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Remarkable Effect of *tert*-Amine Additives in the Asymmetric Direct Michael Reaction of Ketones with β-Arylnitroethenes Catalyzed by an *L*-Hydroxyproline-Based Amino Tf-Amide Organocatalyst

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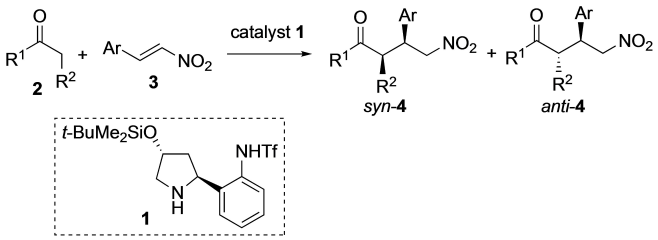
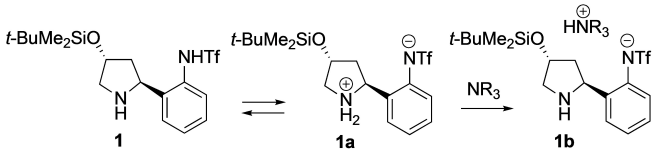
A catalytic asymmetric direct Michael reaction of ketones with *trans*-β-arylnitroethenes can be achieved under the influence of optically pure *L*-hydroxyproline-based *secondary*-amino aromatic Tf-amide organocatalyst. The effect of the trialkylamine base additive such as diethylmethylamine is of paramount importance to accomplish high reactivity and enantioselectivity in this asymmetric Michael reaction.

Of the various chiral organocatalysts that have been developed,[1] chiral bifunctional organocatalysts have significantly contributed to the area of asymmetric organocatalysis[2] due to the important role that they play in asymmetric organocatalytic transformations.[3] Bifunctional organocatalysts that possess both (thio)urea and *tertiary* amino functional groups[4] are well known, as are proline and proline-based bifunctional organocatalysts.[5] The proline-derived class has been widely used in a variety of asymmetric organocatalytic transformations, where the catalysts cooperatively activate a nucleophile and an electrophile simultaneously in a specific spatial configuration to enable various enantioselective addition reactions.[6–8] In line with this study, we have recently reported the practical synthesis of a series of commercially available *L*-hydroxyproline-based *secondary*-amino aromatic Tf-amide organocatalysts. The synthetic utility of these bifunctional organocatalysts was demonstrated in an asymmetric direct aldol reaction between cyclohexanones and substituted benzaldehydes where the corresponding aldol adducts were formed in good yield with good to excellent *anti*-diastereo- and enantioselectivity.[9,10] During the course on our continuous investigations into the synthetic utility of *L*-hydroxyproline-based *secondary*-amino aromatic Tf-amide organocatalysts of type **1** in asymmetric organocatalysis, we found that **1** is an efficient bifunctional organocatalyst for the asymmetric Michael reaction of ketones **2** with *trans*-β-arylnitroethene **3** (Scheme 1). Herein, we wish to report our experimental findings on this subject.

To probe the reactivity and stereoselectivity in the formation of the desired Michael adducts **4**, an asymmetric Michael reaction of cyclohexanone (**2a**) and *trans*-β-nitrostyrene (**3a**) as the model substrates was carried out in the presence of the *L*-hydroxyproline-based *secondary*-amino Tf-amide organocatalyst **1** (Table 1). The asymmetric Michael reaction of **2a** and **3a** catalyzed by 10 mol% of **1** was performed in chloroform at room temperature for 48 h (entry 1). Unfortunately, none of the desired Michael adducts **4a** were formed. This disappointing result was ascribed to the facile intramolecular formation of ionic species **1a** (Scheme 2).[11] Thus, we anticipated that the addition of certain bases may generate the free amino structure **1b**, thereby enhancing the nucleophilic character of catalyst **1**, compared to **1a**.[11] The Michael reaction of **2a** and **3a** catalyzed by 10 mol% of **1** was attempted in the presence of potassium carbonate or 2,6-lutidine as an additive but furnished none of the desired Michael adducts **4a** (entries 2 and 3). In contrast,



Scheme 1. Asymmetric Direct Michael Reaction of Ketones with *trans*-β-Arylnitroethenes Catalyzed by Chiral Bifunctional Organocatalyst **1**.



Scheme 2. Effect of Base Additives on the Reactivity and Enantioselectivity in the Asymmetric Direct Michael Reaction of Ketones with *trans*-β-Nitrostyrene Catalyzed by Chiral Bifunctional Organocatalyst **1**.

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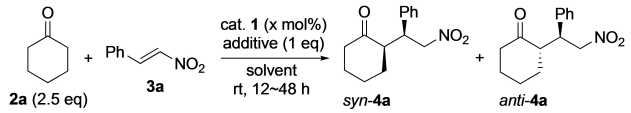
Table 1. Optimization of the Reaction Conditions for the Asymmetric Direct Michael Reactions between **2a** and **3a**.[a]



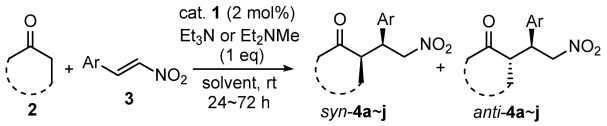
Entry	Catalyst **1** [x]	Additive/Solvent	Time [h]	Yield [%][b] (*syn:anti*)[c]	*ee* [%][d]
1	10	None/$CHCl_3$	48	0	
2	10	K_2CO_3/$CHCl_3$	12	0	
3	10	2,6-Lutidine/$CHCl_3$	12	0	
4	10	Et_3N/$CHCl_3$	12	95 (89:11)	60
5	10	Et_2NMe/$CHCl_3$	12	71 (84:16)	74
6	10	Et_2NCy/$CHCl_3$	12	85 (84:16)	78
7	2	Et_3N/$CHCl_3$	34	65 (82:18)	69
8	2	Et_3N/Hexane	30	22 (83:17)	68
9	2	Et_3N/AcOEt	34	74 (88:12)	77
10	2	Et_3N/THF	34	54 (86:14)	76
11	2	Et_3N/CPME	34	92 (92:8)	91
12	2	Et_3N/MTBE	24	99 (91:9)	92
13	2	Et_2NCy/CPME	48	99 (90:10)	91
14	2	Et_2NMe/CPME	48	99 (90:10)	95
15	2	Et_2NMe/MTBE	48	81 (88:12)	96

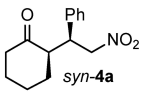
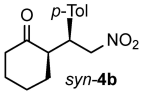
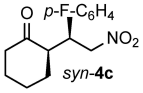
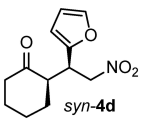
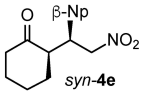
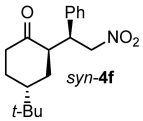
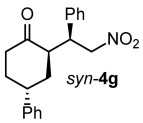
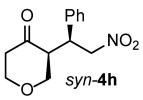
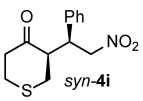
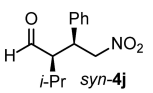
[a] Unless otherwise specified, the asymmetric direct Michael reaction between cyclohexanone (**2a**) (0.5 mmol) and *trans*-β-nitrostyrene (**3a**) (0.2 mmol) was carried out in the presence of 2 or 10 mol% of **1** and an additive (0.2 mmol) in a solvent (1.0 mL) at room temperature. [b] Isolated yield. [c] The *syn/anti* ratio was determined by ^{1}H NMR analysis. [d] % ee of the major *syn*-isomer.

the addition of triethylamine under similar reaction conditions gave a mixture of Michael adducts, *syn*-**4a** and *anti*-**4a** in a 95% yield (89:11, *syn:anti*), with a 60% ee of the major *syn*-**4a** (entry 4). Then, we examined the effect of other *tertiary*-amine bases, which achieved even better enantioselectivity of *syn*-**4a**. Among various types of *tertiary*-amine bases, diethylmethylamine (Et_2NMe; DEMA) and cyclohexyldiethylamine (Et_2NCy; DECHA) were found to be superior to triethylamine in terms of the observed enantioselectivity (entries 5 and 6 vs. 4). The effect of various base additives and the equivalency of triethylamine base was examined in detail, and the results are shown in Tables S1 and S2 in the Supporting Information (SI). Upon lowering the catalyst loading to 2 mol%, we observed higher enantioselectivity for *syn*-**4a** at the expense of the chemical yield (entry 7 vs. 4). We then examined the effect of changing the solvent and found that the use of ethereal solvents, in particular, cyclopentyl methyl ether (CPME) and *tert*-butyl methyl ether (MTBE) gave excellent enantioselectivity values (entries 11 and 12 vs. 7~10). A more detailed analysis of the solvent effect is summarized in Table S3 in SI. The effect of various *tertiary*-amine bases was examined at low catalyst loading (2 mol%) to improve the enantioselectivity toward *syn*-**4a**. (For details, see Table S4 in SI). The use of DECHA gave similar enantioselectivity (entry 13). Fortunately, the use of DEMA afforded *syn*-**4a** in the highest enantioselectivity observed when the asymmetric Michael reaction is conducted in either CPME or MTBE solvent (entries 14 and 15).

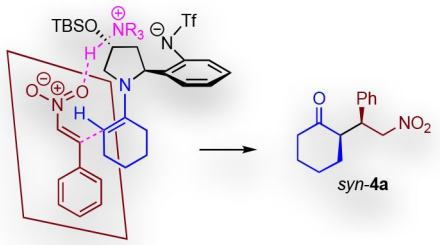
With the optimized reaction conditions for the use of **1** in hand, the substrate scope of the asymmetric direct Michael reactions was examined. Several cycloalkanones **2** and *trans*-β-arylnitroethenes **3** were subjected to the optimized reaction conditions in the presence of an amine additive (triethylamine or DEMA) in either CPME or MTBE solvent at room temperature (Table 2). Initially, the reactions of cyclohexanone with a variety of *trans*-β-arylnitroethenes **3** bearing different aryl groups furnished the corresponding Michael adducts **4a~e** with high *syn*- and enantioselectivity, in high yields (entries 1~18). In

Table 2. Asymmetric Direct Michael Reaction between Several Ketones **2** and *trans*-β-Arylnitroethene **3** Catalyzed by Organocatalyst **1**.[a]



Entry	Major Product	Amine, Solvent, Time (h)	Yield (%)[b]	*syn:anti*[c]	Ee (%)[d]
1		Et_3N, CPME, 34	92	92 : 8	91
2		Et_3N, MTBE, 24	99	91 : 9	92
3		Et_2NMe, CPME, 48	99	90 : 10	95
4	*syn*-**4a**	Et_2NMe, MTBE, 48	81	88 : 12	96
5		Et_3N, CPME, 48	77	90 : 10	91
6		Et_3N, MTBE, 48	62	91 : 9	83
7		Et_2NMe, CPME, 48	96	90 : 10	95
8	*syn*-**4b**	Et_2NMe, MTBE, 48	99	90 : 10	91
9		Et_3N, CPME, 48	88	90 : 10	64
10		Et_3N, MTBE, 48	71	90 : 10	52
11	*syn*-**4c**	Et_2NMe, CPME, 72	75	90 : 10	76
12		Et_3N, CPME, 25	85	86 : 14	87
13		Et_3N, MTBE, 39	81	90 : 10	81
14		Et_2NMe, CPME, 48	59	90 : 10	87
15	*syn*-**4d**	Et_2NMe, MTBE, 48	77	87 : 13	93
16		Et_3N, CPME, 48	92	90 : 10	81
17		Et_3N, MTBE, 48	74	86 : 14	76
18	*syn*-**4e**	Et_2NMe, CPME, 72	64	87 : 13	87
19		Et_3N, CPME, 48	97	91 : 9	91
20		Et_3N, MTBE, 48	85	91 : 9	94
21		Et_2NMe, CPME, 48	43	90 : 10	>99
22	*syn*-**4f**	Et_2NMe, MTBE, 48	40	86 : 14	98
23		Et_3N, CPME, 48	88	86 : 14	82
24		Et_3N, MTBE, 48	82	79 : 21	74
25	*syn*-**4g**	Et_2NMe, CPME, 48	95	86 : 14	82
26		Et_3N, CPME, 36	76	91 : 9	86
27		Et_3N, MTBE, 48	95	86 : 14	83
28	*syn*-**4h**	Et_2NMe, CPME, 48	82	88 : 12	90
29		Et_3N, CPME, 48	99	87 : 13	75
30		Et_3N, MTBE, 24	74	87 : 13	89
31		Et_2NMe, CPME, 48	62	84 : 16	87
32	*syn*-**4i**	Et_2NMe, MTBE, 48	55	84 : 16	88
33		Et_3N, MTBE, 43	98	87 : 13	75

[a] Unless otherwise specified, asymmetric direct Michael reactions between ketones (0.5 mmol) and *trans*-β-arylnitroethene (0.2 mmol) were carried out at room temperature in the presence of 2 mol% of catalyst **1** and Et_3N or Et_2NMe (0.2 mmol) in CPME or TBME (1.0 mL). [b] Isolated yield. [c] The *syn:anti* ratio was determined by ^{1}H NMR spectroscopy. [d] % ee of the major *syn*-isomer.



Scheme 3. Proposed Transition State Structure.

particular, the use of DEMA base additive is important to achieve excellent enantioselectivity (entries 3, 4, 7, 11, 15, and 18). The use of 4-substituted cyclohexanones such as 4-*tert*-butyl- and 4-phenylcyclohexanone afforded the corresponding Michael adducts **4f** and **4g** with both high *syn*- and enantioselectivity in addition to high diastereoselectivity for the 4-*tert*-butyl or 4-phenyl substituent (entries 19 ~ 25). Again, the use of the DEMA base additive is essential for achieving excellent enantioselectivity for *syn*-**4f** (entries 21 and 22). Notably, the enantioselectivity observed in the DEMA/CPME system is almost perfect (entry 21). When heteroatoms were incorporated into the cyclohexanone substrate, the desired Michael adducts **4h** and **4i** were delivered in good to high yield with high *syn*- and enantioselectivity (entries 26 ~ 32). This approach is also applicable to an asymmetric direct Michael reaction between an aldehyde and *trans*-β-nitrostyrene and results in good enantioselectivity (entry 33).

Based on the absolute configuration of the Michael adduct *syn*-**4a**, a transition state structure of asymmetric Michael reaction catalyzed by **1b** was proposed to account for the observed absolute configuration of *syn*-**4a** (Scheme 3). Here, R_3NH^+ moiety activates *trans*-β-nitrostyrene for the smooth transformation to the Michael adduct *syn*-**4a**.

In summary, we have developed an asymmetric direct Michael reaction that is applicable to several ketones and *trans*-β-arylnitroethenes under the influence of commercially available *L*-hydroxyproline-based amino Tf-amide organocatalyst **1** in a practical manner. The use of a trialkylamine adduct, such as triethylamine or DEMA, is of crucial importance to accelerate the reaction and also to achieve high enantioselectivity in the present asymmetric direct Michael reactions catalyzed by bifunctional amino Tf-amide organocatalyst **1**. Further investigations concerning the efficacy and effectiveness of organocatalyst **1** and other related catalysts in other asymmetric reactions are currently in progress in our laboratories.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asymmetric catalysis · Bifunctional catalysts · Michael reaction · Organocatalysis · Synthetic methods

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