JOC Article
pubs.acs.org/joc

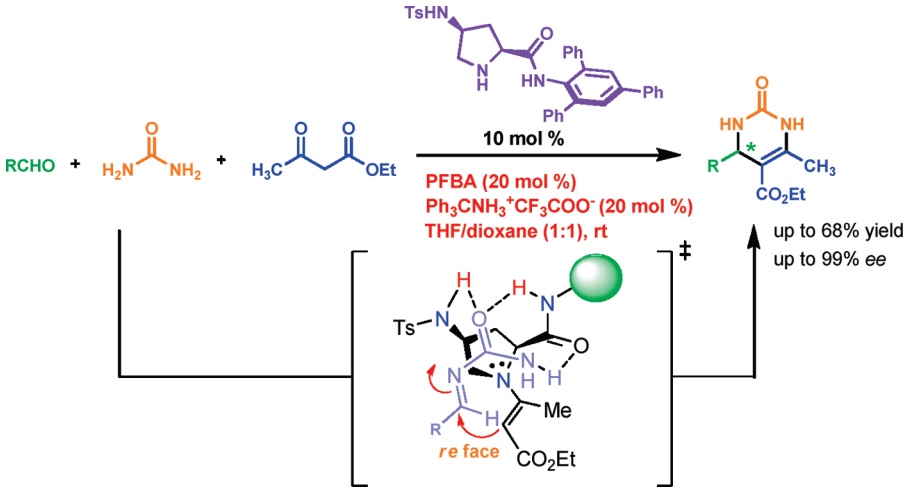
Enantioselective Organocatalytic Biginelli Reaction: Dependence of the Catalyst on Sterics, Hydrogen Bonding, and Reinforced Chirality†

Satyajit Saha and Jarugu Narasimha Moorthy*

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

moorthy@iitk.ac.in

Received August 31, 2010



From a systematic investigation involving the synthesis of a series of catalysts and screening studies, the organocatalyst **16**, which is sterically hindered, contains a strong hydrogen-bonding site, and is endowed with reinforced chirality, is shown to promote the Biginelli cyclocondensation of aromatic as well as aliphatic aldehydes with ethyl acetoacetate and urea in a remarkably high enantioselectivity (ee ca. 94−99%).

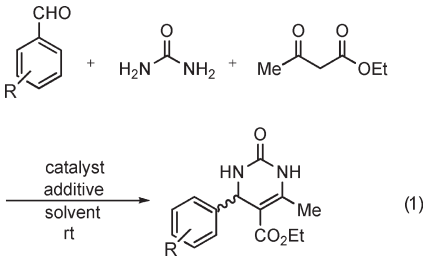
Introduction

While catalysis by nonhazardous and environmentally benign organic molecules is a major breakthrough, rapid construction of structurally complex molecules from simple and readily available precursors in one operation, referred to as a domino reaction, is an exciting prospect.[1] Domino reactions, a new direction in organocatalysis, preclude formation of waste products and increase the efficiencies of reactions.

† Dedicated to Prof. Yashwant D. Vankar on the occasion of his 60th birthday.

(1) (a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; p 39. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (f) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (g) Ramkn, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (h) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (i) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (h) Pellisier, H. *Tetrahedron* **2006**, *62*, 2143. (i) Tietze, L. F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2006.

The Biginelli reaction is an important one such multicomponent one-pot domino reaction, which allows easy access to dihydropyrimidinones (DHPMs) in one step starting from an aldehyde, urea, and a β-ketoester (eq 1).[2] The heterocyclic pyrimidinone products, i.e., DHPMs, are known to exhibit a

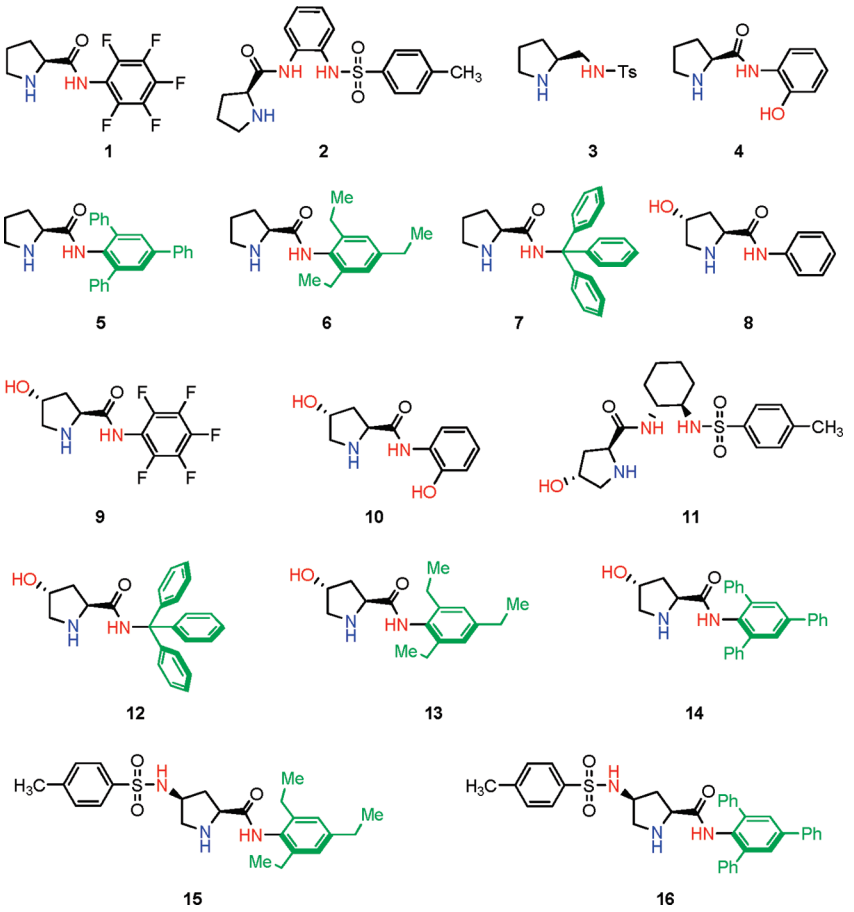


(1)

wide range of important pharmacological properties and make up a large family of medicinally relevant compounds.[3] Indeed, both enantiomers of DHPMs have been found to show

Published on Web 12/30/2010 DOI: 10.1021/jo101717m

CHART 1. Structures of Catalysts Explored for the Asymmetric Biginelli Reaction in the Present Investigation



distinct or opposite pharmacological activities.[4] Thus, the asymmetric version of the Biginelli reaction is of significant contempo-
rary interest. In general, optically pure DHPMs are accessed via resolution[5] and chiral auxiliary methods.[6] We are aware of only a few reports so far in the literature for the synthesis of optically pure DHPMs by employing organocatalysts.[7] In continuation of our recent forays into organocatalysis focusing on catalyst design for enantioselective transformations,[8] we targeted the asymmetric Biginelli reaction based on rationally designed prolinamides. Herein, we report that sterically hindered *N*-arylprolinamides augmented by reinforced chirality and acidic hydrogen bond donors promote the Biginelli reaction in a very high enantioselectivity (ee ca. 94−99%), albeit in the presence of some additives.

Results and Discussion

Our journey in pursuit of the highly enantioselective Biginelli reaction with organocatalysts began with prolinamides **1**−**4** (Chart 1), which either contain an acidic NH or exhibit the potential for double hydrogen bonding. The Biginelli reaction between *p*-methoxybenzaldehyde (a representative case), urea, and ethyl acetoacetate did proceed with these catalysts, but the DHPM was formed with each catalyst in a low enantioselectivity (ee ca. 18%; cf. Table 1). The modified catalysts **5**−**7** that contain a sterically hindered amide site (cf. Chart 1) were no better in terms of enantioselectivity under a variety of solvents and additive screening conditions; cf. Table 1. A recourse, at this stage, to the literature-reported catalysts (Chart 2) that modulate the Biginelli reaction in moderate enantioselectivity suggested that reinforcement of chirality by way of additional stereogenic

(2) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Dondoni, D.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451. (c) Kappe, C. O. In *Multicomponent Reactions*; Zhu, J., Bienaymq, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 95. (d) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (e) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (f) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.

(3) Hurst, E. W. *Ann. N. Y. Acad. Sci.* **1962**, *98*, 275.

(4) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

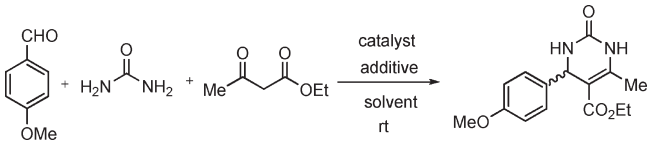
(5) (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629. (b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; Orreilly, B. C. *J. Med. Chem.* **1991**, *34*, 806. (c) Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2002**, *43*, 5913. (d) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473. (e) Sidler, D. R.; Barta, N.; Li, W.; Hu, E.; Matty, L.; Ikemoto, N.; Campbell, J. S.; Chartrain, M.; Gbewonyo, K.; Boyd, R.; Corley, E. G.; Ball, R. G.; Larsen, R. D.; Reider, P. J. *Can. J. Chem.* **2002**, *80*, 646.

(6) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473.

(7) (a) Xin, J. G.; Chang, L.; Hou, Z. R.; Shang, D. J.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2008**, *14*, 3177. (b) Wu, Y.-Y.; Chai, Z.; Liu, X.-Y.; Zhao, G.; Wang, S.-W. *Eur. J. Org. Chem.* **2009**, 904. (c) Wang, Y.; Yang, H.; Yu, J.; Miao, Z.; Chen, R. *Adv. Synth. Catal.* **2009**, *351*, 3057. (d) Olvera, R. D.; Demare, P.; Regla, I.; Juaristi, E. *ARKIVOC* **2008**, 61.

(8) (a) Moorthy, J. N.; Saha, S. *Eur. J. Org. Chem.* **2009**, 739. (b) Saha, S.; Moorthy, J. N. *Tetrahedron Lett.* **2010**, *51*, 912. (c) Saha, S.; Seth, S.; Moorthy, J. N. *Tetrahedron Lett.* **2010**, *51*, 5281. (d) Moorthy, J. N.; Saha, S. *Eur. J. Org. Chem.* **2010**, 6359.

TABLE 1. Screening of the Catalysts 1−7 for the Enantioselective Biginelli Reaction between *p*-Methoxybenzaldehyde, Urea, and Ethyl Acetoacetate[a]



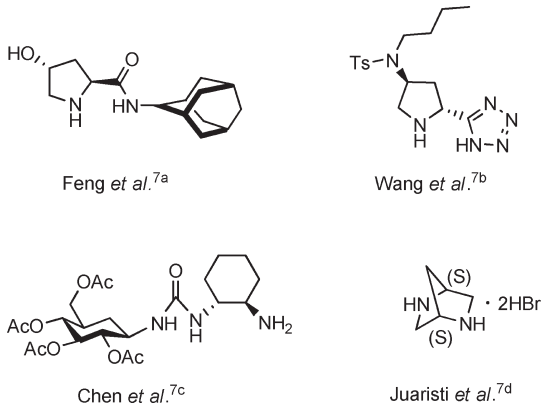
entry	catalyst	solvent	acid[b]	time (h)	yield (%)[c]	ee (%)[d]
1	**1**	DCM	TFA	48	45	9
2	**1**	THF	TFA	48	58	5
3	**1**	IPA	TFA	48	55	8
4	**2**	DCM	*p*-TSA	48	66	9
5	**2**	THF	TFA	48	60	10
6	**2**	IPA	TFA	48	62	12
7	**3**	THF/dioxane	TFA	72	25	4
8	**4**	DCM	tartaric acid	48	58	7
9	**4**	THF	TFA	48	54	6
10	**4**	IPA	TFA	48	40	9
11	**5**	THF/dioxane	TFA	72	45	14
12	**6**	THF	TFA	72	48	15
13	**6**	dioxane	TFA	72	44	14
14	**6**	THF/dioxane	TFA	72	60	18
15	**7**	THF	TFA	72	45	12
16	**7**	dioxane	TFA	72	38	14
17	**7**	THF/dioxane	TFA	72	48	15

[a]All reactions were run on ca. 0.5 mmol of *p*-methoxybenzaldehyde at rt (25 °C) using 2 equiv of urea, 10 equiv of ethyl acetoacetate, and 10 mol % of catalyst. [b]10 mol % of additive was used; *p*-TSA = *p*-toluenesulphonic acid. [c]Isolated yields based on *p*-methoxybenzaldehyde. [d]The enantiomeric excess was determined from chiral HPLC using an OD-H column.

centers is advantageous.[7] In particular, the *trans*-4-hydroxy-L-proline based catalysts by Feng et al. (Chart 2)[7a] as applied to the multicomponent Biginelli reaction spurred us to design and synthesize catalysts **8**−**14** that contain an additional chiral center suitably disposed at the C4 position of L-proline with sterics built at the C2 position. Buoyed by respectable enantioselectivities observed with catalysts **13** and **14** for the Biginelli reaction, further improvisation was accomplished through catalysts **15** and **16** that contain a better hydrogen bond donating sulfonamide group. The catalyst **16** was found to work well with uniformly high enantioselectivity for cyclocondensation of aliphatic as well as aromatic aldehydes with urea and ethyl acetoacetate.

Synthesis of Catalysts 1−16. The synthetic routes for all the catalysts **1**−**7** are shown in Scheme 1. All arylprolinamides **1**−**7** were synthesized starting from Cbz-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. The latter was reacted with substituted amines to yield Cbz-protected *N*-aryl-L-prolinamides, the deprotection of which under catalytic hydrogenation using 10% Pd/C led to *N*-aryl-L-prolinamides **1**−**7** in respectable overall yields; cf. Scheme 1. Catalyst **3** was prepared by following the literature reported procedure.[9]

CHART 2. Structures of Catalysts Reported in the Literature for the Enantioselective Biginelli Reaction



The catalysts **8**−**14** were synthesized starting from Cbz-protected *trans*-4-hydroxy-L-proline following the same protocol described above in Scheme 1. The catalysts **15** and **16** were prepared starting from Boc-protected *trans*-4-hydroxy-L-prolinamide. Mesylation of the Boc-protected *trans*-4-hydroxy-L-prolinamide, followed by nucleophilic substitution with sodium azide, led to the azide derivative with an inverted configuration at the C4 position. Catalytic hydrogenation of the azide derivative yielded the corresponding amine, which on tosylation followed by deprotection of the Boc group, led to catalysts **15** and **16** in respectable yields.

Screening of the Enantioselective Biginelli Reaction with Catalysts 8−16. The efficacy of catalysts **8**−**14** in regulating the stereochemical outcome of the Biginelli reaction was explored for the reaction between *p*-methoxybenzaldehyde, urea, and ethyl acetoacetate in the presence of each of the catalysts in a variety of solvents with or without additives. The results are summarized in Table 2.

SCHEME 1. Synthesis of Organocatalysts 1−16 for the Asymmetric Biginelli Reaction

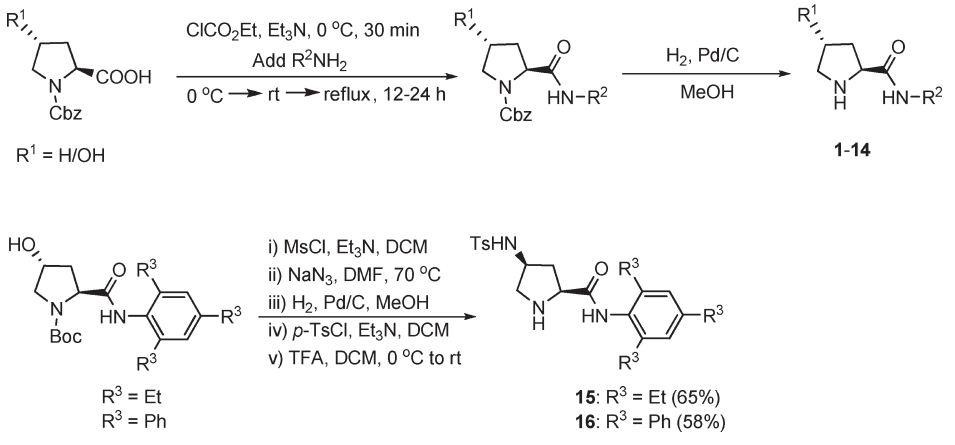
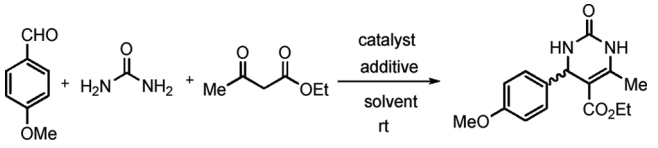


TABLE 2. Screening of the Catalysts 8−16 for the Enantioselective Biginelli Reaction between *p*-Methoxybenzaldehyde, Urea, and Ethyl Acetoacetate[a]



entry	catalyst	solvent[b]	acid[c]	time (h)	yield (%)[d]	ee (%)[e]
1	**8**	THF/dioxane	*p*-TSA	72	40	58
2	**8**	THF/dioxane[f]	PFBA	72	30	57
3	**9**	THF/dioxane	*p*-TSA	72	46	65
4	**9**	THF/dioxane	(+)-CSA	72	30	66
5	**9**	THF/dioxane	*o*-NBA	72	35	62
6	**9**	DCM	PhCOOH	72	trace	nd[h]
7	**9**	IPA	PhCOOH	72	trace	nd[h]
8	**9**	hexane	PhCOOH	72	trace	nd[h]
9	**9**	THF/dioxane[f]	PFBA	72	25	75
10	**10**	IPA	TFA	72	48	50
11	**10**	DCM		98	trace	nd[h]
12	**10**	THF/dioxane	PhCOOH	98	30	50
13	**10**	THF/dioxane	*p*-TSA	98	44	70
14	**10**	THF/dioxane[f]	PFBA	72	34	78
15	**11**	IPA	TFA	96	60	30
16	**11**	THF/dioxane	*p*-TSA	72	55	55
17	**11**	$CHCl_3$	(+)-CSA	72	38	60
18	**11**	THF/dioxane	*o*-NBA	72	46	60
19	**11**	THF/dioxane[f]	PFBA	72	28	82
20	**12**	THF/dioxane	TFA	72	35	48
21	**12**	THF/dioxane[f]	PFBA	72	30	84
22	**13**	THF/dioxane	TFA	96	70	68
23	**13**	THF/dioxane	PhCOOH	72	30	90
24	**13**	THF/dioxane	*p*-TSA	72	30	88
25	**13**	THF/dioxane[f]	PFBA	72	40	97
26	**13**	THF/dioxane[g]	PFBA	72	42	95
27	**13**	pet ether[f]	TFA	72	30	30
28	**13**	DCM[g]	PhCOOH	72	38	32
29	**14**	THF/dioxane	TFA	96	72	65
30	**14**	THF/dioxane	PhCOOH	98	24	90
31	**14**	THF/dioxane	*p*-TSA	98	57	65
32	**14**	THF	TFA	72	52	77
33	**14**	DCM	TFA	72	44	76
34	**14**	IPA	TFA	72	40	60
35	**14**	THF/dioxane[f]	PFBA	72	42	95
36	**15**	THF/dioxane	TFA	88	68	78
37	**15**	THF/dioxane[f]	PFBA	96	60	95
38	**16**	THF/dioxane	TFA	88	65	76
39	**16**	THF/dioxane[f]	PFBA	96	66	99

[a]All the reactions were run on ca. 0.5 mmol of *p*-methoxybenzaldehyde at rt (25 °C) using 2 equiv of urea, 10 equiv of ethyl acetoacetate, and 10 mol % of the catalyst. [b]THF/dioxane (1:1). [c]20 mol % of acid additive was used. Abbreviations: *p*-TSA = *p*-toluenesulphonic acid, PFBA = pentafluorobenzoic acid, TFA = trifluoroacetic acid, *o*-NBA = *o*-nitrobenzoic acid, and (+)-CSA = (+)-camphorsulfonic acid. [d]Isolated yields based on *p*-methoxybenzaldehyde. [e]The enantiomeric excess was determined from chiral HPLC using an OD-H column. [f]20 mol % of $Ph_3CNH_3^+CF_3COO^-$. [g]20 mol % of $^iPrNH_3^+CF_3COO^-$. [h]nd = not determined.

A perusal of Table 2 suggests the following:

(i) Acids such as TFA, *o*-nitrobenzoic acid, (+)-camphorsulfonic acid, etc. afford different results (yields and ees) in different solvent conditions.

(ii) Yields are moderate with added acids, but the enantiomeric excess increases to as high as 90% with additives such as PhCOOH (entry 23).

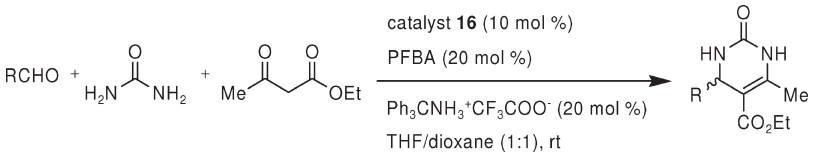
(iii) Addition of organic salt has a dramatic effect, as found by Feng et al.,[7a] leading to ees that are pronouncedly increased at the expense of relatively low yields, when the acid employed is pentafluorobenzoic acid (entries 25 and 35).

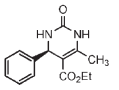
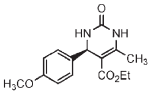
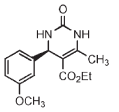
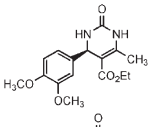
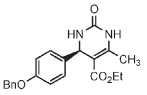
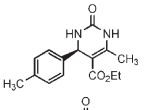
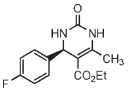
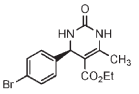
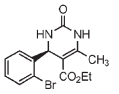
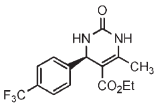
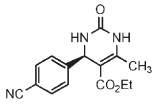
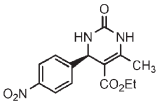
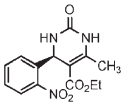
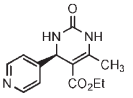
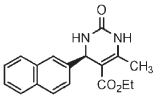
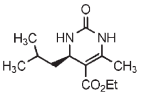
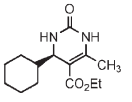
On the basis of the encouraging results with catalysts **13** and **14** that lead to the DHPM in a respectable enantioselectivity, the two catalysts were screened in a variety of solvents and in the presence of acids such as benzoic acid, TFA, *p*-toluenesulphonic acid and pentafluorobenzoic acid (entries 22−24 and 27−34, Table 2). Significantly high enantioselectivities were observed for both catalysts **13** and **14** in the THF/dioxane mixture with an additive such as tritylammonium trifluoroacetate (entries 25 and 35, Table 2); the ee's were typically 95−97%. It should be noted that the additive, such as *iso*-propylammonium trifluoroacetate, also exhibited a similar, but less pronounced effect on the enantioselectivity. These catalysts were further improved by increasing the acidity of the hydrogen donor at C4 by converting the hydroxy functionality in **13** and **14** to that of *p*-toluenesulfonamide as in **15** and **16**; cf. Chart 2.

The Biginelli reaction between *p*-methoxybenzaldeyde, urea, and ethyl acetoacetate with catalyst **16**, under identical

(9) Dahlin, N.; Bogevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101.

TABLE 3. Results of the Enantioselective Biginelli Reaction Using Catalyst 16[a]



entry	product	time (h)	yield[b] (%)	*ee* (%)
1		96	60	98
2		96	66	99
3		96	62	98
4		96	64	98
5		96	66	98
6		96	66	96
7		96	50	98
8		96	55	99
9		96	58	98
10		96	48	98
11		96	44	97
12		96	45	99
13		96	48	96
14		96	54	96
15		96	56	94
16		96	60	96
17		96	68	98

[a]All the reactions were run on ca. 0.5 mmol of the aldehyde at rt (25 °C) using 2 equiv of urea, 10 equiv of ethyl acetoacetate, 10 mol % of the catalyst **16**, 20 mol % of PFBA, and 20 mol % of $Ph_3CNH_3^+CF_3COO^-$. [b]Isolated yields based on aldehyde.

conditions as those employed for **13** and **14**, i.e., with pentafluorobenzoic acid and tritylammonium trifluoroacetate as an additive, led to the DHPM with an optical purity of 99% and in a respectable isolated yield of 66% (entry 39, Table 2). It is noteworthy that the catalysts **15** and **16** exhibited better solubility than **13** and **14** in the THF/dioxane (1:1) mixture.

Enantioselective Biginelli Reactions of Diverse Aldehydes with Catalyst 16. With the conditions established above, the Biginelli reactions of a variety of aromatic as well as aliphatic aldehydes with urea and ethyl acetoacetate were investigated with the catalyst **16** specifically. The results of enantioselective multicomponent Biginelli condensation reactions are collected in Table 3. As can be readily seen, the reaction works very well with almost all aliphatic and aromatic aldehydes, yielding chiral DHPMs in respectable yields (44−68%), but in a remarkably high enantioselectivity (94−99%).

In general, e-rich aldehydes were found to afford DHPMs in a relatively higher yield (60−66%, entries 1−6, Table 3) than the e-poor aldehydes (44−54%, entries 10−14, Table 3). The enantioselectivities observed for the DHPMs collected in Table 3 are in the range of 94−99% regardless of the nature of the aldehyde. Aliphatic aldehydes such as isobutyraldehyde and cyclohexanecarbaldehyde also afforded the DHPMs in moderate yields, but in high enantioselectivities (entries 16 and 17, Table 3). Clearly, the nature of the aldehyde, i.e., aromatic/aliphatic, has no discernible influence on the stereoselectivity of the reaction other than that of the reaction yield. The enantioselectivity in all cases was determined by chiral HPLC analysis using an OD-H column. The stereochemistry in the products was assigned "R" based on comparison of the HPLC profiles reported in the literature,[7] which was also complemented by optical rotation values.

Mechanistic Considerations. Although the catalyst **16** seemingly constitutes a modification of the catalysts reported by Feng and co-workers,[7a] it works remarkably well with high enantioselectivities for the diverse carbonyl compounds investigated. Indeed, the uniformly high ees observed with

(10) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802.

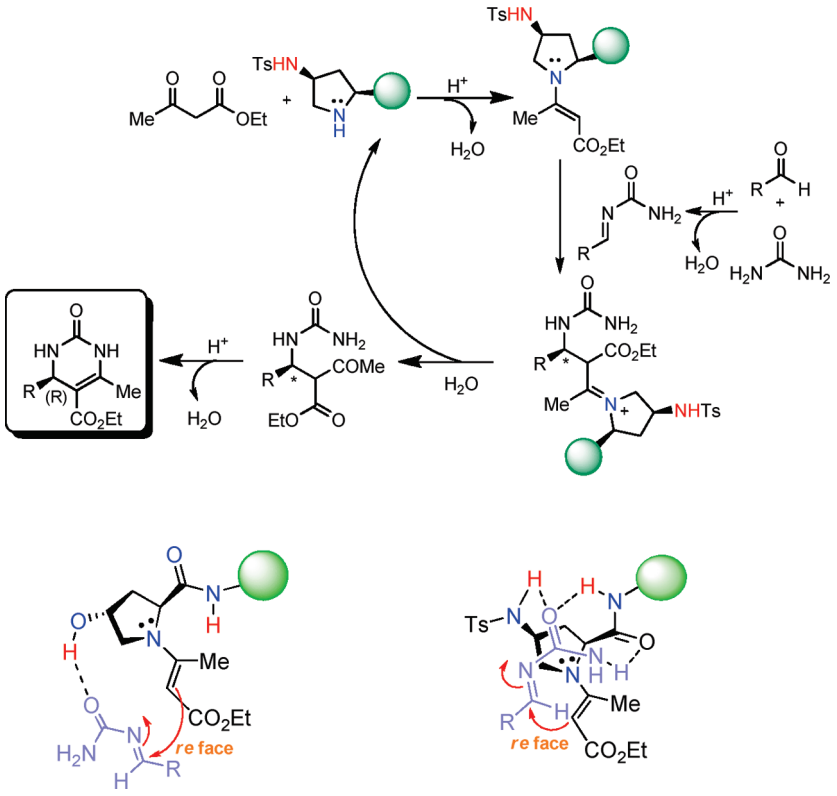


FIGURE 1. Mechanism of the Biginelli reaction and the plausible transition-state structures responsible for enantioselectivity with both trans (left) and cis (right) configured catalysts **14** and **16**, respectively.

catalyst **16** for aliphatic as well as aromatic aldehydes are not replicated with any other catalyst type reported thus far for the asymmetric Biginelli reaction.[2e,f,10] Indeed, the enantioselectivities observed with catalyst **16** in the present investigation constitute the best so far for Biginelli reactions mediated by organocatalysts based on enamine chemistry.

What is the role of tritylammonium trifluoracetate? We believe that the trifluoroacetate salt of the trityl amine somehow constricts the chiral environment of the developing transition state. The role of the acid additive, i.e., pentafluorobenzoic acid, is likely to be in the early stages in catalyzing the imine formation between aldehyde and urea as well as in the enamine formation between catalyst and ethyl acetoacetate (Figure 1). Given the observation in the screening studies that strong acids such as TFA enhance the reaction rate, but depreciate the enantioselectivity of the Biginelli reaction product (Tables 1 and 2), it is also likely that the added trifluoroacetate salt of the trityl amine also acts as a buffer in controlling the acidity of the medium.

Wang et al. reported that proline-derived catalysts with a binding group at C4 in a trans orientation with respect to the group at C2 performs better from the point of view of enantioselectivity as compared with the cis isomer.[7b] Our results reveal no such dependence of the stereochemical outcome on the disposition of the group at the C4 position (entries 35 and 39, Table 2). In other words, the configurational inversion at the C4 position in going from catalysts **13**/**14** to those of the sulfonamides **15**/**16** has no influence on the stereochemical outcome in the product. A perusal of the results in Table 2 on a broad spectrum of catalysts is quite instructive: (i) the fact that one observes a significant rise in ees with catalysts **8**−**14** (Table 2) as compared with those with **1**−**7** (Table 1) suggests that the reinforced chirality at C4 is important, and (ii) a comparison of the results with catalyst **11** (entries 16 and 19, Table 2) with those of **13** and **14** (entries 24, 25, 31, and 35) shows that enhanced acidity of the prolinamide NH at C2 is less important. Rather, sterics as in **13** and **14** improve the enanatioselectivity; enhanced acidity at C4, however, has a pronounced effect on the optical yields, as suggested from a comparison of the results with catalysts **13**/**14** (entries 22 and 29, Table 2) and **15**/**16** (entries 36 and 38). Thus, one may conclude that sterics at the C2 carboxamide, reinforced chirality, and enhanced acidity for hydrogen bonding at the C4 substituent are important for high optical yields in the Biginelli cyclocondensation. In light of these considerations, let us now consider how the cis and trans relationship between the substitutuents at C2 and C4 lead to the products of the same configuration.

In Figure 1 is shown the overall mechanism of the Biginelli reaction.[7a−c] The crucial step responsible for stereoinduction constitutes the attack of the (*E*)-enamino-ester derived from proline and the *β*-ketoester on to the *re*-face of the imino-amide formed between the carbonyl compound and urea. The plausible transition states for organocatalysis with catalysts **13**/**14** (trans relationship between C2 and C4 substituents) and **15**/**16** (cis relationship between C2 and C4 substituents) are shown separately in Figure 1; the enamine nitrogen is considered to be sp^2-hybridized due to possible conjugation. As mentioned earlier, hydrogen bonding via the substituent at the C4 position, i.e., OH or NHTs, crucially controls the optical yield. Thus, the imino-amide is likely to be attacked at the bottom and top faces of the enamines

formed with the catalysts **13**/**14** and **15**/**16**, respectively as shown in Figure 1. In the case of **13**/**14**, the role of the sterically bulky substituent at C2 appears to merely block the approach of the imino-amide from the top face. In contrast, it is likely that it constricts the transition state through sterics in the case of **15**/**16**. In the case of the latter, the transition state may be further stabilized via hydrogen-bonding interactions, as shown in the Figure 1.

Conclusions

From a systematic investigation involving the synthesis of a series of catalysts and screening studies, the catalyst **16**, which is sterically hindered, yet contains a strong hydrogen-bonding site, is shown to promote the Biginelli cyclocondensation of ethyl acetoacetate with aromatic as well as aliphatic aldehydes and urea in a high enantioselectivity. The remarkable ees observed in these reactions demonstrate the fact that chiral prolinamides with reinforced chirality and enhanced hydrogen acidity at the C4 position and sterics built at the C2 position are excellent organocatalysts in asymmetric synthesis. The novel prolinamide catalyst **16** and analogous compounds with readily tunable sterics and hydrogen-bonding attributes are likely to further expand the scope of various other organocatalytic reactions.

Experimental Section

Preparation of Catalysts 15 and 16. The Boc-protected (2*S*,4*R*)-4-hydroxy-*N*-(2,4,6-triethylphenyl)-pyrrolidine-2-carboxamide (4.0 g, 10.2 mmol) was dissolved in dry DCM and cooled to 0 °C, and Et_3N (1.2 g, 12.2 mmol) was added. The reaction mixture was then stirred for 15 min, and methanesulphonyl chloride (1.4 g, 12.2 mmol) was added dropwise. The reaction mixture was then stirred at rt for 16 h and then quenched with the addition of water. The organic matter was and extracted with $CHCl_3$, washed with brine, dried, and concentrated to obtain the product (4.4 g, 92%), which was used as such for the next step.

The mesylate (4.4 g, 9.4 mmol) obtained from the above reaction was dissolved in 15 mL of dry DMF, and sodium azide (1.2 g, 18.8 mmol) was added under a N_2 atmosphere. The reaction mixture was heated at 65−70 °C for 16 h. The reaction mixture was cooled and the solvent evaporated under reduced pressure. The residue was extracted with $CHCl_3$, dried, and concentrated to obtain the crude product, which was finally purified by a short pad column chromatography to obtain the azide (3.5 g, 90%).

To the solution of the azide derivative (3.0 g, 7.2 mmol), obtained from the above step, in 25 mL of MeOH was added a catalytic amount of 10% Pd/C. The container was evacuated by applying vacuum and filled subsequently with a H_2 gas. The reaction mixture was stirred at room temperature for 6 h and was filtered through a Celite pad. The residue obtained, after removing the solvent in vacuo, was purified by a silica gel column chromatography to afford the desired amine (2.7 g, 98% yield).

The amine (2.5 g, 6.4 mmol) thus obtained from the above step was dissolved in 25 mL of dry DCM. The reaction mixture was cooled to 0 °C, and Et_3N (0.77 g, 7.6 mmol) was added, followed by *p*-toluenesulphonyl chloride (1.4 g, 7.6 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 6 h. Subsequently, it was quenched with addition of water and extracted with $CHCl_3$, dried, and concentrated to obtain the crude product, which was further purified by a short pad silica gel column chromatography to obtain the Boc-protected tosyl amide (1.1 g, 85% yield).

The Boc amide (1.0 g, 1.8 mmol) obtained from the above step, was dissolved in 20 mL of dry DCM and cooled to 0 °C. TFA (5.0 mL) was slowly added to this solution at 0 °C and 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 over anhyd Na_2SO_4, and concentrated to obtain the pure (2*S*,4*R*)-4-tosylamido-*N*-(2,4,6-triethylphenyl)-pyrrolidine-2-carboxamide, **15** (0.76 g, 94% yield).

A similar procedure was followed for the preparation of (2*S*,4*R*)-4-hydroxy-*N*-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide, **16**.

(2*S*,4*R*)-4-Tosylamido-*N*-(2,4,6-triethylphenyl)pyrrolidine-2-carboxamide, 15: yield 65%; mp 120 °C; $[\alpha]^{27}_D = -4.0°$ ($c = 0.5$, EtOH); IR (KBr) cm^{-1} 1160, 1329, 1660, 2965, 3273; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (t, 6H, $J = 7.3$ Hz), 1.20 (t, 3H, $J = 7.3$ Hz), 1.78−1.82 (m, 1H), 2.34−2.42 (m, 1H), 2.40 (s, 3H), 2.48 (q, 4H, $J = 7.3$ Hz), 2.58 (q, 2H, $J = 7.3$ Hz), 2.83−2.89 (m, 1H), 3.19−3.22 (m, 1H), 3.72−3.75 (m, 1H), 3.93−3.94 (m, 1H), 6.90 (s, 2H), 7.26 (d, 2H, $J = 9.2$ Hz), 7.71 (d, 2H, $J = 8.2$ Hz), 8.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5, 15.5, 21.5, 24.9, 28.6, 36.7, 53.1, 54.2, 59.5, 125.8, 127.0, 129.5, 129.8, 137.3, 140.8, 143.5, 143.7, 172.6; ESI-MS^+ *m*/*z* calcd for $C_{24}H_{33}N_3O_3S$ 444.2320 [M + H], found 444.2321.

(2*S*,4*R*)-4-Tosylamido-*N*-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide, 16: yield 60%; mp 178−180 °C; $[\alpha]^{27}_D = -12.8°$ ($c = 0.08$, EtOH); IR (KBr) cm^{-1} 1158, 1327, 1493, 1674, 3304, 3505; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.00−2.06 (m, 1H), 2.16−2.19 (m, 1H), 2.41 (s, 3H), 2.89 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 6.5$ Hz), 3.34 (dd, 1H, $J_1 = 9.2$ Hz, $J_2 = 6.5$ Hz), 3.48−3.52 (m, 1H), 4.12 (d, 1H, $J = 6.1$ Hz), 7.24−7.72 (m, 21 H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 27.0, 36.0, 52.7, 54.1, 59.2, 127.0, 127.3, 127.5, 127.7, 128.3, 128.6, 128.9, 129.1, 129.9, 130.3, 140.0, 140.2, 140.5, 141.3, 143.7, 172.8; ESI-MS^+ *m*/*z* calcd for $C_{36}H_{33}N_3O_3S$ 588.2320 [M + H], found 588.2325.

Typical Procedure for the Enantioselective Biginelli Reaction Using Catalyst 16. A mixture of *p*-methoxybenzaldehyde (0.1 g, 0.73 mmol), urea (0.86 g, 1.46 mmol), pentafluorobenzoic acid (0.03 g, 0.14 mmol), and $Ph_3CNH_3^+CF_3COO^-$ (0.05 g, 0.14 mmol) in 0.8 mL of THF/dioxane (1:1) was stirred in a small round-bottom flask at rt for 45 min. Subsequently, the catalyst **16** (0.04 g, 0.07 mmol) was added, followed by ethyl acetoacetate (0.95 g, 7.3 mmol). The reaction mixture was stirred for 96 h. A white solid that formed was filtered, washed with chilled EtOAc, and dried to obtain 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one.

Acknowledgment. J.N.M. is thankful to DST, India, for funding through the Ramanna fellowship, and S.S. is grateful to CSIR, India, for a senior research fellowship.

Supporting Information Available: Synthesis and characterization data of all the catalysts and HPLC profiles for the products of organocatalytic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.