simple aniline derivative **L4** was employed, a racemic product was obtained (Table 1, entry 5). Although increasing the steric hindrance on the mono-*ortho*-position of aniline could enhance the enantioselectivity (Table 1, entries 5–7), it was not as good as *N*,*N*′-dioxide **L3** (Table 1, entry 4 vs. 5–7).

To further improve the reactivity and enantioselectivity, other reaction conditions such as solvent, additive, and reaction temperature were examined (Table 1, entries 8–12).[12,13]

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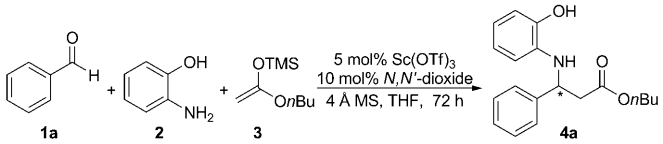
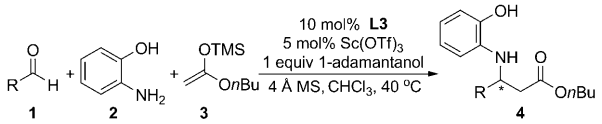
Table 1. Optimization of the Mannich-type reaction of benzaldehyde **1a**, 2-aminophenol **2**, and ketene silyl acetal **3**.[a]



Entry	L	Additive[b]	Yield [%][c]	*ee* [%][d]
1	**L1**[e]	–	53	43
2	**L1**	–	48	70
3	**L2**	–	42	83
4	**L3**	–	38	89
5	**L4**	–	27	0
6	**L5**	–	31	15
7	**L6**	–	40	79
8[f]	**L3**	–	48	93
9[f]	**L3**	*t*BuOH	50	78
10[f]	**L3**	2-adamantanol	53	92
11[f]	**L3**	1-adamantanol	65	91
12[f,g]	**L3**	1-adamantanol	72	93

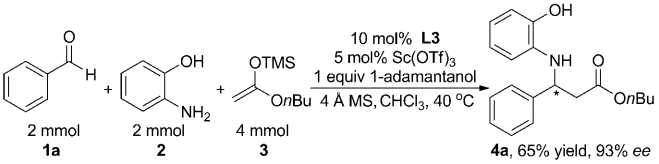
[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide (10 mol%), $Sc(OTf)_3$ (5 mol%), benzaldehyde (**1a**; 0.1 mmol), 2-aminophenol (**2**; 1 equiv), ketene silyl acetal (**3**; 2 equiv), 4 Å MS (7.5 mg), and THF (0.5 mL) under N_2 atmosphere at 23 °C for 72 h. [b] One equivalent of additive was used. [c] Isolated yield. [d] Determined by HPLC analysis (see the Supporting Information). [e] The molar ratio of *N*,*N*′-dioxide **L1** to $Sc(OTf)_3$ was 1:1. [f] $CHCl_3$ was used as the solvent. [g] The reaction was carried out at 40 °C.

Table 2. Substrate scope for the asymmetric Mannich-type reaction.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**1a**)	**4a**	72	72	93 (*R*)[d]
2	4-Me-Ph (**1b**)	**4b**	136	68	90
3	2-Me-Ph (**1c**)	**4c**	136	65	86
4	 (**1d**)	**4d**	136	65	82
5	4-CF_3-Ph (**1e**)	**4e**	120	60	98
6	4-Br-Ph (**1f**)	**4f**	120	58	95
7	4-F-Ph (**1g**)	**4g**	120	55	93
8	4-Cl-Ph (**1h**)	**4h**	96	65	97
9	3,4-Cl_2-Ph (**1i**)	**4i**	136	58	94
10	4-Ph-Ph (**1j**)	**4j**	96	82	93
11	2-naphthyl (**1k**)	**4k**	120	68	92

[a] Unless otherwise noted, reactions were carried out with aldehyde **1** (0.1 mmol), 2-aminophenol (**2**; 0.1 mmol), ketene silyl acetal (**3**; 0.2 mmol), *N*,*N*′-dioxide **L3** (0.01 mmol), $Sc(OTf)_3$ (0.005 mmol), 1-adamantanol (0.1 mmol), 4 Å MS (7.5 mg), and $CHCl_3$ (0.5 mL) under N_2 atmosphere at 40 °C. [b] One equivalent of additive was used. [c] Isolated yield. [d] Absolute configuration was assigned after converting the product **4a** to known compound **7**.[11]



Scheme 1. Scaled-up version of the Mannich-type reaction.

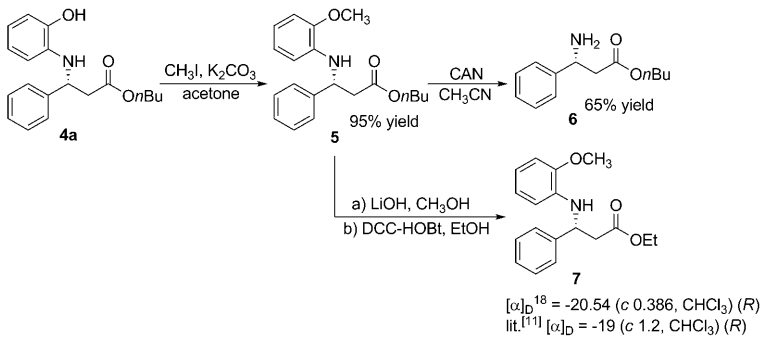
When chloroform was used as the solvent, both the reactivity and enantioselectivity were improved (48% yield, and 93% *ee*, Table 1, entry 8). The addition of one equivalent of secondary or tertiary alcohols evidently enhanced the reactivity (Table 1, entries 9–11). Especially, when 1-adamantanol was employed, the isolated yield was increased to 65% (Table 1, entry 11). Moreover, increasing the reaction temperature to 40 °C led to the desired adduct **4a** with 72% yield and 93% *ee* (Table 1, entry 12).[14]

Under optimized conditions, the scope of this three-component reaction with different aldehydes was investigated. Various aldehydes worked well in this reaction, delivering the corresponding products in excellent *ee* values with moderate to good yields (Table 2).[15] Neither the electronic properties nor the steric hindrance of the substituent at the aromatic ring had any apparent effect on the enantioselectivity (Table 2, entries 1–10). For electron-donating aromatic aldehydes, a range of 82–90% *ee* was obtained (Table 2, entries 2–4). Notably, this method was rather efficient for aromatic aldehydes bearing electron-withdrawing groups at the *para*-position, which provided adducts in excellent enantioselectivities (93–98% *ee*, Table 2, entries 5–9). The condensed aromatic aldehyde (2-naphthaldehyde) was also found to be suitable substrate, giving the corresponding product **4k** in 68% yield with 92% *ee* (Table 2, entry 11).

To test the synthetic potential of the present approach, a large-scale synthesis of the chiral *N*-substituent β-amino esters was performed. As shown in Scheme 1, by treatment of 2 mmol of starting materials under the optimal reaction conditions, the desired product was produced without loss of enantioselectivity.

The absolute configuration of **4a** was determined after converting to known compound **7** (Scheme 2). Methylation of **4a** gave product **5**,[4a] followed by hydroxylation and esterification to afford the adduct **7**, thereby assigning the absolute configuration of **4a** to be *R* by comparing the optical rotation of **7** with that given in the literature.[11] Furthermore, the *N*-substituent of the product **4a** could also be easily removed,[4a] affording β-amino ester **6** in 65% yield.

In summary, we have presented a highly enantioselective one-pot, three-component Mannich-type reaction of aldehydes, 2-aminophenol, and ketene silyl acetal by using 5 mol% of the C_2-symmetric, *N*,*N*′-dioxide **L3** scandium(III) triflate (2:1) complex, which facilitated the asymmetric synthesis of biologically interesting β-amino esters. Various aldehydes could be converted to *N*-substituted β-amino esters with excellent enantioselectivities (up to 98% *ee*) and moderate to good yields under mild conditions. Further investigation on the mechanism of this catalytic system is currently underway.[16]



Scheme 2. Conversion to β-amino ester **6** and known compound **7** for assignment of the absolute configuration of **4a**.

Experimental Section

General experimental procedure: Under N_2 atmosphere, benzaldehyde (**1a**; 10.2 μL, 0.1 mmol) was added through a syringe to the dry tube containing a suspension of 2-aminophenol (**2**; 10.9 mg, 0.1 mmol), *N*,*N*′-dioxide **L3** (7.0 mg, 0.01 mmol), $Sc(OTf)_3$ (2.5 mg, 0.005 mmol), 1-adamantanol (15.2 mg, 0.1 mmol), 4 Å MS (7.5 mg) in $CHCl_3$ (0.5 mL). After the mixture was heated to 40 °C, ketene silyl acetal (**3**; 41.0 μL, 0.2 mmol) was added; the resulting solution was stirred at this temperature for a period of time indicated in Table 2. After cooling, the reaction was quenched with aqueous NaCl, extracted with AcOEt, and the combined organic layer was dried over Na_2SO_4. Filtration, evaporation, and purification by silica gel column chromatography (AcOEt:PET = 1:8–1:6) gave the product **4a** in 72% yield (22.5 mg) with 93% *ee*.

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Keywords: amino esters · asymmetric catalysis · enantioselectivity · Mannich-type reaction · one-pot reactions · scandium

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[12] For details see the Supporting Imformation.

[13] Other ketene silyl acetals such as the methyl isobutyrate and methyl acetate derivatives were also investigated. However, poor enantioselectivities were obtained (less than 35% *ee*).

[14] Further increase in the reaction temperature to 80°C resulted in a dramatic decrease in the enantioselectivity (33% *ee*).

[15] Aliphatic aldehydes were also investigated. The reaction proceeded smoothly to give the corresponding products with only moderate enantioselectivities: *iso*-butyraldehyde (72% yield, 65% *ee*), *n*-hexanal (65% yield, 67% *ee*).

[16] To understand the structure of the catalyst, we tried to obtain a single crystal of **L3**–$Sc(OTf)_3$ (2:1) complex but failed. However, the structure of **L1**–$Sc(OTf)_3$ (1:1) complex was determined by X-ray crystallography. CCDC 704000 contains the supplementary crystallographic data for the **L1**–$Sc(OTf)_3$ (1:1) complex. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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