

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

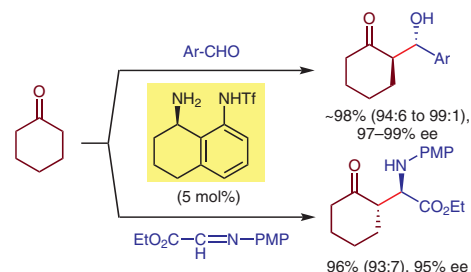
Hyo-Jun Lee^aNatarajan Arumugam^bAbdulrahman I. Almansour^bRaju Suresh Kumar^bKeiji Maruoka^{*a,c}

^a Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
maruoka@kuchem.kyoto-u.ac.jp

^b Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh, 11451, Saudi Arabia

^c 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 bi-functional organocatalysts, amino Tf-amide organocatalysts are very reliable in various asymmetric transformations that include asymmetric aldol, Mannich, and conjugate addition reactions.^{1,2} 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).³ 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.^{5,6} 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**,^{3,4} the design and synthesis of easily accessible reactive amine Tf-amide organocatalysts represent a desirable research target.^{7,8} Our

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

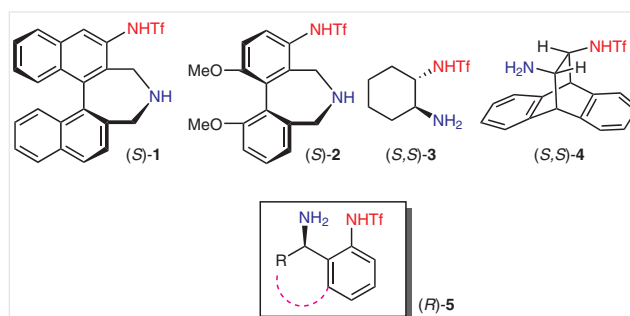
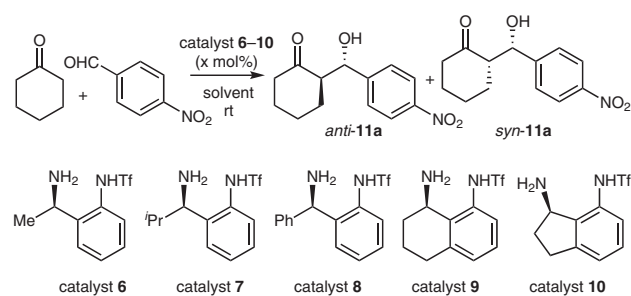


Figure 1 Previously and newly designed amino Tf-amide organocatalysts 1–5

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).⁹ Among these catalysts, **9** afford the highest stereoselectivity, giving the *anti*-aldol product (*anti*-**11a**) with 97% *anti*-selectivity 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-

nishing **anti-11a** in high yield with excellent stereoselectivity.¹⁰ However, the low reactivity and selectivity were observed in the reaction in anhydrous DMSO (Table 1, entry 11).^{5b} 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^a



Entry	Catalyst (x mol%)	Solvent	Time (h)	Yield (%) ^b	<i>anti</i> / <i>syn</i> ^c	ee (%) ^d
1	6 (10)	THF/H ₂ O	168	32	75:25	89
2	7 (10)	THF/H ₂ O	168	8	45:55	11
3	8 (10)	THF/H ₂ O	48	96	90:10	97
4	9 (10)	THF/H ₂ O	120	60	97:3	99
5	10 (10)	THF/H ₂ O	120	96	93:7	86
6	9 (10)	DMSO/H ₂ O	40	92	97:3	99
7	9 (10)	EtOH/H ₂ O	120	72	87:13	83
8	9 (10)	neat	24	69	94:6	99
9	9 (10)	H ₂ O	20	91	97:3	99
10	9 (10)	brine	12	91	97:3	99
11	9 (10)	DMSO	72	62	95:5	98
12	9 (5)	brine	24	92	97:3	99
13	9 (2)	brine	48	92	97:3	99

^a 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.

^b Isolated yield.

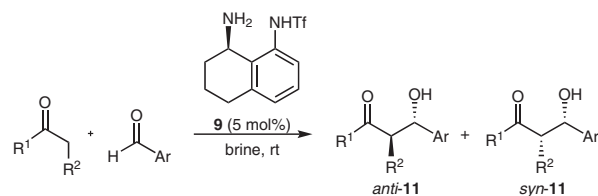
^c The *anti*/*syn* ratio was determined by ¹H NMR analysis.

^d % 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).¹¹ The reactions involving benzaldehydes bearing strong electron-withdrawing 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 **11l** (Ar = Ph; R¹ and R² = -(CH₂)₄-) 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-NO₂-C₆H₄; R¹ and R² = -(CH₂)₃-; 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).

Table 2 Asymmetric Direct Aldol Reaction of Cycloalkanone and Substituted Benzaldehydes Catalyzed by Organocatalyst **9**^a



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

^a 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.

^b Isolated yield.

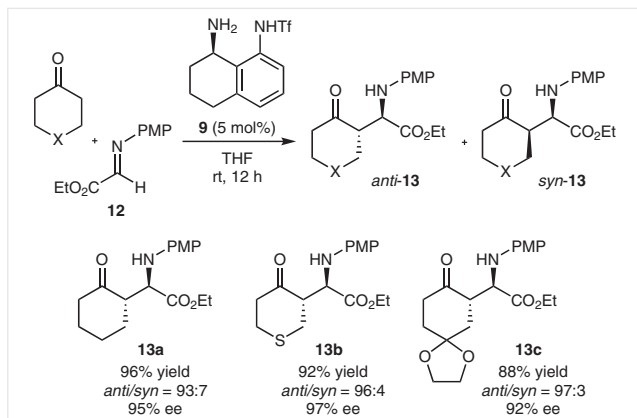
^c The *anti*/*syn* ratio was determined by ¹H NMR analysis.

^d % ee of major *anti*-isomer.

^e 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 α -imino ester **12** in the presence of catalytic amounts of **9** in

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.¹²



Scheme 1 Asymmetric Mannich reaction between cyclic ketone and α -amino ester **13** catalyzed by organocatalyst **9**.

Funding Information

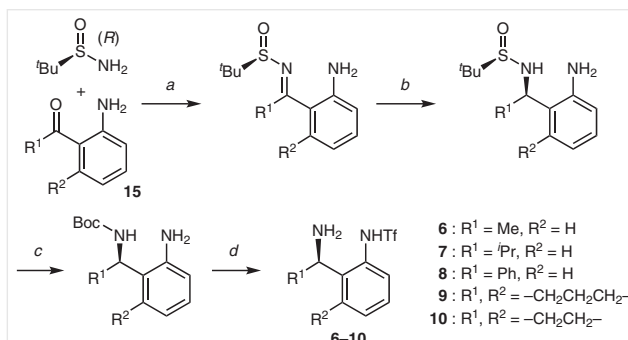
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Supporting Information

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

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- 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) $\text{Ti}(\text{OEt})_4$, THF, 70 °C or 90 °C; (b) DIBAL-H, THF, -78 °C; (c) (i) HCl, dioxane, MeOH, rt; (ii) Boc_2O , CH_2Cl_2 , rt; (d) (i) Tf_2O , Et_3N , CH_2Cl_2 , -78 °C; (ii) TFA, CH_2Cl_2 , rt.

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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 NH₄Cl solution was added, and the mixture was extracted with dichloromethane. The organic layer was dried over Na₂SO₄, 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. ¹H NMR (CDCl₃, 500 MHz): δ = 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). ¹³C NMR (CDCl₃, 125 MHz): δ = 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 C₁₃H₁₅O₄NNa: 272.0893 [M + Na]⁺; found: 272.0895. [α]_D²⁴ –11.2 (CHCl₃, *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 α-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 NH₄Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄, 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-oxocyclohexyl]-acetate (anti-13a)

Colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ = 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). ¹³C NMR (CDCl₃, 125 MHz): δ = 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 C₁₇H₂₃O₄NNa: 328.1519 [M + Na]⁺; found: 328.1526. [α]_D²⁴ –22.4 (CHCl₃, *c* 0.7, 95% ee).