DOI: 10.1002/ejoc.201000569

C_3-Symmetric Proline-Functionalized Organocatalysts: Enantioselective Michael Addition Reactions

Jarugu Narasimha Moorthy*[a] and Satyajit Saha[a]

Keywords: Asymmetric synthesis / Michael addition / Organocatalysis / Amino acids

C_3-Symmetric, tripodal catalyst **4** based on 1,3,5-triethylbenzene, which incorporates the features of a molecular receptor, is shown to catalyze Michael addition reactions of carbonyl compounds to β-nitrostyrenes in a high stereoselectivity (up to 99:1 *dr* and up to 98 % *ee*).

Introduction

The obvious advantage with catalysts of higher symmetry in the realm of asymmetric synthesis is the reduction in number of reaction pathways, which is expected to manifest in higher selectivity.[1] However, C_2 symmetry is more conspicuous in the design of catalysts in comparison to C_3 symmetry.[2] One of the reasons for this appears to be the skepticism with which the use of C_3 symmetry in catalyst design was regarded; initially, the argument put forward for the possible failure of C_3-symmetric receptors in guest binding is that the steric requirements for possible diastereomeric transition states would be the same or less distinguishable, leading to no or poor enantiodiscrimination.[3] Notwithstanding this notion, there is growing interest in the exploitation of C_3 symmetry in chiral recognition, and recent reports have sufficiently demonstrated utilization of C_3 symmetry in the development of chiral catalysts as well as in the design of receptors for molecular recognition.[4]

In our research, we have been concerned with exploitation of sterics to control molecular order and otherwise to develop functional organic materials.[5] We surmised that sterically favored geometries of 2,4,6-substituted 1,3,5-trialkylbenzenes should be appealing for convenient exploitation in the development of C_3-symmetric catalysts for application in organocatalysis. Notably, 1,3,5-triethylbenzene has been exploited as a nice platform to develop receptor systems for a range of sensing applications.[6] We designed the threefold proline-functionalized C_3-symmetric 1,3,5-trialkylbenzenes **1**–**4** (Figure 1) as organocatalysts with the expectation that the tethered pyrrolidine moieties based on chiral proline would enclose a void space over the aromatic

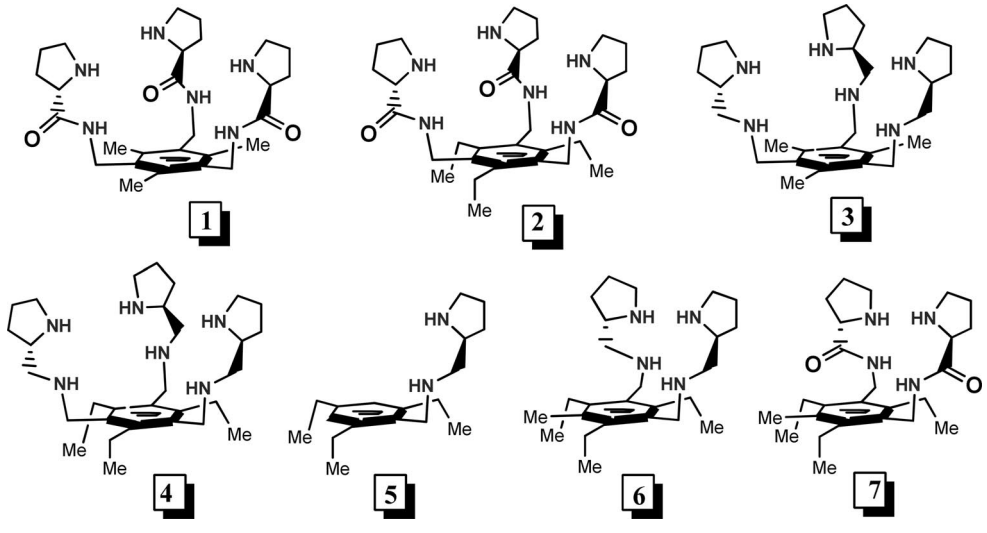


Figure 1. Structures of proline-derived catalysts **1**–**7** examined for enantioselective Michael reactions.

[a] Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India
E-mail: moorthy@iitk.ac.in

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000569.

benzene platform within which enamine catalysis may be carried out with high enantioselectivity.

Our premise was that whereas one of the tethered prolines would be utilized for enamine formation with a nucleophilic ketone, the N–H bonds of the other two tethered prolines should in some way form hydrogen bonds to the electrophile in a highly diastereoselective manner to permit high enantioselectivity. We particularly chose nitroolefins as electrophilic partners, as the oxygen atoms of the nitro group may involve a maximum number of hydrogen bonds with catalysts **1**–**4**. Thus, we explored the latter in mediating Michael additions of carbonyl compounds to nitroalkenes enatioselectively. While our investigations were in progress, Fujioka et al. reported an analogous 1,3,5-triimidazoline C_3-symmetric catalyst for Michael additions of 1,3-diketones to β-nitrostyrenes.[7] Herein, we show that the C_3-symmetric catalyst **4** catalyzes the Michael addition of a variety of ketones to nitroolefins to afford conjugate addition products with high diastereo- and enantioselectivities.

Results and Discussion

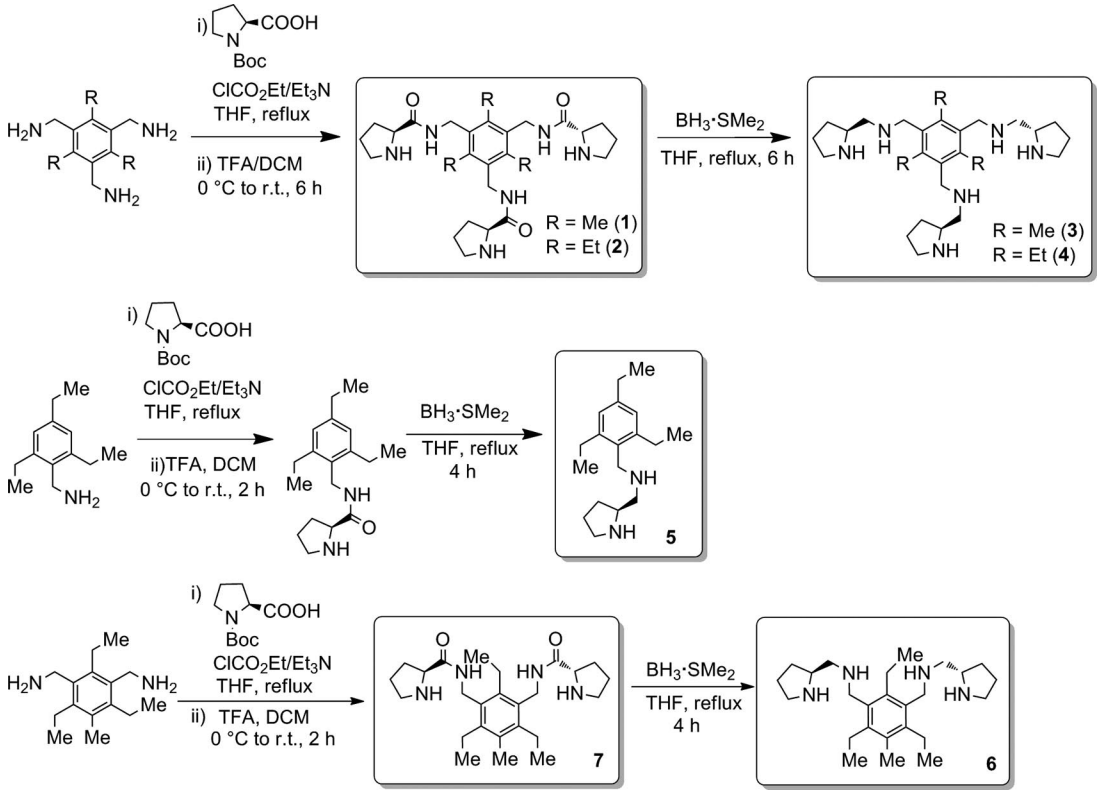
Synthesis of Catalysts 1–7

Arylprolinamides **1**, **2**, and **7** (Figure 1) were synthesized starting from Boc-protected L-proline, which was treated with ethyl chloroformate in THF in the presence of Et_3N at 0 °C to afford the mixed anhydride (Scheme 1). The latter was treated with substituted amines to afford Boc-protected *N*-aryl-L-prolinamides, the deprotection of which under standard conditions involving 20% TFA in DCM at 0 °C led to *N*-aryl-L-prolinamides **1**, **2**, and **7** in respectable overall yields. Catalysts **3**–**6** were synthesized by reduction of the corresponding prolinamides with $BH_3{\cdot}SMe_2$ in THF.

Enantioselective Michael Additions with Catalysts 1–7

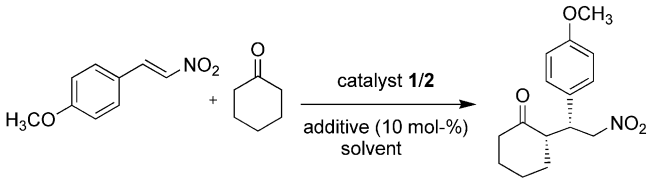
Initially, catalysts **1** and **2** were conjectured to be ideal for binding the electrophilic nitroolefin through N–H···O hydrogen bonds involving the amide hydrogen atoms. Thus, triamide catalysts **1** and **2** were explored for their ability to mediate Michael addition of cyclohexanone to β-nitrostyrene under a variety of conditions (Table 1).

As revealed by the results in Table 1, the enantioselectivity was found to be frustratingly poor even with some additives, whereas the reactions proceeded smoothly to afford the Michael adducts in respectable yields and diastereoselectivity. We thus reasoned that the tethered-prolinamides **1** and **2** are presumably locked conformationally by intramolecular N–H···O hydrogen bonding as shown in Figure 2a, leading to the observed reactivity that seemingly occurs from the nitroolefin, which is not bound in the enclosure over the benzene surface. This fact together with our observation that organocatalytic Michael additions are generally promoted by 2-aminomethylpyrrolidine derivatives and not as much with prolinamides[8] spurred us to consider reduced analogs **3** and **4**. We believed that the in-



Scheme 1.

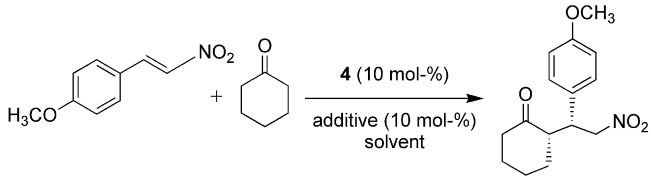
Table 1. Screening of catalysts **1** and **2** for the enantioselective Michael addition reaction of cyclohexanone to *p*-methoxy-β-nitrostyrene in various solvents with different additives.[a]



Catalyst	Solvent	Additive [10 mol-%]	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1[e]	DCM	–	30	90	98:2	24
1	DCM	TFA	16	88	98:2	25
1	DMF	TFA	16	86	95:5	22
1	dioxane	TFA	18	92	96:4	26
1	H_2O	TFA	18	60	95:5	18
2[e]	DCM	–	28	87	98:2	38
2	DCM	–	15	90	98:2	22
2	DCM	TFA	15	85	95:5	20
2	DMF	–	15	90	96:4	22
2	dioxane	TFA	16	92	96:4	34
2	H_2O	TFA	16	56	95:5	36
2	hexane	TFA	20	88	96:4	32
2	IPA	TFA	90	92	95:5	28

[a] The reactions in all solvents were run with *p*-methoxy-β-nitrostyrene (0.3–0.4 mmol) at 3 ± 1 °C under identical conditions by employing the catalyst (20 mol-%), unless mentioned otherwise. [b] Based on *p*-methoxy-β-nitrostyrene. [c] The *syn*/*anti* ratio was determined by 500 MHz ^{1}H NMR spectroscopy. [d] Based on chiral HPLC analyses for the major *syn* diastereomer. [e] 10 mol-% was employed.

Table 2. Screening of catalyst **4** in mediating the enantioselective Michael addition of cyclohexanone to *p*-methoxy-β-nitrostyrene.[a]



Entry	Solvent	Additive[b] [10 mol-%]	Time [h]	Yield[c] [%]	*dr*[d]	*ee*[e] [%]
1	DMSO	none	32	>90	85:15	64
2	DMF	none	32	>88	90:10	73
3	THF	none	36	slow	nd[f]	nd[f]
4	IPA	none	36	60	95:5	88
5	DCM	none	32	88	98:2	98
6	toluene	none	56	<15	nd[f]	nd[f]
7	CH_3CN	none	32	88	96:4	85
8	brine	none	32	67	98:2	93
9	NMP	none	48	65	95:5	85
10	DCM	TFA	36	85	98:2	90
11	brine	TFA	48	<30	nd[f]	nd[f]
12	DCM	*p*-TsOH	48	slow	nd[f]	nd[f]
13	DCM	Mosher's acid	48	slow	nd[f]	nd[f]
14	IPA	DNBA	24	85	95:5	87

[a] The reactions were run with *p*-methoxy-β-nitrostyrene (0.3–0.4 mmol) at 3 ± 1 °C under identical conditions. [b] TFA = trifluoroacetic acid; *p*-TsOH = *p*-toluenesulfonic acid; DNBA = 3,5-dinitrobenzoic acid. [c] Based on *p*-methoxy-β-nitrostyrene. [d] The *syn*/*anti* ratio was determined by 500 MHz ^{1}H NMR spectroscopy. [e] Based on chiral HPLC analyses for the major *syn* diastereomer. [f] Not determined.

creased entropy of the pyrrolidines introduced through the CH_2–NH–CH_2 tether might allow the appropriate transition-state geometries for Michael additions to be adopted rather easily. Thus, catalyst **4** in which the ethyl groups supposedly ensure all the tethered aminomethylpyrrolidines to be *syn*[9] was screened for mediating the Michael addition of cyclohexanone to *p*-methoxy-β-nitrostyrene at ca. 3 °C under various conditions shown in Table 2; a perusal of the results shows that the reaction proceeds well in dichloromethane with a very high stereoselectivity (Table 2, Entry 5).

The enantioselective Michael addition of cyclohexanone to *p*-methoxy-β-nitrostyrene under these conditions was examined uniformly for amide catalysts **1**, **2**, and **7** and for aminomethylpyrrolidine derivatives **3**, **5**, and **6**. C_1- and C_2-Symmetric aminomethylpyrrolidine functionalized 1,3,5-triethylbenzenes **5** and **6** and C_2-symmetric amide derivative **7** were synthesized and examined for their enantiocatalytic behavior in regulating the Michael addition reaction of cyclohexanone to *p*-methoxy-β-nitrostyrene to establish the influence of enclosure inherent to the C_3-symmetric catalysts (i.e., **3** and **4**) vis-à-vis C_1- and C_2-symmetric catalysts

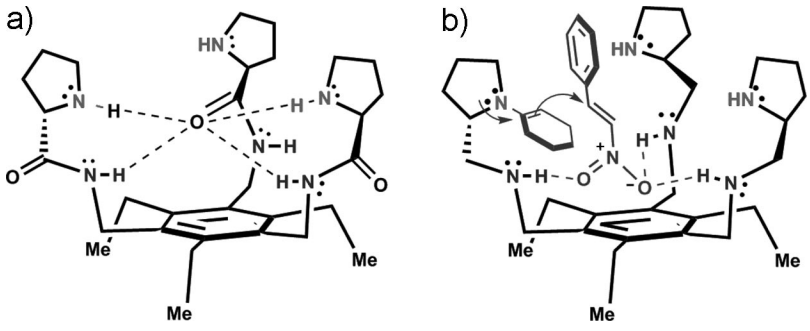
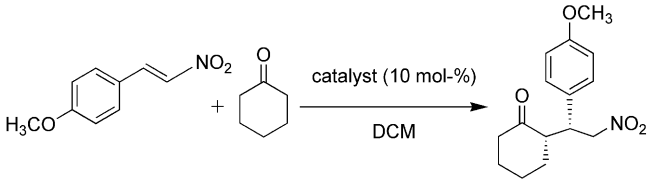


Figure 2. (a) Possible N–H···O H-bond mediated conformational locking in amide catalyst **2**, and (b) plausible transition-state geometry for Michael addition with catalyst **4**.

(i.e., **5** and **6**). In Table 3 are consolidated the results of the Michael addition reactions between cyclohexanone and *p*-methoxy-β-nitrostyrene for catalysts **1**–**7** under uniform reaction conditions at 10 mol-% catalyst loading.

Table 3. Screening of catalyst **4** in mediating the enantioselective Michael addition of cyclohexanone to *p*-methoxy-β-nitrostyrene.[a]



Entry	Catalyst	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**1**	38	84	96:4	32
2	**2**	38	82	96:4	34
3	**3**	32	82	95:5	86
4	**4**	32	88	98:2	98
5	**5**[e]	64	45	96:4	78
6	**6**[e]	42	88	96:4	90
7	**7**[e]	42	86	97:3	34

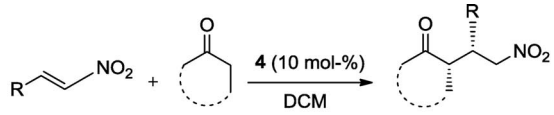
[a] The reactions were run with *p*-methoxy-β-nitrostyrene (0.3–0.4 mmol) at 3 ± 1 °C under identical conditions. [b] Based on *p*-methoxy-β-nitrostyrene. [c] The *syn*/*anti* ratio was determined by 500 MHz ^{1}H NMR spectroscopy. [d] Based on chiral HPLC analyses for the major *syn* diastereomer. [e] No perceptible difference in stereochemistry was observed when the catalyst loading was increased to 30 mol-% for **5** and 15 mol-% for **6** and **7**.

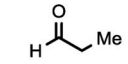
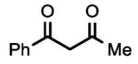
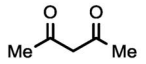
The following are readily evident from Table 3: (i) C_3-Symmmetric amide-based catalysts **1** and **2** lead to poor *ee* values. (ii) C_1-Symmetric catalyst **5** does not lead to high enantioselectivity under catalyst loading (30 mol-%) that is comparable to that of **4**; indeed, C_2-symmetric catalyst **6** also does not afford the Michael adduct in an optical purity comparable to that obtained with catalyst **4**. (iii) One observes a gradual increase in the *ee* value on going from C_1- to C_2- to C_3-symmetric catalyst **4** (Table 3, Entries 4, 5, and 7). These results amply attest to the fact that the enclosure formed by the tethered aminomethylpyrrolidines in C_3-symmetric catalyst **4** contributes to better enantioselectivity. Supposedly, the CH_2–NH–CH_2 tether also permits the suitable transition-state geometry to be adopted rather easily, as was presupposed. In Figure 2b is shown the plausible geometry for binding of the nitroolefin and the ketone that accounts for the observed enantioselectivity.

Buoyed by the results with catalyst **4**, we investigated the enantioselective Michael addition of cyclic as well as acyclic ketones and 1,3-diketones to a variety of conjugated nitroolefins (Table 4); the nitroolefins were both aliphatic as well as aromatic, and the latter were varied in terms of electron-poor/rich attributes.

Under a catalytic loading of 10 mol-% in dichloromethane at ±3 °C, the reactions went to completion in 20–42 h. As shown in Table 3, the diastereoselectivity was found to be very high for the addition of cyclohexanone to a variety of nitroolefins, with the *syn* diastereomer predominating

Table 4. Results of the enantioselective Michael reaction by using C_3-symmetric tripodal catalyst **4**.[a]



Entry	Ketone	R	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1		Ph	20	88	97:3	92
2		4-$MeOC_6H_4$	32	92	98:2	98
3		4-MeC_6H_4	22	88	97:3	97
4		3-$MeOC_6H_4$	22	87	99:1	96
5		2-$MeOC_6H_4$	26	92	97:3	97
6		2,3-$(MeO)_2C_6H_3$	32	90	97:3	92
7		3,4-$(MeO)_2C_6H_3$	34	90	98:2	94
8		4-BrC_6H_4	22	86	95:5	92
9		4-FC_6H_4	28	85	94:6	91
10		4-$BnOC_6H_4$	26	87	97:3	96
11		4-$Me_2NC_6H_4$	26	88	97:3	96
12		4-$NO_2C_6H_4$	18	89	95:5	89
13		4-$CF_3C_6H_4$	28	88	97:3	88
14		2-napthyl	24	73	97:3	90
15		cyclohexyl	24	60	94:6	90
16		*i*Bu	42	55	96:4	86
17		Ph	40	45	75:25	80
18		4-$MeOC_6H_4$	40	48	75:25	80
19		4-$NO_2C_6H_4$	40	48	77:23	75
20		4-$MeOC_6H_4$	28	85	50:50	82
21		4-$MeOC_6H_4$	36	87	50:50	82
22		Ph	36	83	–	76
23		4-$MeOC_6H_4$	36	88	–	78
24		4-$NO_2C_6H_4$	36	88	–	76
25		Ph	28	56	–	76
26		4-$MeOC_6H_4$	28	56	–	78
27		4-$NO_2C_6H_4$	28	62	–	78

[a] The reactions in all cases were run with β-nitrostyrene derivatives (0.3–0.4 mmol) at 3 ± 1 °C under identical conditions. [b] Based on the β-nitrostyrene derivative. [c] The *syn*/*anti* ratio was determined by 500 MHz ^{1}H NMR spectroscopy. [d] Based on chiral HPLC analyses of the major *syn* diastereomer.

(Table 4, Entries 1–16); whereas a high diastereoselectivity was observed for electron-rich nitroolefins (*syn*/*anti* up to 99:1), marginally less selectivity was observed for electron-deficient olefins (up to 94:6; Table 4, Entries 8, 9, 12, and 13). In the same vein, low enantioselectivity (ca. 88%) was observed for electron-poor nitroolefins in contrast to their electron-rich counterparts (ca. 97–98%). Rather attenuated enantioselectivity was observed for nitroolefins substituted with aliphatic groups such as cyclohexyl and isobutyl (ca. 86–90% *ee*; Table 4, Entries 15 and 16). For conjugate addition of cyclopentanone to β-nitrostyrenes substituted with electron-rich and poor substituents, both diastereo- and enantioselectivities were found to be significantly less as compared to those for cyclohexanone (Table 4, Entries 17–19). Whereas virtually no diastereodiscrimination was observed for the addition of acyclic propanaldehyde

and benzoylacetone, a 1,3-diketone, to *p*-methoxy-β-nitrostyrene, notable enantioselectivity was found for the *syn* diastereomer. The Michael addition of both acetone and acetylacetone to both electron-rich and poor nitrostyrene led to the corresponding products in respectable yields with *ee* values in the range 75–80% (Table 4, Entries 22–27). The relatively poor stereoselectivities for acyclic aldehyde and ketones should be traceable to the considerable flexibility of the tether, which otherwise is also an advantage for stabilizing the appropriate geometries of the transition states, as mentioned earlier. However, it is the tradeoff between the size/shape and the flexibility of the tether that is apparently crucial for best results, as observed for the addition of cyclohexanone to a variety of nitroolefins. The results uncovered herein compellingly signify the influence of C_3-symmetric tripodal catalysts as applied to the Michael reaction, which is one of the most important C–C bond-forming reactions.[10] The addition of carbon-centered nucleophiles to nitroolefins that leads to functionalized products with multiple stereogenic centers is of tremendous importance in view of the fact that the nitro functionality can be easily transformed into a broad spectrum of optically enriched intermediates.[11] A wide variety of catalysts has been developed for this particular reaction based on readily available chiral amines,[12,13] due to the fact that the reaction affords enantiomerically enriched products with two contiguous stereocenters in a single step. Despite excellent results with diverse catalysts, the design and development of new and novel chiral organocatalysts is an enduring effort in the pursuit of enantiomerically pure compounds in organic synthesis.

Conclusions

We have designed and synthesized C_3-symmetric tripodal organocatalysts with receptor features based on 1,3,5-trialkylbenzenes for application in enantioselective reactions. From a systematic investigation that entailed modification of the catalyst structure in light of the observed selectivities with catalysts **1** and **2**, the catalyst **4** that enjoys conformational flexibility was designed and shown to be effective for highly diastereo- and enantioselective Michael additions of carbonyl compounds to β-nitrostyrenes. To account for the high stereoselectivities observed with organocatalyst **4** for Michael additions, the transition state structure involving attack of the enamine derived from the carbonyl compounds is presumed to attack the β-nitrostyrene that is bound through N–H···O hydrogen bonds in the cavity enclosed by the CH_2–NH–CH_2 tethers over the benzene surface. Thus, the results reported herein with the tripodal catalysts based on 1,3,5-triethylbenzene exemplify a new approach for organocatalysis in general.

Experimental Section

The required substituted amines, viz., 1,3,5-tris(aminomethyl)-2,4,6-trimethylbenzene, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, 1,3-bis(aminomethyl)-5-methyl-2,4,6-triethylbenzene, and 1-(aminomethyl)-2,3,6-triethylbenzene, were prepared by following the literature-reported procedures.

General Procedure for the Preparation of Catalysts 1–7: To a two-necked, round-bottomed flask containing Boc-L-proline (10.08 g, 48.1 mmol) in dry THF (60 mL) was added triethylamine (4.86 g, 48.1 mmol) under a N_2 atmosphere. The resultant solution was cooled to 0 °C. Subsequently, ethyl chloroformate (5.22 g, 48.1 mmol) was introduced dropwise over a period of 45 min. After the solution was stirred at this temperature for 1 h, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (2.0 g, 8.0 mmol) was added under a N_2 atmosphere in small portions. The reaction mixture was stirred at 0 °C for 1 h, at room temperature for 2 h, and heated at reflux for 48 h; the reaction was continually monitored by TLC analyses. At the end of the reaction, as judged by TLC analysis, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to afford the crude product, which was further purified by silica-gel column chromatography. For deprotection of the above Boc-protected prolinamide derivative, the substrate was dissolved in dry DCM (40 mL) and cooled to 0 °C. TFA (12 mL) was slowly added to this solution at 0 °C, which was then stirred for 3 h at room temperature. The reaction mixture was evaporated in vacuo and washed thoroughly with petroleum ether. The oil was dissolved in a minimum amount of water and basified with NH_4OH, extracted with chloroform, washed thoroughly with water, dried with anhydrous Na_2SO_4, and concentrated to yield the pure carboxamide.

General Procedure for the Reduction of *N*-Arylprolinamides: The pure prolinamide available from the above reaction (2.52 g, 4.6 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. To the solution was added $BH_3{\cdot}SMe_2$ (2.12 g, 28 mmol) slowly with vigorous stirring. Later, the reaction mixture was heated at reflux for 7 h, cooled, and carefully acidified with 10% HCl. The contents were further heated at reflux for 6 h. The reaction mixture was then cooled to 0 °C and basified with 2 N NaOH solution, and the solvent was removed in vacuo. The organic matter was extracted with DCM, washed with water, dried, and concentrated to obtain the pure amine in respectable yield.

1: Yield 86%; m.p. 102–104 °C. $[a]_D^{25}$ = –35.26 (*c* = 0.2, DCM). IR (KBr): $\tilde{\nu}$ = 1530, 1642, 2866, 2964, 3297 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.66–1.72 (m, 6 H), 1.87–1.94 (m, 3 H), 2.10–2.18 (m, 3 H), 2.30 (s, 9 H), 2.77–2.88 (m, 3 H), 2.93–2.99 (m, 3 H), 3.79 (dd, *J* = 5.3, 6.2 Hz, 3 H), 4.38–4.46 (m, 6 H), 7.57 (br. s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 26.0, 30.7, 38.6, 47.1, 60.3, 133.0, 137.0, 174.4 ppm. HRMS (ESI+): calcd. for $C_{27}H_{42}N_6O_3$ $[M + H]^+$ 499.3396; found 499.3384.

2: Yield 90%; m.p. 72–74 °C. $[a]_D^{25}$ = –49.31(*c* = 0.2, DCM). IR (KBr): $\tilde{\nu}$ = 1501, 1658, 2871, 2965, 3320 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.6 Hz, 9 H), 1.63–1.72 (m, 6 H), 1.90–2.02 (m, 3 H), 2.13–2.18 (m, 3 H), 2.59–2.73 (m, 6 H), 2.77–2.82 (m, 3 H), 2.92–2.97 (m, 3 H), 3.74 (dd, *J* = 5.7, 8.9 Hz, 3 H), 4.38 (dd, *J* = 4.5, 14.3 Hz, 3 H), 4.47 (dd, *J* = 2.9, 12.5 Hz, 3 H), 7.45 (br. s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 23.0, 26.2, 30.7, 37.7, 47.2, 60.5, 132.2, 144.1, 174.8 ppm. HRMS (ESI+): calcd. for $C_{30}H_{48}N_6O_3$ $[M + H]^+$ 541.3866; found 541.3867.

3: Yield 78%; gummy liquid. $[a]_D^{25}$ = +9.09 (*c* = 0.2, DCM). IR (KBr): $\tilde{\nu}$ = 1265, 2875, 2966, 3420 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31–1.37 (m, 6 H), 1.61–1.75 (m, 3 H), 1.81–1.93 (m, 3 H), 2.41 (s, 9 H), 2.61–2.72 (m, 6 H), 2.81–2.93 (m, 6 H), 3.16–3.24 (m, 3 H), 3.74 (d, *J* = 5.8 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 25.4, 29.4, 29.6, 46.2, 48.7, 55.0, 58.2.135.0 ppm.

HRMS (ESI+): calcd. for $C_{27}H_{48}N_6$ $[M + H]^+$ 457.4018; found 457.4018.

4: Yield 78%; gummy liquid. $[\alpha]_D^{25}$ = +13.9 (*c* = 0.2, DCM). IR (KBr): $\tilde{\nu}$ = 2869, 2960, 3307 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 6.5 Hz, 9 H), 1.32–1.39 (m, 6 H), 1.65–1.79 (m, 3 H), 1.82–1.89 (m, 3 H), 2.08 (br. s, 3 H), 2.64–2.96 (m, 18 H), 3.16–3.23 (m, 3 H), 3.69 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0, 22.9, 25.2, 29.4, 46.1, 47.8, 54.6, 58.7, 134.1, 142.2 ppm. HRMS (ESI+): calcd. for $C_{30}H_{54}N_6$ $[M + H]^+$ 541.3866; found 541.3867.

5: Yield 76%; gummy liquid. $[\alpha]_D^{27}$ = –61.5 (*c* = 0.1, DCM). IR (KBr): $\tilde{\nu}$ = 1265, 2875, 2966, 3420 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.15–1.28 (m, 9 H), 1.35–1.43 (m, 2 H), 1.68–1.78 (m, 1 H), 1.85–1.91 (m, 1 H), 2.27 (br. s, 1 H), 2,54–2.58 (m, 2 H), 2.64–2.77 (m, 4 H), 2.89–2.96 (m, 2 H), 3.27–3.34 (m, 1 H), 3.73 (d, *J* = 5.4 Hz, 2 H), 6.87 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 15.8, 23.7, 26.7, 28.6, 29.4, 31.6, 47.7, 55.2, 56.1, 143.7, 144.2, 144.8, 145.1 ppm. HRMS (ESI+): calcd. for $C_{18}H_{30}N_2$ $[M + H]^+$ 275.2487; found 275.2487.

6: Yield 80%; gummy liquid. $[\alpha]_D^{27}$ = –51.23 (*c* = 0.2, DCM). IR (KBr): $\tilde{\nu}$ = 1265, 2870, 2963, 3318 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 6 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 1.33–1.40 (m, 4 H), 1.66–1.80 (m, 2 H), 1.83–1.90 (m, 2 H), 2.25 (s, 3 H), 2.67–2.80 (m, 10 H), 2.82–2.96 (m, 4 H), 3.19–3.25 (m, 2 H), 3.70 (d, *J* = 3.8 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 15.1, 17.1, 22.8, 23.2, 25.1, 29.3, 46.1, 47.9, 54.7, 58.5, 132.3, 133.6, 140.0, 141.2 ppm. HRMS (ESI+): calcd. for $C_{25}H_{44}N_4$ $[M + H]^+$ 401.3644; found 401.3644.

7: Yield 88%; m.p. 68–70 °C. $[\alpha]_D^{27}$ = –20.2 (*c* = 0.1, DCM). IR (KBr): $\tilde{\nu}$ = 1450, 1502, 1657, 2869, 2964, 3309 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13–1.16 (m, 9 H), 1.64–1.70 (m, 4 H), 1.89–1.96 (m, 2 H), 2.10–2.18 (m, 2 H), 2.29 (s, 3 H), 2.60–2.70 (m, 6 H), 2.76–2.79 (m, 2 H), 2.90–2.94 (m, 2 H), 3.73 (dd, *J* = 5.3, 9.1 Hz, 2 H), 4.38 (dd, *J* = 4.2, 14.3 Hz, 2 H), 4.44 (dd, *J* = 4.6, 14.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8, 15.1, 16.6, 22.9, 23.3, 26.1, 30.7, 37.9, 47.2, 60.5, 131.2, 132.9, 141.1, 142.7, 174.8 ppm. HRMS (ESI+): calcd. for $C_{25}H_{40}N_4O_2$ $[M + H]^+$ 429.3229; found 429.3233.

Typical Procedure for the Enantioselective Michael Reaction using Catalyst 4: A mixture of the catalyst (0.023 g, 0.048 mmol) and ketone (0.50 g, 4.8 mmol) in DCM was stirred at room temperature for 45 min. Subsequently the temperature was cooled to 3 °C and *p*-methoxy-β-nitrostyrene (0.09 g, 0.5 mmol) was introduced. The reaction mixture was stirred at 3 °C until the reaction was judged to be complete based on TLC analysis. Upon completion, the reaction mixture was purified rapidly by passing through a short pad of neutral silica gel column. The crude product before silica gel chromatography was submitted to ^1H NMR spectroscopic analysis to determine the diastereomeric ratio. The product after SiO_2 chromatography was analyzed by HPLC to determine the enantiomeric as well as the diastereomeric ratios. The *syn* and *anti* diastereomers of the Michael addition products were readily distinguished by ^1H NMR spectroscopy by the diagnostic chemical shifts of the –C*H*Ar-proton (see the Supporting Information for the chemical shift data).

Supporting Information (see footnote on the first page of this article): Details of synthesis, copies of the ^1H and ^{13}C NMR spectra of catalysts **1**–**7**, ^1H NMR diagnostic chemical shift data for *syn* and *anti* Michael addition products, and HPLC profiles for all results in Table 4.

Acknowledgments

J. N. M. is thankful to Department of Science and Technology (DST), New Delhi for generous financial support. S. S. is grateful to Council of Scientific and Industrial Research (CSIR), New Delhi for a Senior Research Fellowship.

[1] a) C. Moberg, *Angew. Chem. Int. Ed.* **1998**, *37*, 248–268; b) M. T. Powell, A. M. Porte, K. Burgess, *Chem. Commun.* **1998**, 2161–2164; c) T. Fang, D.-M. Du, S.-F. Lu, J. Xu, *Org. Lett.* **2005**, *7*, 2081–2084; d) S. E. Gibson, M. P. Castaldi, *Angew. Chem. Int. Ed.* **2006**, *45*, 4718–4720; e) S. L. Wiskur, H. A. Haddou, J. J. Lavigne, E. V. Anslyn, *Acc. Chem. Res.* **2001**, *34*, 963–972; f) C. Foltz, B. Stecker, G. Marconi, S. B.-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2007**, *13*, 9912–9923; g) L. H. Gade, S. B.-Laponnaz, *Chem. Eur. J.* **2008**, *14*, 4142–4152.

[2] a) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561–3651; b) V. A. Pavlov, *Tetrahedron* **2008**, *64*, 1147–1179.

[3] a) S.-G. Kim, K.-H. Kim, J. Jung, S. K. Shin, K. H. Anh, *J. Am. Chem. Soc.* **2002**, *124*, 591–596; b) C. Moberg, *Angew. Chem. Int. Ed.* **2006**, *45*, 4721–4723.

[4] a) H.-J. Choi, Y. S. Park, S. H. Yun, H.-S. Kim, C. S. Cho, K. Ko, K. H. Ahn, *Org. Lett.* **2002**, *4*, 795–798; b) S. L. Tobey, B. D. Jones, E. V. Anslyn, *J. Am. Chem. Soc.* **2003**, *125*, 4026–4027; c) D.-M. Du, T. Fang, J. Xu, S.-W. Zhang, *Org. Lett.* **2006**, *8*, 1327–1330; d) N. Singh, D. O. Jang, *Org. Lett.* **2007**, *9*, 1991–1994; e) A. Ard, C. Venturi, C. Nativi, O. Francesconi, G. Gabrielli, F. J. Cacada, J. J. Barbero S. Roelens, *Chem. Eur. J.* **2010**, *16*, 414–418; f) M. Arunachalam, P. Ghosh, *Org. Lett.* **2010**, *12*, 328–331; g) M. Arunachalam, P. Ghosh, *Inorg. Chem.* **2010**, *49*, 943–951; h) J. Han, H. Wu, M. Teng, Z. Li, Y. Wang, Y. Pan, *Synlett* **2009**, *6*, 933–936.

[5] a) J. N. Moorthy, P. Natarajan, P. Venugopalan, *J. Org. Chem.* **2009**, *74*, 8566–8577; b) J. N. Moorthy, P. Venkatakrishnan, P. Natarajan, D.-F. Huang, T. J. Chow, *J. Am. Chem. Soc.* **2008**, *130*, 17320–17333.

[6] a) S.-G. Kim, K. H. Anh, *Chem. Eur. J.* **2000**, *6*, 3399–3403; b) A. Vacca, C. Nativi, M. Cacciarini, R. Pergoli, S. Roelens, *J. Am. Chem. Soc.* **2004**, *126*, 16456–16465; c) D. R. Turner, M. J. Paterson, J. W. Steed, *J. Org. Chem.* **2006**, *71*, 1598–1608; d) Z. Zhong, E. Anslyn, *J. Am. Chem. Soc.* **2002**, *124*, 9014–9015; e) J. C. Manimala, S. L. Wiskur, A. D. Ellington, E. V. Anslyn, *J. Am. Chem. Soc.* **2004**, *126*, 16515–16519.

[7] K. Murai, S. Fukushima, S. Hayashi, Y. Yakahara, H. Fujioka, *Org. Lett.* **2010**, *12*, 964–966.

[8] a) S. S. Mosse, A. Alexakis, *Chem. Commun.* **2007**, 3123–3126; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716.

[9] S. Simaan, J. S. Seigel, S. E. Biali, *J. Org. Chem.* **2003**, *68*, 3699–3701.

[10] a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) A. Berkessel, H. Groger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; e) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**.

[11] a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* **2003**, *115*, 1726–1727; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591.

[12] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; c) P. Melchiorre, K. A. Jorgensen, *J. Org. Chem.* **2003**, *68*, 4151–4157; d) T. Okino, Y. Hoashi, Y. T. Sakemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; e) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; f) N. Masse, R. Thayumanavan, F.

Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; g) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; h) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; i) S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, *Chem. Commun.* **2006**, 3687–3790; j) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; k) S. Mosse, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Chem. Eur. J.* **2008**, *14*, 7504–7507; l) Y. Xu, W. Zou, H. Sunden, H. Ibrahem, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 418–424; m) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; n) L.-Q. Gu, G. Zhao, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632; o) Vishnumaya, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117–1119; p) G.-L. Zhao, Y. Xu, H. Sunden, L. Eriksson, M. Sayah, A. Cordova, *Chem. Commun.* **2007**, 734–737; q) C.-L. Cao, X.-L. Sun, J.-L. Zhou, Y. Tang, *J. Org. Chem.* **2007**, *72*, 4073–4076; r) D. Almasi, D. A. Alonso, E. G. Bengoa, Y. Nagel, C. Najera, *Eur. J. Org. Chem.* **2007**, 2328–2343; s) T. Mandal, C.-G. Zhao, *Angew. Chem. Int. Ed.* **2008**, *47*, 7714–7717; t) Z. Yang, J. Liu, X. Liu, Z. Wang, X. Feng, Z. Su, C. Hu, *Adv. Synth. Catal.* **2008**, *350*, 2001–2006; u) F. Xue, S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* **2008**, *350*, 2194–2198 and references cited therein; v) R. J. Reddy, H.-H. Kuan, T.-Y. Chou, K. Chen, *Chem. Eur. J.* **2009**, *15*, 9294–9298; w) B. Tan, X. Zeng, Y. Lu, P. J. Chua, G. Zhong, *Org. Lett.* **2009**, *11*, 1927–1930; x) C. Wang, C. Yu, C. Liu, Y. Peng, *Tetrahedron Lett.* **2009**, *50*, 2363–2366; y) D.-Z. Xu, S. Shi, Y. Wang, *Eur. J. Org. Chem.* **2009**, 4848–4853.

[13] a) D. Lu, Y. Gong, W. Wang, *Adv. Synth. Catal.* **2010**, *352*, 644–650; b) A. Lu, R. Wu, Y. Wang, Z. Zhou, G. Wu, J. Fang, C. Tang, *Eur. J. Org. Chem.* **2010**, 732–737; c) L. Peng, X.-Y. Peng, J. Huang, J.-F. Bai, Q.-C. Huang, L.-X. Wang, *Eur. J. Org. Chem.* **2010**, 456–461.

Received: April 23, 2010
Published Online: October 1, 2010

