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List-Barbas-Mannich Reaction Catalyzed by Modularly Designed Organocatalysts

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Abstract: The List-Barbas-Mannich reaction of ethyl (*p*-methoxyphenylimino)acetate (*p*-methoxyphenyl = PMP) with unmodified aldehydes or ketones catalyzed by modularly designed organocatalysts (MDOs) that are self-assembled from proline and cinchona alkaloid thioureas (such as a quinidine-derived thiourea) produces the corresponding γ-oxo-α-amino acid derivatives in high yields and excellent stereoselectivities. No solvent is necessary for this reaction. Aldehydes are especially good substrates for this reaction: The reaction takes only a few minutes to yield the corresponding List-Barbas-Mannich products in excellent dr (up to > 99:1) and ee values (up to > 99% ee).

Keywords: Modularly designed organocatalysts, List-Barbas-Mannich reaction, aldehyde, ketone, imine, and amino acid derivatives

INTRODUCTION

The Mannich reaction is a highly efficient method for the synthesis of β-amino carbonyl compounds.[1] It is also one of the most important carbon-carbon bond formation reactions in

organic chemistry.[1] Since the seminal work reported by List and Barbas on a proline-catalyzed direct Mannich reaction,[2] organocatalyzed List-Barbas-Mannich reactions have been undergoing vigorous development in the past decade.[3] Amino acid derivatives, mainly those derived from proline,[4] have been used as the catalysts in List-Barbas-Mannich reactions, and high diastereoselectivities and/or enantioselectivities have been achieved in many cases.[3,4]

Organocatalysts self-assembled in situ from precatalysts through hydrogen bonding or ionic interactions have received a lot of attention in recent years,[5,6] As compared to traditional organocatalysts, these macromolecular catalysts are very amenable to structure modification. Moreover, a library of catalysts can be readily obtained for a high throughput screening by simply combining the precatalysts.[5,6] Nonetheless, despite the great progresses made on organocatalyzed List-Barbas-Mannich reactions,[1,3] reports on conducting asymmetric List-Barbas-Mannich reactions using self-assembled organocatalysts are still rare.[7]

A few years ago we reported the modularly designed organocatalysts (MDOs) self-assembled between amino acids and cinchona alkaloid derivatives.[8a] We have shown that these MDOs are highly efficient catalysts for Michael,[8a-c] hetero-Diels-Alder,[8d] and aldol[8e] reactions. Since the Mannich reaction and the aldol reaction are very similar in terms of the reaction mechanism, we reasoned that MDOs should be also good catalysts for the List-Barbas-Mannich reaction. Herein, we wish to disclose that MDOs self-assembled from proline and cinchona alkaloid thioureas are indeed highly efficient catalysts for the List-Barbas-Mannich reaction between ethyl (*p*-methoxyphenylimino)acetate and aldehydes or ketones. Aldehydes are especially good substrates for this reaction, with which the reaction can be carried out under neat conditions for just a few minutes to give the desired α-amino acid derivatives in high yields and excellent diastereoselectivities and ee values.

RESULTS AND DISCUSSION

Using dodecanal (**3a**) and ethyl (*p*-methoxyphenylimino)acetate (**4**) as the model substrates, we initially screened MDOs formed in situ in the reaction medium from the precatalyst modules (Figure 1) to identify the best MDO for the List-Barbas-Mannich reaction. The results are summarized in Table 1. When L-proline (**1a**) and a quinidine-derived thiourea **2a** (10 mol % each) were used as the precursors of the MDO in toluene at rt, the desired Mannich product **5a** was obtained in 95% yield with a dr of 95:5 for the major *syn* product as an essentially pure enantiomer (ee > 99%, entry 1). Unlike those reported organocatalysts, which normally take hours to complete this reaction, a high product yield was achieved in just 20 min. without the need to use a large excess of the aldehyde. In contrast, under identical conditions, the reactions using these two individual modules as the catalyst did not yield the desired product at all (entries 2 and 4). Although by prolonging the reaction time, product **5a** could be obtained in poor yields using these two modules individually, the obtained dr and ee values were much worse (entries 3 and 5). These data unequivocally show that the MDO formed from **1a** and **2a** is indeed responsible for the observed catalysis. Similarly, the MDO of D-proline (**1b**) and **2a** generated the opposite enantiomer of **5a** in an equally high dr and ee value, although the reaction was a little slower (entry 6). We next screened some additional amino acids using **2a** as the stereocontrolling module.[8a] Proline derivatives, such as L-4-thioproline (**1c**, entry 7), *trans*-4-hydroxy-L-proline (**1d**, entry 8), L-prolinamide (**1e**, entry 9), and (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (**1f**, entry 10), proved to be bad reaction-center modules as they generated low product yields, drs, and ee values. Similarly, L-pipecolic acid (**1g**, entry 11) and primary amino acids (*S*)-β-phenylalanine (**1h**, entry 12) and L-2-chlorophenylglycine (**1i**, entry

13) are also poor reaction-center modules. Thus, this screen identified proline **1a** and **1b** as the best reaction-center modules.

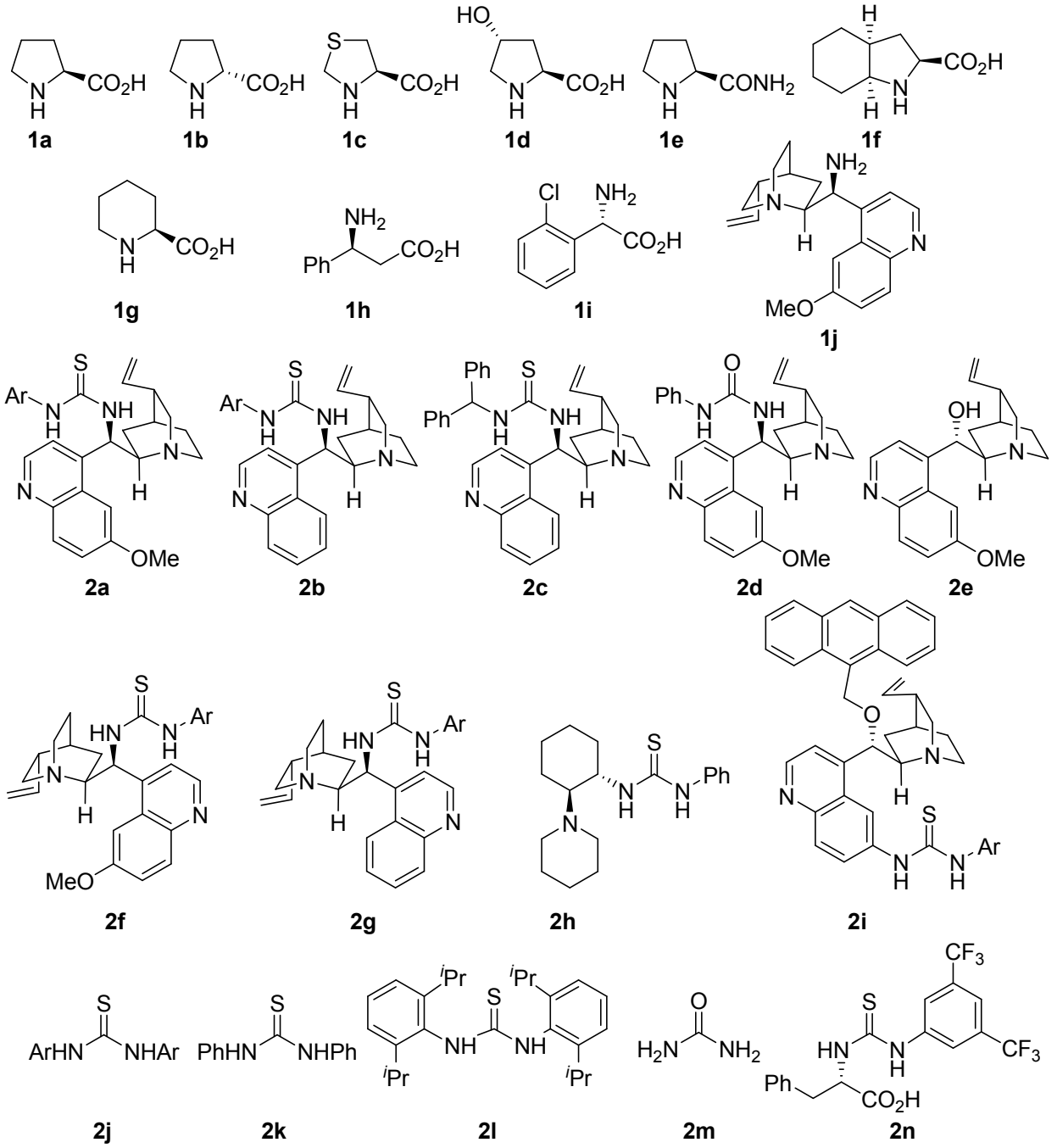
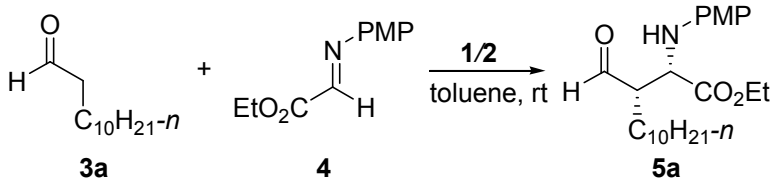


Figure 1: Precatalyst modules tested in the List-Barbas-Mannich reaction [Ar = 3,5-$(CF_3)_2C_6H_3$-]

Table 1: Catalyst screening and reaction condition optimization for the List-Barbas-Mannich reaction[a]



3a **4** **5a**

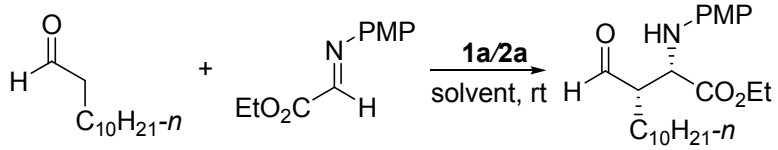
entry	modules		time	yield	dr[c]	ee
	1	**2**	(min)	(%)[b]		(%)[d]
1	**1a**	**2a**	20	95	95:5	>99
2	**1a**	-	20	0	-	-
3	**1a**	-	480	24	47:53	nd[e]
4	-	**2a**	20	0	-	-
5	-	**2a**	1200	22	35:65	0
6[f]	**1b**	**2a**	30	92	95:5	>99
7	**1c**	**2a**	180	<5	53:47	nd
8	**1d**	**2a**	120	0		
9	**1e**	**2a**	240	<5	50:50	nd
10	**1f**	**2a**	240	<5	50:50	nd
11[g]	**1g**	**2a**	120	44	59:41	81
12	**1h**	**2a**	180	40	29:71	0
13	**1i**	**2a**	180	38	41:59	0
14	**1a**	**2b**	30	93	92:8	93
15	**1a**	**2c**	150	90	91:9	96
16	**1a**	**2d**	45	94	93:7	95
17	**1a**	**2e**	240	51	88:12	77
18	**1a**	**2f**	30	92	91:9	>99
19	**1a**	**2g**	15	84	97:3	96
20	**1a**	**2h**	240	51	96:4	85
21	**1a**	**2i**	50	91	94:6	96
22[h]	**1a**	**2j**	20	90	80:20	95
23	**1a**	**2j**	240	64	55:45	90
24[h]	**1a**	**2k**	30	83	78:22	92
25[h]	**1a**	**2l**	50	76	75:25	92
26	**1a**	**2m**	240	35	38:62	0
27	**1j**	**2n**	30	0	-	-

[a]Unless noted otherwise, all reactions were carried out with **3a** (0.24 mmol, 1.2 equiv.), **4** (0.20 mmol) and the specified catalyst modules (0.020 mmol, 10 mol % each) in toluene (1.0 mL) at room temperature (ca. 25 °C). [b]Yield of isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis of the purified product on a ChiralPak IC column. [e]Not determined. [f]The opposite enantiomer was obtained as the major product. [g]The *anti* diastereomer was obtained in 69% ee. [h]Et_3N (0.020 mmol, 10 mol %) was also added.

Using **1a** as the reaction-center module, we next screened different stereocontrolling modules. Besides quinidine thiourea **2a**, cinchonine-derived thioureas **2b** and **2c** also generated product **5a** in high yields and excellent dr and ee values, although the reactions were slower (entries 14 and 15). Similarly, high product yield, dr, and ee value were also obtained for a quinidine-derived urea **2d** (entry 16). However, a lower product ee value and dr were obtained when quinidine (**2e**) was used. Moreover, the reaction was also much slower (entry 17). When the quinine-derived thiourea **2f** was employed, the high reactivity and stereoselectivity were restored (entry 18). Slightly inferior yield and ee value were obtained with a cinchonidine-derived thiourea **2g** (Table 1, entry 19), but the dr was slightly higher than that obtained with **2f**. When a cyclohexanediamine-derived thiourea **2h** (entry 20) was applied, the reaction was very sluggish and the ee value obtained was much lower (85% ee). Nonetheless, good results were also obtained for a quinidine-derived 6′-thiourea **2i** (entry 21). To further elucidate the role of the cinchona alkaloid thioureas in this reaction, the reaction was also conducted with **1a** and an achiral thiourea **2j** in the presence of a tertiary amine (Et_3N). As the results in Table 1 show, although this mixture shows good reactivity and a good product ee value (95% ee) was obtained, the dr ratio obtained was much lower (only 80:20, entry 22). In the absence of Et_3N, the combination of **1a** and **2j** was much less reactive, and a poor dr (55:45) and a lower ee value of 90% were obtained (entry 23). Similarly, the combinations of **1a** and achiral thioureas **2k** and **2l** gave worse results in terms of the diastereoselectivities and ee values in the presence of Et_3N (entries 24 and 25) as compared to those of the MDO of **1a** and **2a** (entry 1). Additionally, the combination of **1a** and an achiral urea **2m** also led to poor results (entry 26). Thus, the cinchona thiourea module is essential for achieving the optimal stereoselectivities in this reaction. On the other hand, poor results were also obtained with the combination of **1j** and **2n**, in which the

amine and thiourea moieties were switched among the reaction-center and the stereocontrolling modules (entry 27). Through the above screening, the combination of **1a** and **2a** was identified as the best MDO in terms of both the reactivity and stereoselectivity (entry 1). The opposite enantiomer of product **5a** may be readily obtained using the MDO of **1b** and **2a** (entry 6).

Table 2: Effects of different solvents on the List-Barbas-Mannich reaction[a]



3a **4** **5a**

entry	solvent	time (min)	yield (%)[b]	dr[c]	ee (%)[d]
1	toluene	20	95	95:5	>99
2[e]	toluene	50	93	94:6	97
3	benzene	20	95	92:8	>99
4	xylene	20	94	98:2	94
5	hexane	25	94	90:10	>99
6	CCl_4	20	94	>99:1	94
7	CH_2Cl_2	20	92	98:2	94
8	THF	15	92	94:6	94
9	DMSO	10	95	>99:1	>99
10[f]	DMSO	50	90	95:5	94
11	neat	< 5	98	>99:1	>99
12[g]	neat	10	92	97:3	>99
13[h]	neat	25	85	90:10	99
14[i]	neat	90	50	50:50	96
15[j]	dioxane	150	79	80:20	98

[a]Unless noted otherwise, all reactions were carried out with **3a** (0.24 mmol, 1.2 equiv.), and the imine **4** (0.20 mmol) in the presence of L-proline (**1a**, 0.020 mmol, 10 mol %) and quinidine thiourea (**2a**, 0.020 mmol, 10 mol %) in 1 mL of specified solvent at room temperature (ca. 25 °C). [b]Yield of isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis of the purified product on a ChiralPak IC column. [e]The reaction was carried out at 0 °C. [f]10 mol % of **1a** was used only. [g]The loading of **1a** and **2a** was 5 mol % each. [h]The loading of **1a** and **2a** was 3 mol % each. [i]The loading of **1a** and **2a** was 1 mol % each. [j]10 mol % **1a** was used in 0.20 mL of 1,4-dioxane.

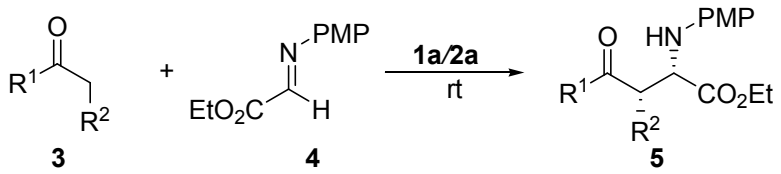
The reaction conditions were further optimized for the MDO of **1a**/**2a** and the results are summarized in Table 2. Common organic solvents only show some modest influence on the

reactivity and stereoselectivity of this MDO-catalyzed List-Barbas-Mannich reaction (entries 1-9). Among these screened solvents, the best results were obtained in DMSO, since only the *syn* product was formed as a single enantiomer (entry 9). While proline itself has been reported to be a good catalyst for the List-Barbas-Mannich reaction of aldehydes in DMSO,[9] we found that, under identical conditions, the reaction catalyzed by L-proline alone was slower and led to a slightly lower dr and ee value of **5a**. Most gratifyingly, we found that the presence of a solvent was not necessary for this reaction: Under neat conditions, the reaction finishes almost instantaneously, and the product was obtained almost quantitatively as a single *syn* diastereomer (dr > 99:1) with >99% ee (entry 11). When the catalyst loading was reduced to 5 mol %, the reaction took 10 min to finish, yielding product **5a** in very similar stereoselectivities (entry 12). However, further lowering the catalyst loading led to poorer results (entries 13 and 14). In order to make sure that the increased reactivity and stereoselectivity achieved by the MDO of **1a**/**2a** were not simply due to the increased solubility of proline in the organic solvents (through the formation of a salt), a control reaction was also conducted using a high concentration of L-proline in 1,4-dioxane, in which L-proline has good solubility. As the data in Table 2 show, the reaction was much slower, and the diastereoselectivity and ee value obtained were also lower (entry 15). Thus, there are some synergistic effects by forming the MDO.

Once the reaction conditions were optimized, the reaction scope was then established by varying the donor substrates. Since 5 mol % and 10 mol % catalyst loadings generated slightly different results for our model substrate **3a**, both loadings were used for each of these substrates. The results are summarized in Table 3. As is evident from the data in Table 3, straight-chain aliphatic aldehydes, such as, dodecanal (**3a**, entries 1 and 2), nonanal (**3b**, entries 3 and 4), heptanal (**3c**, entries 5 and 6), pentanal (**3d**, entries7 and 8), and propanal (**3e**, entries 9 and 10),

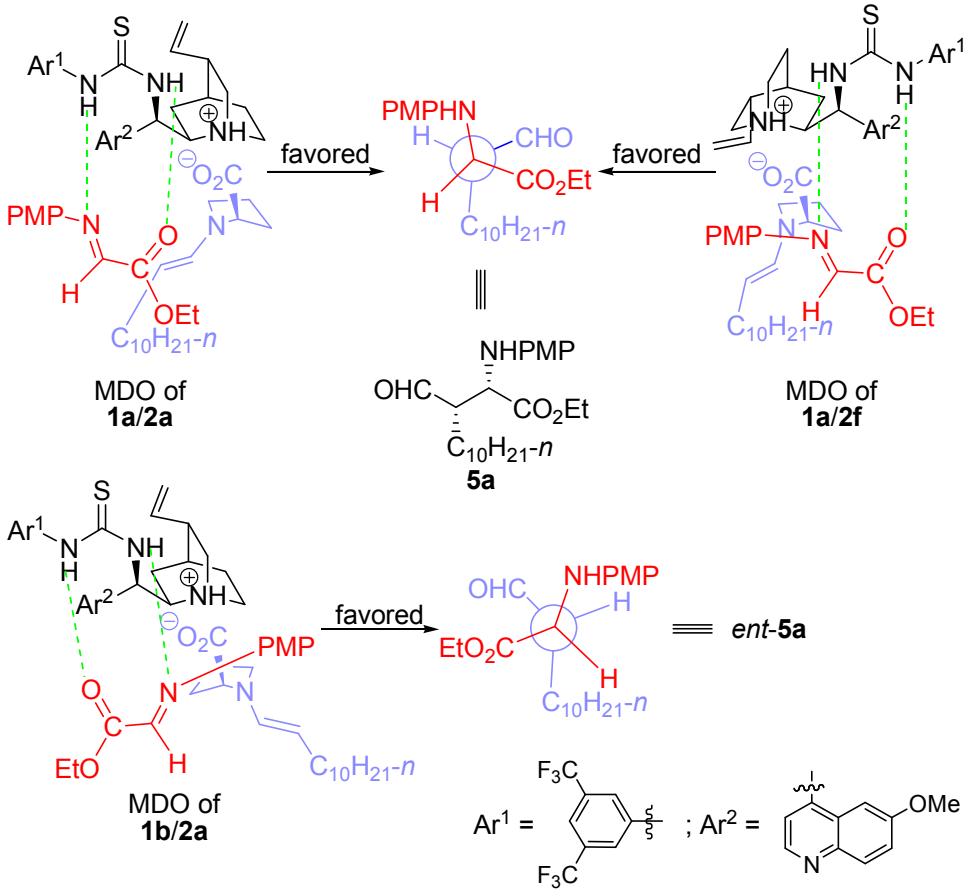
all generate the *syn*-diastereomers as a pure enantiomer (ee >99%) with excellent diastereoselectivities. Similarly, the Mannich product of dihydrocinnamaldehyde (**3f**) was obtained in high dr and ee values (entries 11 and 12). Excellent results were also obtained with the branched 3-methylbutanal (**3g**, entries 13 and 14). For these aldehyde substrates, it was found that these two loadings did not show any difference in the product ee values, although the reactions were faster with the 10 mol % loading and sometimes the dr were also slightly higher. Ketones may also be applied in this reaction, although a higher loading of 10 equivalents is necessary because the reactions with ketones are slower. Cyclohexanone (**3h**) leads to the desired Mannich product **5h** in 98% ee with a 91:9 dr in 60 min. with a loading of 5 mol % catalyst (entry 15) or 40 min. with a loading of 10 mol % (entry 16). In contrast, a much lower dr (around 3:1) and ee value (70%) were obtained when 4-oxacyclohexanone (**3i**) was applied (entries 17 and 18). When acetone (**3j**) was employed as the donor substrate, the expected Mannich product **5j** was obtained in 84% ee (entries 19 and 20). The reaction with a 10 mol % catalyst loading (entry 20) was much faster than that of 5 mol % loading (entry 19).

Table 3: Substrate Scope of the List-Barbas-Mannich reaction[a]



entry	R^1	R^2	3/5	time (min)	yield (%)[b]	dr[c]	ee (%)[d]
1	H	$CH_3(CH_2)_9$-	**a**	10	92	97:3	>99
2[e]				<5	98	>99:1	>99
3	H	$CH_3(CH_2)_6$-	**b**	10	88	95:5	>99
4[e]				<5	94	97:3	>99
5	H	$CH_3(CH_2)_4$-	**c**	10	89	92:8	>99
6[e]				<5	98	97:3	>99
7	H	$CH_3(CH_2)_2$-	**d**	10	92	98:2	>99
8[e]				<5	93	98:2	>99
9	H	CH_3-	**e**	10	88	95:5	>99[f]
10[e]				<5	95	95:5	>99[f]
11	H	$PhCH_2$-	**f**	10	92	96:4	94[f]
12[e]				<5	96	96:4	94[f]
13	H	$(CH_3)_2CH$-	**g**	10	85	96:4	>99
14[e]				<5	95	98:2	>99
15[g]	-$(CH_2)_4$-		**h**	60	89	91:9	98
16[e, g]				40	92	91:9	98
17[g]	-$(CH_2)_2OCH_2$-		**i**	60	70	76:24	70
18[e, g]				30	85	75:25	70
19[g]	Me	H	**j**	120	77		84
20[e, g]				60	80		84

[a]Unless otherwise specified, the reactions were carried out with compound **3** (0.24 mmol, 1.2 equiv) and the imine **4** (0.20 mmol) in presence of L-proline (**1a**, 0.010 mmol, 5.0 mol %) and quinidine thiourea (**2a**, 0.010 mmol, 5.0 mol %) under neat condition at room temperature (ca. 25 °C). [b]Yield of isolated product **5** after column chromatography. [c]Determined by analysis of ^{1}H NMR of the crude reaction mixture. [d]Determined by HPLC analysis of the purified product using a ChiralPak IC column. The absolute configuration of the products was assigned by comparing the observed spectral data and optical rotation values with the reported data. [e]Carried out with **1a** (0.020 mmol, 10.0 mol %) and **2a** (0.020 mmol, 10.0 mol %). [f]Determined by using the corresponding reduced aminol. [g]2.0 mmol (10.0 equiv.) of the ketone was used.



Scheme 1: Proposed Favored Transition States for the MDO-Catalyzed List-Barbas-Mannich Reactions

The relative stereochemistry was assigned by comparing the ^{1}HNMR spectra of the aldehyde Mannich products obtained with MDO of **1a**/**2a** with the reported data. The absolute stereochemistry of was assigned as (2*S*,3*S*) by comparing the measured optical rotations of compounds **5b** and **5j** with the reported data. Moreover, the major enantiomers obtained in our study is the same as those out of L-proline catalysis, which is known to yield (2*S*,3*S*) products in such a List-Barbas-Mannich reaction.[9] Our data also indicate that the product absolute configuration depends only on the absolute stereochemistry of the reaction-center module, whereas the cinchona alkaloid thioureas do not affect the stereochemical outcome (Table 1).

These results may be explained by the proposed transition states in Scheme 1. As shown in Scheme 1, dodecanal (**3a**) reacts with the L-proline moiety (**1a**) of the MDOs to form an (*E*)-enamine, whereas ethyl (*p*-methoxyphenylimino)acetate (**4**) is hydrogen-bonded to the thiourea moiety of the MDOs. In both cases of the MDOs of **1a**/**2a** and **1a**/**2f**, the attack of the enamine onto the *Si* face of imine **4** is favored. Thus, both MDOs of **1a**/**2a** (Table 1, entry 1) and **1a**/**2f** (Table 1, entry 18) should produce the same enantiomers of the *syn*-**5a**, even though these two MDOs are pseudo diastereomeric (Scheme 1, upper equations). On the other hand, the (*E*)-enamine formed between D-proline and the MDO of **1b/2a** attacks the *Re* face of the imine in the favored transition state (Scheme 1, lower equation), which should lead to the formation of the enantiomer of *syn*-**5a** (Table 1, entry 6). Thus, although the cinchona thiourea modules are crucial for achieving the observed high stereoselectivities, they do not cause stereochemical switches in the List-Barbas-Mannich products.

CONCLUSION

In summary, MDOs self-assembled from proline and cinchona alkaloid thioureas are high efficient catalysts for the List-Barbas-Mannich reaction of aldehydes and ketones with ethyl (*p*-methoxyphenylimino)acetate. The desired List-Barbas-Mannich products may be obtained in excellent diastereoselectivities (up to > 99:1) and ee values (up to > 99% ee) in short times under solvent-free conditions.

EXPERIMENTAL SECTION

General Experimental Methods: All reactions were carried out in oven dried glassware. Solvents were dried using standard protocols. Aldehydes and ketones were freshly distilled before use. Ethyl (*p*-methoxyphenylimino)acetate (**4**) was prepared following the known

procedure.[10] Precatalyst modules **1a-1i**, **2e** and **2k** were commercially available. Precatalyst modules **1j**,[11] **2a-2d**,[11] **2f-2g**,[11] **2h**,[12] **2i**,[13] **2j**,[14] **2l**[15], **2m**[14] and **2n**[14] were synthesized following the reported procedures. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz, respectively) spectra were recorded at 25 ºC using $CDCl_3$ as solvent. Known compounds were identified by comparing their spectral and optical data with those reported in literature.[16-19] High resolution mass spectra were recorded using electrospray ionization (ESI) technique with a TOF analyzer.

General Procedure for the List-Barbas-Mannich reaction catalyzed by modularly designed organocatalyst: L-Proline (**1a**, 2.4 mg, 0.020 mmol, 10 mol %) and quinidine-derived thiourea **2a** (11.9 mg, 0.020 mmol, 10 mol %) were added to dodecanal (**3a**, 44.2 mg, 0.24 mmol, 1.2 equiv.) while stirring at rt. (Note: Precatalysts **1a** and **2a** were first taken in 1.0 mL of the corresponding solvent and the mixture was stirred for 15 min. before the addition of aldehyde, if the reaction was conducted in a solvent). The mixture was further was stirred at room temperature for 10 min. Then the imine (**4**, 41.4 mg, 0.20 mmol) was added. The reaction finished almost instantaneously (monitored by TLC). Upon completion, the whole reaction mixture was transferred to a column packed with silica gel and hexane and eluted with a 90:10 hexane/EtOAc mixture to yield product **5a** as a colorless gummy liquid (76.7 mg, 98% yield; dr >99:1, >99% ee).

(2*S*,3*S*)-Ethyl 3-formyl-2-[(4-methoxyphenyl)amino]tridecanoate (5a): Colorless gummy liquid; 76.7 mg, 98% yield; dr > 99:1, >99% ee; $[\alpha]_D^{25}$ = -36.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.71 (d, *J* = 1.9 Hz, 1H), 6.77 – 6.75 (m, 2H), 6.66 – 6.63 (m, 2H), 4.34 (dd, *J* = 9.7, 4.9 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.93 (d, *J* = 9.9 Hz, 1H), 3.74 (s, 3H), 2.71 (dtd, *J*

= 6.7, 4.8, 1.9 Hz, 1H), 1.86 (ddd, *J* = 18.7, 9.2, 4.7 Hz, 1H), 1.65 – 1.53 (m, 1H), 1.41 (dd, *J* = 8.9, 4.0 Hz, 1H), 1.35 – 1.18 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 172.6, 153.4, 140.6, 116.2, 114.9, 61.7, 58.5, 55.8, 53.9, 32.0, 29.71, 29.69, 29.68, 29.5, 29.4, 27.6, 25.3, 22.8, 14.3, 14.3. ν_{max} (neat, cm^{-1}): 2922, 2852, 1723, 1511, 1464, 1443, 1239, 1180, 1033, 821; HRMS (EI) calcd. *m/z* for $C_{23}H_{38}NO_4$ $[M+H]^+$ = 392.2801, found 392.2795.

(2*S*,3*S*)-Ethyl 3-formyl-2-[(4-methoxyphenyl)amino]decanoate (5b):[16] Colorless gummy liquid; 65.7 mg, 94% yield; dr = 97:3, >99% ee; $[\alpha]_D^{25}$ = -21.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$)) δ 9.71 (d, *J* = 1.9 Hz, 1H), 6.77 – 6.75 (m, 2H), 6.66 – 6.64 (m, 2H), 4.34 (d, *J* = 4.9 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.96 (s, 1H), 3.73 (s, 3H), 2.71 (dtd, *J* = 6.7, 4.8, 1.9 Hz, 1H), 1.86 (ddd, *J* = 18.8, 9.2, 4.7 Hz, 1H), 1.60 (ddd, *J* = 14.2, 10.1, 4.8 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.36 – 1.21 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 172.6, 153.4, 140.6, 116.2, 114.9, 61.7, 58.5, 55.8, 53.9, 31.9, 29.6, 29.1, 17.6, 15.3, 22.7, 14.3, 14.2.

(2*S*,3*S*)-Ethyl 3-formyl-2-[(4-methoxyphenyl)amino]octanoate (5c):[9,16] Colorless gummy liquid; 63.0 mg, 98% yield; dr = 97:3, >99% ee; $[\alpha]_D^{25}$ = -28.4 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.9 Hz, 1H), 6.79 – 6.76 (m, 2H), 6.68 – 6.64 (m, 2H), 4.36 (d, *J* = 5.0 Hz, 1H), 4.22 – 4.15 (m, 2H), 3.75 (s, 3H), 2.73 (dtd, *J* = 6.7, 4.7, 1.9 Hz, 1H), 1.87 (ddd, *J* = 14.1, 9.4, 5.0 Hz, 1H), 1.63 – 1.56 (m, 1H), 1.45 – 1.39 (m, 1H), 1.36 – 1.28 (m, 5H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.91 – 0.87 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 172.6, 154.5, 140.5, 116.3, 114.9, 61.7, 58.6, 55.8, 53.8, 31.8, 27.3, 25.2, 22.5, 14.3, 14.1.

(2*S*,3*S*)-Ethyl 3-formyl-2-[(4-methoxyphenyl)amino]hexanoate (5d):[16,17] Colorless gummy liquid; 54.6 mg, 93% yield; dr = 98:2, >99% ee; $[\alpha]_D^{25}$ = -36.4 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.9 Hz, 1H), 6.85 – 6.70 (m, 2H), 6.70 – 6.58 (m, 2H), 4.41 – 4.29 (m, 1H), 4.23 – 4.12 (m, 2H), 3.95 (s, 1H), 3.73 (s, 3H), 2.77 – 2.68 (m, 1H), 1.92 – 1.81 (m, 1H), 1.62 – 1.53 (m, 1H), 1.46 (tdd, *J* = 10.1, 7.4, 5.2 Hz, 1H), 1.42 – 1.32 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 172.5, 153.4, 140.6, 116.2, 114.9, 61.7, 58.5, 55.8, 53.6, 27.4, 20.9, 14.3, 14.2.

(2*S*,3*S*)-Ethyl 2-[(4-methoxyphenyl)amino]-3-methyl-4-oxobutanoate (5e):[9,17,18] Colorless gummy liquid; 50.4 mg, 95% yield; dr = 95:5, >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, *J* = 0.7 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.71 – 6.61 (m, 2H), 4.46 (s, 1H), 4.19 (dtt, *J* = 10.8, 7.1, 3.7 Hz, 2H), 3.92 (s, 1H), 3.74 (s, 3H), 2.88 (qdd, *J* = 7.2, 4.4, 0.7 Hz, 1H), 1.28 – 1.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 172.5, 153.6, 140.6, 116.5, 114.9, 61.7, 58.7, 55.8, 48.4, 14.3, 9.2. Enantiomeric excess was determined for the corresponding alcohol, after reduction of the Mannich product.

(2*S*,3*S*)-Ethyl 3-benzyl-2-((4-methoxyphenyl)amino)-4-oxobutanoate (5f):[16,18] Colorless gummy liquid; 65.5 mg, 96% yield; dr = 96:4, 94% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.1 Hz, 1H), 7.33 (dd, *J* = 10.4, 4.2 Hz, 2H), 7.28 – 7.20 (m, 3H), 6.78 – 6.68 (m, 2H), 6.54 – 6.45 (m, 2H), 4.34 – 4.27 (m, 1H), 4.18 – 4.06 (m, 3H), 3.73 (s, 3H), 3.25 (dd, *J* = 14.0, 7.4 Hz, 1H), 3.13 (tdd, *J* = 7.3, 4.4, 1.1 Hz, 1H), 2.98 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 201.9, 172.2, 153.3, 140.2, 138.1, 129.2, 128.4, 127.0,

116.0, 114.9, 61.8, 57.5, 55.6, 31.7, 14.3. Enantiomeric excess was determined for the corresponding alcohol, after reduction of the Mannich product.

(2*S*,3*S*)-Ethyl 3-formyl-2-[(4-methoxyphenyl)amino]-4-methylpentanoate (5g):[16,18,19] Colorless gummy liquid; 55.7 mg, 95% yield; dr = 98:2, >99% ee; $[\alpha]_D^{25}$ = -43.2 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, *J* = 3.0 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.68 – 6.65 (m, 2H), 4.33 (dd, *J* = 10.2, 6.9 Hz, 1H), 4.17 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.87 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 2.56 (td, *J* = 7.1, 3.0 Hz, 1H), 2.32 (dq, *J* = 13.9, 6.9 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 172.8, 153.2, 140.3, 115.9, 115.0, 61.6, 59.8, 57.1, 55.8, 26.4, 21.1, 19.4, 14.3.

(*S*)-Ethyl 2-[(4-methoxyphenyl)amino]-2-[(*S*)-2-oxocyclohexyl]acetate (5h):[16,18] Colorless gummy liquid; 56.2 mg, 92% yield; dr = 91:9, 98% ee; $[\alpha]_D^{25}$ = -38.6 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 – 6.74 (m, 2H), 6.74 – 6.70 (m, 2H), 4.23 (d, *J* = 5.1 Hz, 1H), 4.18 – 4.10 (m, 2H), 3.73 (s, 3H), 2.85 – 2.77 (m, 1H), 2.49 – 2.42 (m, 1H), 2.36 – 2.26 (m, 1H), 2.20 (ddd, *J* = 9.1, 5.7, 2.7 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.98 – 1.92 (m, 1H), 1.81 (ddd, *J* = 25.5, 12.6, 3.5 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 173.6, 153.1, 141.2, 116.2, 114.8, 61.3, 58.2, 55.9, 53.7, 42.0, 29.7, 27.0, 24.9, 14.3.

(*S*)-Ethyl 2-[(4-methoxyphenyl)amino]-2-[(*R*)-4-oxotetrahydro-2*H*-pyran-3-yl]acetate (5i):[16] Colorless gummy liquid; 52.2 mg, 85% yield; dr = 75:25; 70% ee $[\alpha]_D^{25}$ = -51.6 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 – 6.74 (m, 2H), 6.74 – 6.68 (m, 2H), 4.25 (d, *J* =

5.7 Hz, 1H), 4.21 – 4.07 (m, 4H), 4.01 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.91 (ddd, *J* = 11.3, 7.6, 5.5 Hz, 1H), 3.74 (s, 3H), 2.96 – 2.87 (m, 1H), 2.64 – 2.53 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 172.7, 153.5, 140.9, 116.4, 115.0, 69.7, 68.2, 61.7, 56.8, 55.8, 54.6, 42.2, 14.2.

(*S*)-Ethyl 2-[(4-methoxyphenyl)amino]-4-oxopentanoate (5j):[16,18] Colorless gummy liquid; 42.3 mg, 80% yield, 84% ee; $[\alpha]_D^{25}$ = -22.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 – 6.75 (m, 2H), 6.68 – 6.62 (m, 2H), 4.33 (t, *J* = 5.6 Hz, 1H), 4.17 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.74 (s, 3H), 2.96 (d, *J* = 5.6 Hz, 2H), 2.18 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 173.2, 153.2, 140.6, 115.9, 115.0, 61.6, 55.8, 54.4, 46.0, 30.5, 14.3.

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Supporting Information Available: Copies of NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) For general reviews, see: (a) Akiyama, T. In *Comprehensive Chirality* Carreira, E. M.; Yamamoto, H. Eds, Elsevier B.V.: Amsterdam, Vol. *6*, **2012**, pp 69-96. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev*. **2011**, *111*, 2626-2704. (c) Hart, D. J.; Ha, D. C. *Chem. Rev*. **1989**, *89*, 1447-1465.

(2) (a) List, B. *J. Am. Chem. Soc*. **2000**, *122*, 9336-9337. (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett*. **2001**, *42*, 199-201.

(3) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138-5175. (b) Marques, M. M. B. *Angew. Chem., Int. Ed*. **2006**, *45*, 348-352. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471-5569. (d) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P.; Rutjes, F. *Chem. Soc. Rev*. **2008**, *37*, 29-41. (e) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem*. **2008**, *6*, 2047-2053. (f) Bhadury, P. S.; Song, B.-A. *Curr. Org. Chem*. **2010**, *14*, 1989-2006. (g) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev*. **2009**, *38*, 1940-1948. (h) Xiao-Hua, C.; Hui, G.; Bing, X. *Eur. J. Chem*. **2012**, *3*, 258-266. (i) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797-5815.

(4) For some leading examples, see: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc*. **2002**, *124*, 827-833. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc*. **2002**, *124*, 1842-1843. (c) Córdova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc*. **2002**, *124*, 1866-1867. (d) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 1101-1104. (e) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 6058-6063. (f) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed*. **2004**, *43*, 6528-6531. (g) Sunden, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed*. **2005**, *44*, 4877-4880. (h) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 3677-3680. (i) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc*. **2003**, *125*, 11208-11209. (j) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed*. **2007**, *46*, 609-611. (k) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc*. **2007**, *130*, 875-886. For an example of *anti*-selective List-Barbas-Mannich reaction, see: (l)

Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041.

(5) For reviews, see: (a) Briere, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev*. **2012**, *41*, 1696-1707. (b) Meeuwissen, J.; Reek, J. N. H. *Nat. Chem*. **2010**, *2*, 615-621. (c) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 6216-6232.

(6) For some selected examples, see: (a) Clarke, M. L.; Fuentes, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 930-933. (b) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120-123. (c) El-Hamdouni, N.; Companyó, X.; Rios, R.; Moyano, A. *Chem. Eur. J*. **2010**, *16*, 1142-1148. (d) Xia, A.-B.; Xu, D.-Q.; Luo, S.-P.; Jiang, J.-R.; Tang, J.; Wang, Y.-F.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, *16*, 801-804. (e) Fuentes, J. A.; Lebl, T.; Slawin, A. M. Z.; Clarke, M. L. *Chem. Sci*. **2011**, *2*, 1997-2005. (f) Ma, G.; Bartoszewicz, A.; Ibrahem, I.; Córdova, A. *Adv. Synth. Catal*. **2011**, *353*, 3114-3122. (g) Yao, Y.; Li, J.-L.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Chem. Eur. J*. **2013**, *19*, 9447-9451. (h) Ramachary, B. D.; Madhavachary, R.; Prasad, M. S. *Org. Biomol. Chem*. **2012**, *10*, 5825-5829. (i) Ramachary, B. D.; Sakthidevi, R.; Shruthi, K. S. *Chem. Eur. J*. **2012**, *18*, 8008-8012.

(7) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J*. **2012**, *18*, 4088-4098.

(8) (a) Mandal, T.; Zhao, C.-G. *Angew. Chem. Int. Ed*. **2008**, *47*, 7714-7717. (b) Muramulla, S.; Zhao, C.-G. *Tetrahedron Lett*. **2011**, *52*, 3905-3908. (c) Muramulla, S.; Ma, J.-A.; Zhao, J. C.-G. *Adv. Synth. Catal*. **2013**, *355*, 1260-1264. (d) Sinha, D.; Perera, S.; Zhao, J. C.-G. *Chem. Eur. J.* **2013**, *19*, 6976-6979. (e) Sinha, D.; Mandal, T.; Gogoi, S.; Goldman, J. J.; Zhao, J. C.-G. *Chin. J. Chem.* **2012**, *30*, 2624-2630.

(9) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., *J. Org. Chem*. **2003**, *68*, 9624-9634.

(10) Marin, S. D. L.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem*. **2005**, *70*, 10592-10595.

(11) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967-1969.

(12) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *Eur*. *J. Org. Chem*. **2011**, 4472-4478.

(13) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc*. **2009**, *131*, 418-419.

(14) (a) Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem*. **2012**, 5919-5927. (b) Štrukil, V.; Igrc, M. D.; Fábián, L.; Eckert-Maksić, M.; Childs, S. L.; Reid, D. G.; Duer, M. J.; Halasz, I.; Mottillo, C.; Friščič, T. *Green Chem*. **2012**, *14*, 2462-2473. (c) Findlater, M.; Hill, N. J.; Cowley, A. H. *Dalton Trans*. **2008**, 4419-4423.

(15) Li, Z.-B.; Luo, S.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem*. **2010**, *8*, 2505-2508.

(16) (a) Wang, W.; Wang, J.; Li, H. *PCT Int. Appl*., 2006007586, 19 Jan 2006; (b) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett*. **2004**, *45*, 7243-7246.

(17) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett*. **2008**, *10*, 21-24.

(18) (a) Barbas, C. F.; Cordova, A.; Notz, W. *PCT Int. Appl.*, 2003059915, 24 Jul 2003; (b) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbasa, C. F. *J. Am. Chem. Soc*. **2002**, *124*, 1866-1867; (c) Cordova, A.; Barbas, C. F. *Tetrahedron Lett*. **2003**, *44*, 1923-1926.

(19) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem*. **2005**, *3*, 84-96.

Graphic Abstract