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#### Letter

## Design of New Amino Tf-Amide Organocatalysts: Environmentally Benign Approach to Asymmetric Aldol Synthesis

Hyo-Jun Lee<sup>a</sup> Natarajan Arumugam<sup>b</sup> Abdulrahman I. Almansour<sup>b</sup> Raju Suresh Kumar<sup>b</sup> Keiji Maruoka \* a, c 💿

<sup>a</sup> Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan maruoka@kuchem.kvoto-u.ac.ip

<sup>b</sup> Department of Chemistry, College of Science, King Saud University,

P.O. Box 2455, Riyadh, 11451, Saudi Arabia

<sup>c</sup> School of Chemical Engineering and Light Industry, Guangdong University

of Technology, No.100, West Waihuan Road, HEMC, Panyu District, Guangzhou, 510006, P. R. of China

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Abstract A new type of optically pure primary amino aromatic Tf-amide organocatalyst can be easily prepared from 8-amino-1-tetralone, and its chemical behavior was investigated in the context of asymmetric aldol and Mannich reactions. Most notably, the asymmetric aldol reaction proceeded smoothly in brine.

Key words asymmetric synthesis, aldol reaction, organocatalyst, brine. Mannich reaction

Among various types of amine-based, chiral, and bifunctional organocatalysts, amino Tf-amide organocatalysts are very reliable in various asymmetric transformations that include asymmetric aldol, Mannich, and conjugate addition reactions.<sup>1,2</sup> In 2005, we reported the design of chiral binaphthyl-modified secondary amino Tf-amide organocatalysts of the type 1, which effectively promote anti-selective direct asymmetric Mannich reactions and syn-selective direct asymmetric cross-aldol reactions (Figure 1).<sup>3</sup> Later, we prepared structurally similar chiral biphenyl-modified secondary amino Tf-amide organocatalysts of type 2.4 Moreover, we also designed primary amino Tf-amide organocatalysts of the type 3 and 4 for asymmetric aldol reactions and asymmetric conjugate additions.<sup>5,6</sup> Compared to primary amino aliphatic Tf-amide organocatalysts of the type **3** and **4**, which are not applicable to asymmetric Mannich-type reactions, the catalysts 1 and 2 exhibit a high nucleophilicity of the secondary amino moiety in addition to the acidic, aromatic Tf-amide hydrogen atom. However, due to the laborious synthesis of **1** and **2**.<sup>3,4</sup> the design and synthesis of easily accessible reactive amine Tf-amide organocatalysts represent a desirable research target.<sup>7,8</sup> Our



strategy is based on the enhancement of the reactivity of the acidic Tf-amide moiety by introducing an aromatic Tfamide moiety as illustrated in primary amino Tf-amide organocatalysts of type 5, which could accelerate asymmetric aldol and Mannich reactions.





Initially, we prepared various types of *primary* amino aromatic Tf-amide organocatalysts (6-10) and evaluated their reactivity and selectivity in asymmetric direct aldol reactions (Table 1). For this purpose, a series of aldol reactions between 4-nitrobenzaldehyde and cyclohexanone was carried out in the presence of catalysts 6-10 in aqueous THF at room temperature (Table 1, entries 1–5).<sup>9</sup> Among these catalysts, 9 afford the highest stereoselectivity, giving the anti-aldol product (anti-11a) with 97% antiselectivity and 99% ee. albeit that 120 h are required for 60% yield (Table 1, entry 4). Subsequently, we carried out a solvent screening in order to improve the reactivity (Table 1, entries 6–11). Among the solvents tested, aqueous solvents. in particular brine, dramatically accelerated the rate of the asymmetric aldol reactions (Table 1, entries 9 and 10), fur-

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nishing *anti*-**11a** in high yield with excellent stereoselectivity.<sup>10</sup> However, the low reactivity and selectivity were observed in the reaction in anhydrous DMSO (Table 1, entry 11).<sup>5b</sup> Lowering the catalyst loading to 5 mol% did not affect the *anti*- or enantioselectivity (Table 1, entry 12). However, carrying out the reaction with 2 mol% of **9** slightly diminished the reactivity and afforded *anti*-**11** with lower stereoselectivities (Table 1, entry 13).

 Table 1
 Optimization of the Catalysts and Reaction Conditions in the

 Asymmetric Direct Aldol Reactions between 4-Nitrobenzaldehyde and
 Cyclohexanone<sup>a</sup>



<sup>a</sup> Unless otherwise specified, the asymmetric direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was carried out in the presence of 2–10 mol% of **6–10** at room temperature.

<sup>b</sup> Isolated vield.

<sup>c</sup> The *anti/syn* ratio was determined by <sup>1</sup>H NMR analysis.

<sup>d</sup> % ee of major anti-isomer.

Subsequently, the scope of the asymmetric direct aldol reaction between cycloalkanones and various benzaldehydes in brine solvent was investigated under the optimized conditions using 5 mol% of **9** (Table 2).<sup>11</sup> The reactions involving benzaldehydes bearing strong electronwithdrawing substituent(s) at any position of the phenyl group furnished the corresponding aldol products **11** in high yields, with excellent *anti*- and enantioselectivity (Table 2, entries 1–7). Especially the heteroaromatic nicotinic and isonicotinic aldehydes afforded **11** in excellent yield and selectivity (Table 2, entries 8 and 9). Even though the reactivity for 4-halobenzaldehydes was slightly lower, these reactions still showed excellent stereoselectivity (Table 2, entries 10 and 11). When benzaldehyde was employed, the corresponding aldol product **111** (Ar = Ph; R<sup>1</sup> and R<sup>2</sup> = -(CH<sub>2</sub>)<sub>4</sub>-) was obtained in moderate yield with high *anti*- and enantioselectivity (Table 2, entry 12). The use of cyclopentanone as the aldol donor also showed high reactivity and stereoselectivity for the corresponding aldol product **11m** (Ar = 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>; R<sup>1</sup> and R<sup>2</sup> = -(CH<sub>2</sub>)<sub>3</sub>-; Table 2, entry 13). Cycloheptanone and acetone provided the corresponding aldol products in good yield with high stereoselectivity, though 10 mol% of **9** were required (Table 2, entries 14 and 15).



Entry	Ar, R <sup>1</sup> , R <sup>2</sup>	11	Time (h)	Yield (%) <sup>b</sup>	an- ti/syn <sup>c</sup>	ee (%) <sup>d</sup>	
1	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11a	24	92	97:3	99	
2	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11b	30	96	95:5	99	
3	4-CN-C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11c	30	96	97:3	98	
4	4-CO <sub>2</sub> Me-C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11d	48	88	97:3	99	
5	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , -(CH <sub>2</sub> ) <sub>4</sub> -	11e	24	88	97:3	99	
6	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , -(CH <sub>2</sub> ) <sub>4</sub> -	11f	48	84	98:2	99	
7	C <sub>6</sub> F <sub>5</sub> , -(CH <sub>2</sub> ) <sub>4</sub> -	11g	30	88	99:1	97	
8	3-pyridyl, –(CH <sub>2</sub> ) <sub>4</sub> –	11h	36	92	96:4	99	
9	4-pyridyl, –(CH <sub>2</sub> ) <sub>4</sub> –	11i	20	98	94:6	99	
10	4-Cl-C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11j	48	55	97:3	99	
11	4-Br-C <sub>6</sub> H <sub>4</sub> , –(CH <sub>2</sub> ) <sub>4</sub> –	11k	48	72	97:3	99	
12	C <sub>6</sub> H <sub>5</sub> , -(CH <sub>2</sub> ) <sub>4</sub> -	111	48	47	94:6	98	
13	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , -(CH <sub>2</sub> ) <sub>3</sub> -	11m	18	89	91:9	99	
14 <sup>e</sup>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , -(CH <sub>2</sub> ) <sub>5</sub> -	11n	48	92	88:12	89	
15 <sup>e</sup>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> , CH <sub>3</sub> , H	11o	48	80	-	87	

<sup>a</sup> Unless otherwise specified, the asymmetric direct aldol reaction between cycloalkanone and the substituted benzaldehydes was carried out in brine in the presence of 5 mol% of **9** at room temperature.

<sup>b</sup> Isolated yield.

<sup>c</sup> The *anti/syn* ratio was determined by <sup>1</sup>H NMR analysis.

<sup>d</sup> % ee of major *anti*-isomer.

° 10 mol% of **9** was used.

In order to demonstrate the applicability of the catalyst **9** in asymmetric transformations, we carried out asymmetric direct Mannich reaction between cyclic ketones and  $\alpha$ -imino ester **12** in the presence of catalytic amounts of **9** in

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THF at room temperature (Scheme 1), which afforded the *anti*-Mannich products **13a** (*anti*/*syn* = 93:7; 95% ee (*anti*)), **13b** (*anti*/*syn* = 96:4; 97% ee (*anti*)), and **13c** (*anti*/*syn* = 97:3; 92% ee (*anti*)) in high yield.<sup>12</sup>



Scheme 1 Asymmetric Mannich reaction between cyclic ketone and  $\alpha$ -imino ester 13 catalyzed by organocatalyst 9.

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### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610408.

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- (7) The synthesis of the *primary* amino aromatic Tf-amide organocatalysts 6–10 was carried out according to Scheme 2 (see Supporting Information for details).



**Scheme 2** *Reagents and conditions:* (*a*) Ti(OEt)<sub>4</sub>, THF, 70 °C or 90 °C; (*b*) DIBAL-H, THF, -78 °C; (*c*) (*i*) HCl, dioxane, MeOH, rt; (*ii*) Boc<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, rt; (*d*) (*i*) Tf<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (*ii*) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt.

- (8) The absolute configurations of the catalysts were assigned based on the X-ray diffraction analysis of the sulfonamide intermediate of catalyst **9b**. The corresponding data have been deposited at the Cambridge Crystallographic Data Center and can be obtained free of charge via www.ccdc.cam.ac.uk/getstructures. CCDC 1870339 contains the supplementary crystallographic data for this paper.
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#### (11) General Procedure for the Asymmetric Aldol Reaction Using the Catalyst 9 for the Preparation of 11

To a mixture of catalyst **9** (3 mg, 5 mol%) and benzaldehyde (0.2 mmol) in brine (1.2 mL) was added ketone (6.0 mmol). The homogenous mixture was stirred at room temperature for the appropriate time until the reaction was completed (TLC). Then, a saturated NH<sub>4</sub>Cl solution was added, and the mixture was extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/hexane = 1:3) to afford the product **11**.

# (*R*)-2-[(*S*)-Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (*anti*-11a)

White solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  = 8.22–8.11 (m, 2 H), 7.52–7.49 (m, 2 H), 4.90 (d, *J* = 8.0 Hz, 1 H), 4.07, (br s, 1 H), 2.61–2.56 (m, 1 H), 2.52–2.47 (m, 1 H), 2.40–2.33, (m, 1 H), 2.14–2.08 (m, 1 H), 1.85–1.80 (m, 1 H), 1.72–1.62 (m, 1 H), 1.60–1.51 (m, 2 H), 1.42–1.33 (m, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  = 214.7, 148.3, 147.5, 127.8, 123.5, 74.0, 57.1, 42.6,

30.7, 27.6, 24.6. HRMS (ESI): m/z calcd for  $C_{13}H_{15}O_4NNa$ : 272.0893 [M + Na]<sup>+</sup>; found: 272.0895. [ $\alpha$ ]<sub>D</sub><sup>24</sup> –11.2 (CHCl<sub>3</sub>, *c* 0.9, 99% ee).

#### (12) General Procedure for the Asymmetric Mannich Reaction Using Catalyst 9 for the Preparation of 13

To a mixture of catalyst **9** (3 mg, 5 mol%) and  $\alpha$ -imino ester **12** (42 mg, 0.2 mmol) in THF (1.2 mL) was added ketone (6.0 mmol). The mixture was stirred at room temperature for 12 h. Then, a saturated NH<sub>4</sub>Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford the product **13**.

# Ethyl (*R*)-2-[(4-Methoxyphenyl)amino]-2-[(*S*)-2-oxocyclo-hexyl]-acetate (*anti*-13a)

Colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta = 6.77-6.73$  (m, 2 H), 6.64–6.61 (m, 2 H), 4.24 (br s, 1 H), 4.18–4.10 (m, 2 H), 3.98 (d, *J* = 4.5 Hz, 1 H), 3.73 (s, 3 H), 3.12–3.08 (m, 1 H), 2.45–2.40 (m, 1 H), 2.35–2.29 (m, 1 H), 2.13–2.09 (m, 1 H), 2.07–2.02 (m, 1 H), 1.96–1.87 (m, 2 H), 1.78–1.62 (m, 2 H), 1.21 (t, *J* = 7.5 Hz, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta = 210.9$ , 173.0, 152.7, 142.1, 115.6, 114.7, 61.1, 59.0, 55.7, 53.5, 41.8, 30.5, 26.8, 24.5, 14.1. HRMS (ESI): *m/z* calcd for C<sub>17</sub>H<sub>23</sub>O<sub>4</sub>NNa: 328.1519 [M + Na]<sup>+</sup>; found: 328.1526. [ $\alpha$ ]<sub>D</sub><sup>24</sup>–22.4 (CHCl<sub>3</sub>, c 0.7, 95% ee).