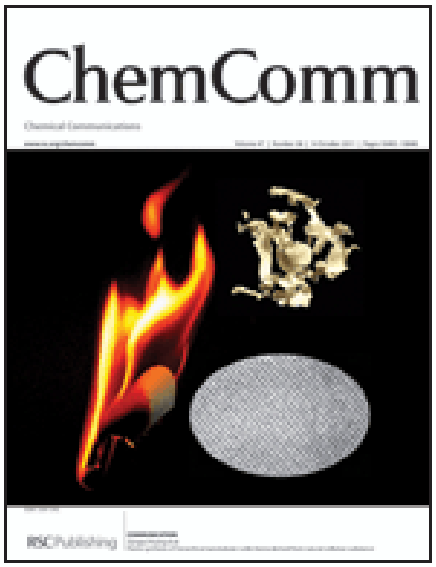
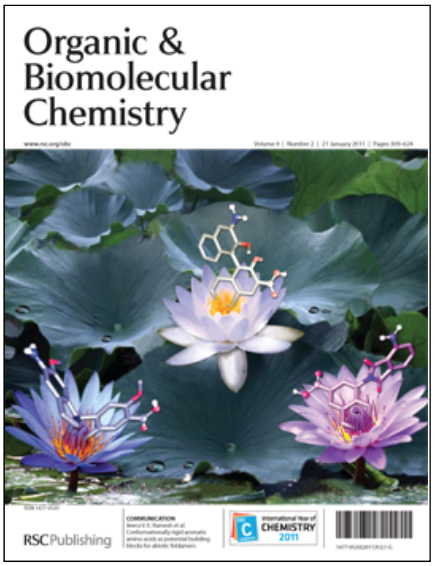




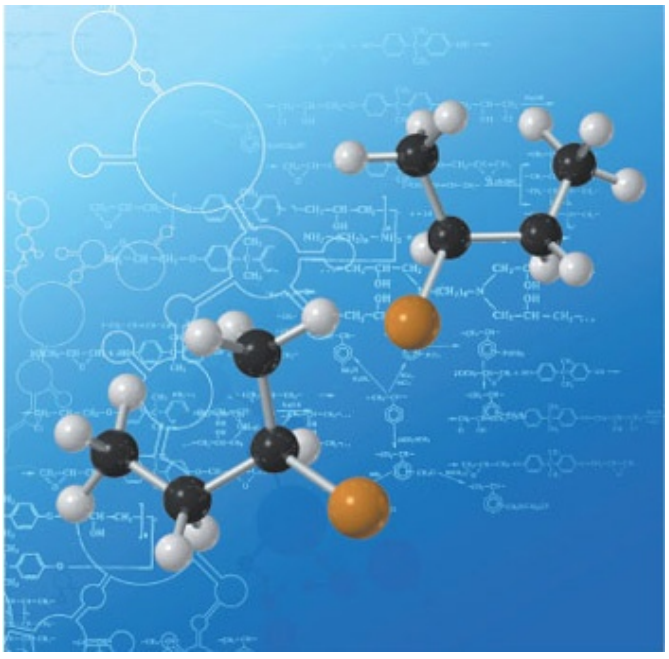
This article is part of the

Organocatalysis

web themed issue

Guest editors: Professors Keiji Maruoka, Hisashi Yamamoto, Liu-Zhu Gong and Benjamin List

All articles in this issue will be gathered together online at www.rsc.org/organocatalysis



Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5094

www.rsc.org/obc

PAPER

Direct catalytic asymmetric synthesis of highly functionalized (2-ethynylphenyl)alcohols *via* Barbas–List aldol reaction: scope and synthetic applications†‡

Dhevalapally B. Ramachary,* Rumpa Mondal and R. Madhavachary

Received 15th March 2012, Accepted 25th April 2012
DOI: 10.1039/c2ob25563d

A high-yielding asymmetric synthesis of functionalized (2-ethynylphenyl)alcohols **5**/**6** with good diastereo- and enantioselectivities was achieved by Barbas–List aldol (BLA) reaction of 2-alkynylbenzaldehydes **1** with various ketones **2** in the presence of *trans*-4-OH-L-proline or L-prolinamide derivative **3**/**4** as catalyst at the ambient temperature or −35 °C. This method also gives first time access to the novel double aldol addition compounds **6**, which are of medicinal importance. Chiral functionalized (2-ethynylphenyl)alcohols **5**/**6** were transformed into acyclic and cyclic 1,4-triazoles **8**/**9** and *cis*-1,3-diols **10** in good yields with high selectivity through double click-reaction and Lewis acid-mediated $NaBH_4$ reduction respectively. Chiral products **8**–**10** may become good ligands and inhibitors in medicinal chemistry.

Introduction

Although the potential of L-proline-catalyzed asymmetric intramolecular aldol reactions has been known since long back,[1] the pioneering discovery of L-proline-catalyzed direct intermolecular asymmetric aldol reactions of aldehydes with acetone by Barbas *et al.*,[2] opened a new gateway for green asymmetric reactions. Following this pioneering "Barbas–List aldol (BLA)" reaction, the last decade has seen a tremendous development in the field of "amine-/amino acid-catalyzed asymmetric aldol reactions" both in terms of catalyst design as well as reaction engineering.[3] A vast number of organocatalysts, mostly based on the L-proline moiety has been synthesized and utilized under finely tuned reaction conditions to provide aldol products with high selectivities in both aqueous and organic media with broad range of substrates.[3] The transition state of the BLA reaction has been studied extensively providing evidences for an enamine based mechanism where hydrogen-bonding plays a key role to achieve the high enantioselectivity.[4]

In BLA reactions, mainly an aldehyde acts as the acceptor or the electrophile and ketone or another aldehyde acts as the donor or nucleophile. The scope of a large number of aliphatic and aromatic aldehydes has been explored so far as the acceptor in the BLA reaction with both acyclic and cyclic ketone donors, providing aldol products with high diastereo- and enantioselectivities using different organocatalysts.[3] As expected, aromatic aldehydes containing electron withdrawing groups at the *ortho* or *para* position are "highly reactive" towards *in situ* generated enamines and furnished the aldol adducts with high yields and high selectivities. Whereas, the presence of electron donating groups at the *ortho* or *para* position decreases both the reactivity and selectivity. Moreover, the reactivity of the aldehydes, in some instances, considerably affect the product ratio leading to the formation of double aldol addition products along with the mono aldol addition products from "highly-reactive" aromatic aldehydes.[5] But high yielding asymmetric synthesis of 1,5-dihydroxy-pentan-3-one (double aldol addition) products from "less-reactive" aromatic aldehydes are rare in organocatalysis.

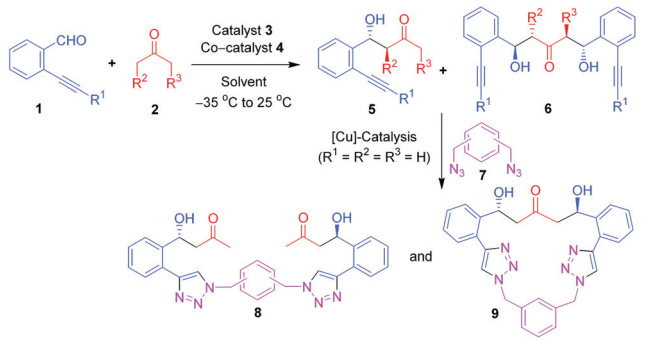
As a matter of fact, aromatic aldehydes containing electron donating or neutral *ortho* groups are much less explored in organocatalytic BLA reactions. It was envisaged that both the electronic and stereochemical properties of the group at the *ortho* position of aromatic aldehyde play a crucial role as neighboring group participation in the transition state of the organocatalytic BLA reaction and therefore can significantly control the selectivity of the aldol products.[3q] Hence, aldol reactions of aromatic aldehydes containing *ortho* groups could be an interesting subject to study in organocatalysis.

As a part of ongoing research in our laboratory on organocatalytic asymmetric synthesis,[6] the scope of 2-alkynylbenzaldehydes **1** as acceptor in organocatalytic BLA reaction with

Catalysis Laboratory, School of Chemistry, University of Hyderabad, Hyderabad-500 046, India. E-mail: ramsc@uohyd.ernet.in, ramchary.db@gmail.com; Fax: +91-40-23012460

† This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. CCDC 804553. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25563d



Scheme 1 Direct organocatalytic BLA reaction of 2-alkynylbenzaldehydes **1** with ketones **2** and their synthetic applications.

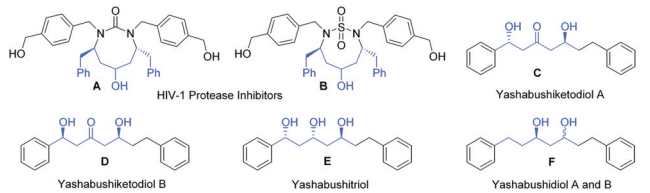


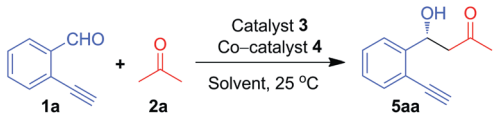
Fig. 1 Important compounds to study from the double BLA products **6**.

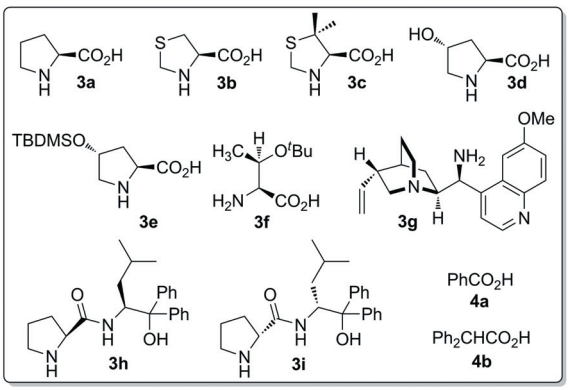
various cyclic and acyclic ketones **2** was studied and the findings are disclosed in the next section (Scheme 1). The expected BLA adducts **5** were obtained with high yields and high ee and de's, as well as in some cases 1,5-dihydroxy-pentan-3-one (double aldol addition) derivatives **6** were isolated as the major product with >99% ee and >99% de. Therefore these studies also give an insight into the highly enantioselective synthesis of 1,5-dihydroxy-pentan-3-one derivatives **6** from "less reactive" aromatic aldehydes **1** through BLA reaction. These double aldol addition products **6** can be utilized as chiral synthons for the analogues synthesis of potent HIV-1 protease inhibitors **A**, **B** and natural products diarylheptanoids **C–F** from the male flowers of *Alnus sieboldiana* (Fig. 1).[7]

Results and discussion

Structure–activity relationships of amino acid catalysts on BLA reaction of 1a with 2a: reaction optimization. The study was initiated by employing a number of known and novel organocatalysts on BLA reaction of **1a** with **2a** in variety of solvents at 25 °C and L-proline **3a** being the first choice as it is unequivocally accepted as the universal asymmetric catalyst (Table 1). It was observed that 20 mol% of L-proline **3a** was able to catalyze the reaction between 2-ethynylbenzaldehyde **1a** and 34 equiv. of acetone **2a** in DMSO at 25 °C to give the desired BLA adduct **5aa** in 84% yield with only 60% ee within 1 h (Table 1, entry 1). The same BLA reaction of **1a** with **2a** under 20 mol% of **3a** catalysis at 25 °C for 2 h using DMF or NMP as solvent, also gave similar results. In DMF, **5aa** was furnished in 87% yield with 65% ee while in NMP the yield and ee were 85% and 68% respectively (Table 1, entries 2 and 3). CH_3CN proved to be inferior as compared to other polar aprotic solvents in the above reaction and afforded **5aa** in only 35% yield with 59% ee under similar reaction conditions even after longer reaction time (Table 1, entry 4). Replacing the catalyst L-proline **3a** with L-thiaproline **3b** (20 mol%) for the reaction of **1a** with **2a** in DMSO for 24 h at 25 °C furnished **5aa** in low yield albeit with 71% ee (Table 1, entry 5). Interestingly, the same reaction using the costly catalyst 5,5-dimethyl-thiazolidinium-4-carboxylate (DMTC) **3c** furnished the **5aa** in 75% yield with 85% ee, significantly better than L-proline **3a**-catalysis (Table 1, entry 6). When the BLA reaction of **1a** with 34 equiv. of **2a** was catalyzed by 20 mol% of *trans*-4-OH-L-proline **3d** in DMSO at 25 °C, the aforesaid product **5aa** was isolated with 85% yield and 73% ee (Table 1, entry 7). The BLA adduct **5aa** was isolated with comparable yields and ee's when reaction catalyzed by *trans*-4-OH-

Table 1 Preliminary optimization of the BLA reaction of **1a** with **2a**





Entry	Catalyst **3**/**4**	Solvent (0.125–0.3 M)	Time (h)	Yield[a] (%)	ee **5aa**[b] (%)
1[c]	**3a**	DMSO	1	84	60
2[c]	**3a**	DMF	2	87	65
3[c]	**3a**	NMP	2	85	68
4[c]	**3a**	CH_3CN	24	35	59
5[c]	**3b**	DMSO	24	25	71
6[c]	**3c**	**DMSO**	**30**	**75**	**85**
7[c]	**3d**	**DMSO**	**24**	**85**	**73**
8[c]	**3d**	DMF	19	87	67
9[c]	**3d**	**NMP**	**24**	**83**	**74**
10[c]	**3e**	DMSO	7	82	66
11[d]	**3d**	DMSO	9	74	71
12[c]	**3f**	DMSO	24	<10	—
13[e]	**3g**/**4b**	DCM	72	<10	—
14[f]	**3h**/**4a**	—	2	60	54
15[f]	**3i**/**4a**	—	3	61	−43

[a] Yield refers to the column purified products. [b] Ee was determined by CSP HPLC analysis. [c] Reactions were carried out in solvent (0.125 M) with 34 equiv. of **2a** relative to **1a** (0.3 mmol) in the presence of 20 mol% of catalyst **3**. [d] Reaction was carried out in solvent (0.25 M) with 14 equiv. of **2a** relative to **1a** (0.3 mmol) in the presence of 20 mol% of catalyst **3**. [e] Reaction was carried out in DCM (0.3 M) with 28 equiv. of **2a** relative to **1a** (0.3 mmol) in the presence of each 10 mol% of catalyst **3g** and co-catalyst **4b**. [f] Reactions were carried out in neat acetone (0.3 M) with each 10 mol% of catalyst **3h–i** and co-catalyst **4a**.

L-proline **3d** under similar reaction conditions in both DMF and NMP solvents (Table 1, entries 8 and 9). *Trans*-4-OTBDMS-L-proline **3e** (20 mol%) also afforded the product **5aa** in 82% yield with only 66% ee in DMSO solvent within 7 h. When the amount of acetone **6a** was reduced from 34 equiv. to 14 equiv., then also the BLA adduct **5aa** was obtained with an optical purity of 71% but at the expense of yield (74%) under **3d** catalysis in DMSO (Table 1, entry 11). Use of O-*t*Bu-L-threonine **3f** as a catalyst in the above BLA reaction in DMSO, did not appear to be promising and furnished **5aa** in only <10% yield even after 24 h (entry 12).[3l–n] The bifunctional catalyst Q-NH_2 **3g**/Ph_2CHCO_2H **4b** also gave similar result in the above reaction (Table 1, entry 13). After moderate to good selectivity with L-proline based catalysts on BLA reaction of **1a** with **2a**, we further showed interest to screen L-prolinamide catalysts as shown in Table 1, entries 14–15.

Among the various L-prolinamide catalysts developed for BLA reaction till date, the best results were achieved by Yun-Dong Wu, Liu-Zhu Gong and V. K. Singh *et al.* by using a small class of prolinamides **3h** and **3i** where the acidity and strong hydrogen-bonding capacity of the catalysts **3h**/**3i** guided the selectivity.[8] Inspired by these results, the catalyst **3h** was chosen for testing the BLA reaction of 2-ethynylbenzaldehyde **1a** with acetone **2a** under the neat conditions. Unexpectedly, when **1a** was treated with **2a** (0.3 M) using 10 mol% **3h**/**4a** as catalyst at 25 °C, the BLA product **5aa** was formed in only 60% yield with 54% ee (Table 1, entry 14). The same reaction under 10 mol% of **3i**/**4a**-catalysis also furnished the BLA product **5aa** in 61% yield with reduced (43%) ee as shown in Table 1, entry 15.

BLA reaction of **1a** with **2a** under only **3h**-catalysis furnished the product **5aa** with improved yield and ee at 25 °C for 6 h as shown in Table 2, entry 1. Surprisingly, lowering the reaction temperature from 25 °C to −35 °C, had a profound impact on the outcome of the above reaction. We were pleased to find that the reaction of **1a** with **2a** (0.3 M) catalyzed by 10 mol% of **3h** at −35 °C, not only furnished the expected BLA adduct **5aa** in moderate yield and ee but also furnished the double aldol addition product **6aa** in 44% yield with >99% de and >99% ee, which is so far the highest optical purity obtained for the 1,5-dihydroxy-pentan-3-one derivatives (Table 2, entry 2).[5] When the reaction was carried out using each 10 mol% of the catalyst **3h** and co-catalyst **4a** in neat acetone (0.3 M) at −35 °C for 24 h, the BLA adduct **5aa** was furnished with an improved yield (34%) and ee (93%) accompanied by **6aa** in 38% yield with >99% de and >99% ee (Table 2, entry 3). The catalyst **3i** (10 mol%) in combination with **4a** (10 mol%) also catalyzed the same reaction under identical reaction conditions to afford the opposite enantiomers of **5aa** and **6aa** with high ee and de's albeit with less yields (Table 2, entry 4). The structure of the double BLA product (*R*,*R*)-(+)-**6aa** was determined by NMR analysis and the absolute configuration was confirmed by X-ray structure analysis (Fig. 2).[9] Therefore, two optimized reaction conditions were finalized for the BLA reaction of 2-ethynylbenzaldehyde **1a** with acetone **2a**. Method-B involved the usage of 20 mol% of **3c** or **3d** as the catalyst at 25 °C in DMSO (0.125 M) solvent, whereas in Method-A, the reaction was carried out at −35 °C using each 10 mol% of the catalyst **3h** or **3i** and co-catalyst **4a** in neat acetone **2a** (0.3 m). The overall structure–activity relationship garnered from the catalyst screen on the asymmetric BLA reaction of **1a** and **2a** was similar to that basic aldol reaction[2] with optimal yield and enantioselectivity being provided by proline-like catalysts.

Synthetic scope of L-DMTC, *trans*-4-OH-L-proline and L-prolinamide catalyzed BLA reactions. With the optimized reaction conditions in hand, the scope of other acyclic and cyclic ketones **2b–h** as donors in the BLA reaction with **1a** and **1b** was explored and the results are summarized in Table 3. The reaction of 2-ethynylbenzaldehyde **1a** with 2-butanone **6b** (0.3 M) catalyzed by **3h**/**4a**, each 10 mol% at −35 °C for 24 h furnished only the mono aldol addition products **5ab** and **5′ab** in 3.1 : 1 ratio. Interestingly, even though double aldol addition product was not observed in the above reaction, the regioselectivity,

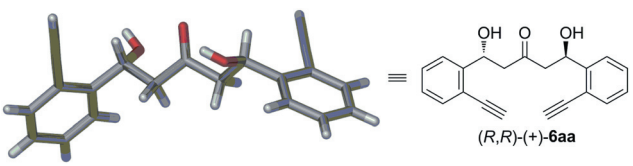
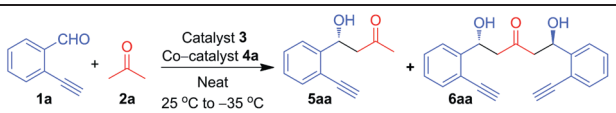


Fig. 2 Crystal structure of 1,5-bis-(2-ethynylphenyl)-1,5-dihydroxy-pentan-3-one (**6aa**).

Table 2 General optimization of the BLA reaction of **1a** with **2a**



Entry	Catalyst **3** (10 mol%)	Co-catalyst **4a** (10 mol%)	Temp (°C)	Time (h)	Yield[a] (%)		ee[b] (%)		de[b] (%)
					5aa	**6aa**	**5aa**	**6aa**	**6aa**
1[c]	**3h**	—	25	6	68	—	65	—	—
2[c]	**3h**	—	−35	28	20	44	65	>99	>99
3[d]	**3h**	**4a**	**−35**	**24**	**34**	**38**	**93**	**>99**	**>99**
4[d]	**3i**	**4a**	−35	24	16	30	−95	>−99	>99

[a] Yield refers to the column-purified products. [b] ee and de was determined by CSP-HPLC analysis. [c] Reactions were carried out in neat acetone (0.3 M) with 10 mol% of catalyst **3h**. [d] Reactions were carried out in neat acetone (0.3 M) with each 10 mol% of catalysts **3h** or **3i** and co-catalyst **4a**.

Table 3 Direct BLA reaction of 2-ethynylbenzaldehydes **1a**/**1b** with various acyclic and cyclic ketones **2b–h**

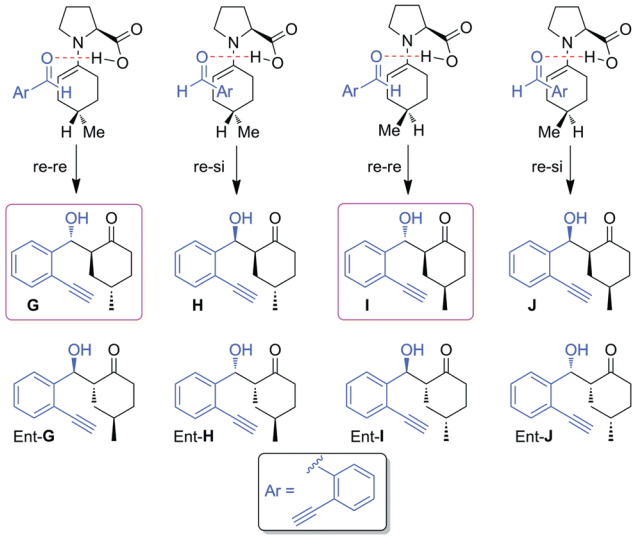
Entry	Ketone **2**	Time (h)	Products (**5**/**5′**)		Yield[a] (%)	dr[b] *anti* : *syn*	ee[c](%) *anti*	ee[c](%) *syn*
1[d]	**2b**	24	**5ab** (major)	**5'ab** (minor)	71 (23)[e]	>99 : 1	99(>99)[f]	—
2[d]	**2c**	30	**5ac** (minor)	**5'ac** (major)	61 (30)[e]	1 : 1	41(90)[f]	53
3[g]	**2c**	24	*anti*-**5'ac** (major)	*syn*-**5'ac** (minor)	61	3 : 1	93	26
4[d]	**2d**	24	*anti*–**5ad**	*syn*–**5ad**	83	11.6 : 1	96	91
5[d]	**2e**	60	*anti*–**5ae**	*syn*–**5ae**	72	1 : 1.9	95	0
6[d]	**2f**	24	(2*S*,4*S*,1′*R*)–**5af**		80	>99 : 1	96	—
7[h]	**2f**	24	(2*R*,4*R*,1′*S*)–**5af**		85	>99 : 1	96	—
8[g]	**2f**	72	(2*S*,4*R*,1′*R*)–**5af**	(2*S*,4*S*,1′*R*)–**5af**	90	1.4 : 1	77(53)[i]	—
9[d]	**2g**	24	*anti*–**5ag**	*syn*–**5ag**	83	8.2 : 1	93	6
10[g]	**2g**	24	*anti*–**5ag**	*syn*–**5ag**	73	1 : 1	0	0
11[j]	**2h**	72	*anti*–**5ah**	*syn*–**5ah**	40	>99 : 1	88	—
12[d]	**2f**	24	(2*S*,4*S*,1′*R*)–**5bf**		92	>99 : 1	86	—
13[h]	**2f**	24	(2*R*,4*R*,1′*S*)–**5bf**		85	>99 : 1	90	—

[a] Yield refers to the column-purified products. [b] dr was determined by NMR analysis on crude products. [c] ee was determined by CSP-HPLC analysis. [d] **Method-A**: Reactions were carried out in neat ketone (0.3 M) with each 10 mol% of **3h** and **4a** at −35 °C. [e] Values in parentheses refer to the yields of the minor regioisomers. [f] Value in parentheses refers to the ee of the minor regioisomer. [g] **Method-B:** Reaction was carried out in DMSO (0.25 M) in presence of 20 mol% of **3d** at 25 °C. [h] Reaction performed with each 10 mol% of **3i**/**4a** as catalyst. [i] Value in parentheses refers to the ee of the minor diastereomer. [j] Reaction were carried out in THF (0.3 M) with each 10 mol% of **3h**/**4a** at −35 °C.

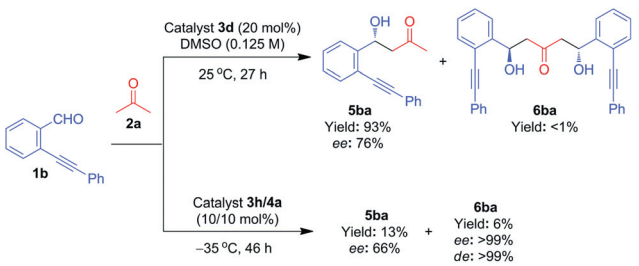
diastereoselectivity, yields and optical purities of the BLA products **5ab** and **5′ab** were excellent (Table 3, entry 1). Similarly, hydroxyacetone **2c** also reacted with **1a** under identical reaction conditions to afford the mono aldol addition products **5ac** and **5′ac** in 30% and 61% yields respectively (Table 3, entry 2). Minor BLA product **5ac** furnished with 90% ee, but major product **5′ac** were in 1 : 1 isomeric mixture with moderate ee's as shown in Table 3, entry 2. Interestingly, same BLA reaction of **2c** with **1a** under the catalysis of **3d** (20 mol%) in DMSO at 25 °C for 24 h furnished the selectively *anti*-**5′ac** and *syn*-**5′ac** in 61% yield with 3 : 1 dr ratio and 93/26% ee respectively (Table 3, entry 3). When 2-ethynylbenzaldehyde **1a** was treated with neat cyclohexanone **2d** (0.3 M) in the presence of 10 mol% of **3h**/**4a** at −35 °C, the only mono BLA adduct **5ad** was formed in 83% yield with a diastereomeric ratio of 11.6 : 1 in favour of *anti*-**5ad**. The ee's of the BLA products *anti*-**5ad** and *syn*-**5ad** were 96% and 91% respectively (Table 3, entry 4). In a similar manner, cyclopentanone **2e** (0.3 M) also reacted with **1a** following Method-A to afford the only mono BLA products *anti*-**5ae** and *syn*-**5ae** in 72% yield with 1 : 1.9 dr respectively (Table 3, entry 5). Interestingly the optical purity of *anti*-**5ae** was 95% ee, but *syn*-**5ae** was found to be almost racemic (Table 3, entry 5). Structure and regioselectivity of products **5** were obtained based on the NMR analyses and also by correlation with previous L-proline catalyzed BLA reactions.[3]

Finally, the important concept of asymmetric desymmetrization (ADS) of 4-methylcyclohexanone **2f** was studied using the BLA reaction of **1a**/**1b** with **2f** following both Method-A and B to furnish optically pure highly functionalized (2-ethynylphenyl) alcohols **5af–bf**. Surprisingly, neat reaction of **1a** with **2f** under the catalysis of **3h**/**4a** at −35 °C, led to the formation of the single diastereomer (2*S*,4*S*,1′*R*)-**5af** in 80% yield with 96% ee (Table 3, entry 6). Same neat reaction of **1a** with **2f** under the catalysis of **3i**/**4a** at −35 °C, led to the formation of the single diastereomer of opposite enantiomer (2*R*,4*R*,1′*S*)-**5af** in 85% yield with 96% ee (Table 3, entry 7). But when the same reaction was carried out following Method-B, the diastereomers (2*S*,4*R*,1′*R*)-**5af** and (2*S*,4*S*,1′*R*)-**5af** were formed in 1.4 : 1 ratio in 90% yield with 77% and 53% ee's respectively (Table 3, entry 8). In a similar manner, neat reaction of **1a** with tetrahydropyran-4-one **2g** under the catalysis of **3h**/**4a** at −35 °C, led to the formation of the BLA products *anti*-**5ag** and *syn*-**5ag** in 83% yield with 8.2 : 1 dr and 93 and 6% ee's respectively (Table 3, entry 9). But surprisingly, same reaction through Method-B conditions furnished the BLA products *anti*-**5ag** and *syn*-**5ag** in 73% yield with 1 : 1 dr and 0/0% ee respectively (Table 3, entry 10). In a further support, BLA reaction of **1a** with tetrahydrothiopyran-4-one **2h** under the catalysis of **3h**/**4a** at −35 °C for 72 h in THF led to the formation of the single diastereomer *anti*-**5ah** in 40% yield with 88% ee (Table 3, entry 11). Interestingly, BLA reaction of 2-phenylethynyl-benzaldehyde **1b** with **2f** under the catalysis of **3h**/**4a** at −35 °C for 24 h furnished the single diastereomer (2*S*,4*S*,1′*R*)-**5bf** in 92% yield with 86% ee (Table 3, entry 12). Same neat reaction of **1b** with **2f** under the catalysis of **3i**/**4a** at −35 °C for 24 h, led to the formation of the single diastereomer of opposite enantiomer (2*R*,4*R*,1′*S*)-**5bf** in 85% yield with 90% ee (Table 3, entry 13).

The absolute configuration of the ADS products (2*S*,4*S*,1′*R*)-**5af**, (2*R*,4*R*,1′*S*)-**5af**, (2*S*,4*S*,1′*R*)-**5bf** and (2*R*,4*R*,1′*S*)-**5bf** were assigned based on analogy with the literature reports.[8,10] The possible pre-transition states for the ADS of 4-methylcyclohexanone **2f** with **1a**/**1b** through enamine-based BLA reaction and also for the structures of all possible stereoisomers of the BLA adduct **5af** under the simple L-proline catalysis are depicted in Scheme 2.[10] The most favorable pre-transition states for the ADS of **2f** with **1a**/**1b** through **3**/**4**-catalysis were re–re face approach, in which formation of the enantiomer **G** is thermodynamically stable as shown in Scheme 2.

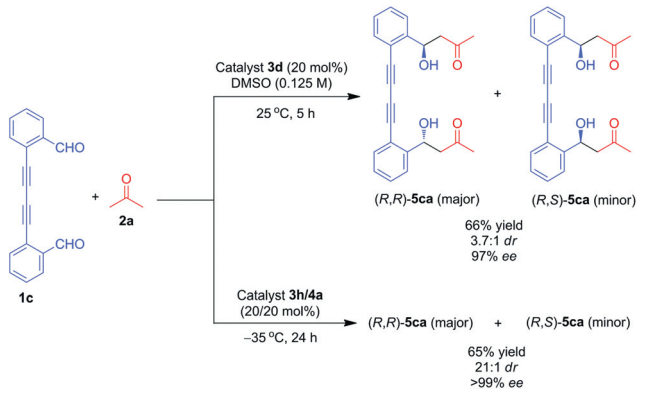


Scheme 2 Proposed pre-transition states for the ADS of **2f** with **1a**/**1b** through BLA reaction.



Scheme 3 Direct BLA reaction of 2-phenylethynylbenzaldehyde **1b** with acetone **2a**.

After successful synthesis of the asymmetric mono BLA products **5ab–ah**/**5′ab–ah** from **1a** with various acyclic and cyclic ketones **2a–h**, we further showed interest to screen different substituted alkynylbenzaldehydes **1b–c** as acceptors for the BLA reaction with acetone **2a** to check the formation of double BLA products **6** as shown in Schemes 3 and 4. As expected, BLA reaction of 2-phenylethynylbenzaldehyde **1b** with 34 equiv. of acetone **2a** under **3d**-catalysis at 25 °C for 27 h in DMSO furnished the desired mono BLA product **5ba** in 93% yield with 76% ee. Interestingly, the same reaction when catalyzed by each 10 mol% of the catalyst **3h**/**4a** at −35 °C for 46 h under neat condition (0.3 M) furnished the mono BLA adduct **5ba** in only 13% yield with 66% ee, which is accompanied by 6% of the double BLA product **6ba** with >99% ee and >99% de as shown in Scheme 3.



Scheme 4 Direct BLA reaction of dialdehyde **1c** with acetone **2a**.

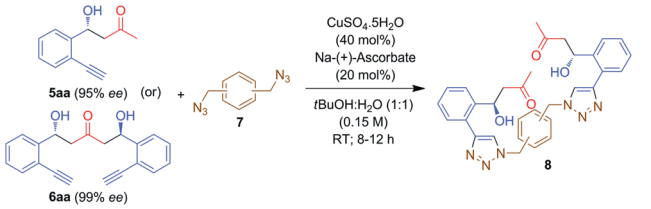
The BLA reaction of the diyne-dialdehyde **1c** with 34 equiv. of acetone **2a** catalyzed by 20 mol% of **3d** at 25 °C for 5 h in DMSO afforded the novel BLA products (*R*,*R*)-**5ca** and (*R*,*S*)-**5ca** in 66% yield with 3.7 : 1 dr and 97% ee respectively. Interestingly, when the same reaction was carried out under the catalysis of **3h**/**4a** at −35 °C for 24 h furnished the BLA products (*R*,*R*)-**5ca** and (*R*,*S*)-**5ca** in 65% yield with 21 : 1 dr and >99% ee respectively as shown in Scheme 4. Interestingly, in both reaction conditions, optically inactive BLA product (*R*,*S*)-**5ca** furnished as minor isomer. The structure of the BLA products (*R*,*R*)-**5ca** and (*R*,*S*)-**5ca** was confirmed by NMR analysis and also by high resolution mass spectral analysis.

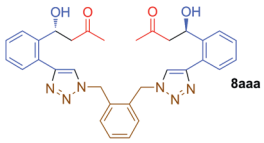
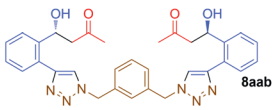
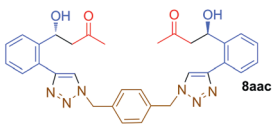
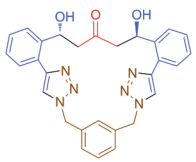
Applications of chiral BLA products

Synthesis of functionalized chiral acyclic and cyclic 1,2,3-triazole compounds 8–9 and syn-diols 10 based on the asymmetric BLA platform. In order to explore the utility of the chiral BLA products **5** and **6**, we subjected them to simple reactions like copper-catalyzed azide-alkyne cycloaddition (CuAAC) or click and reduction protocol to furnish the highly functionalized molecules **8–10** (Table 4 and Scheme 5). Fascinatingly, [Cu]-induced click reaction on chiral product (+)-**5aa** (95% ee) with 1,2-bis-(azidomethyl)benzene **7a** in *t*BuOH + H_2O for 8–12 h at 25 °C resulted in the formation of double click product (+)-**8aaa** in 55% yield with 95% ee (Table 4, entry 1). The selective double click strategy was demonstrated with two more substrates of bis(azides) **7b** and **7c** with (+)-**5aa** (95% ee) to furnish the products (+)-**8aab** and (+)-**8aac** in 55% and 65% yields with 95% ee respectively (Table 4, entries 2–3). Interestingly, [Cu]-induced click reaction of chiral product (+)-**6aa** (99% ee) with 1,3-bis (azidomethyl)benzene **7b** in EtOH for 8 h at 25 °C furnished the 22-membered cyclic double click product (+)-**9aab** in 30% yield without racemization (Table 4, entry 4). The acyclic and cyclic chiral 1,2,3-triazole compounds **8–9** may become good candidates to study in medicinal chemistry,[11] which is highlighting the importance of sequential BLA-double click approach to synthesize these important compounds.

To further demonstrate the synthetic application of the chiral BLA products **5** in the synthesis of analogous natural products of diarylheptanoids **C–F**, (+)-**5aa** was successfully transformed into the both isomers of *syn*-**10aa** and *anti*-**10aa** through the

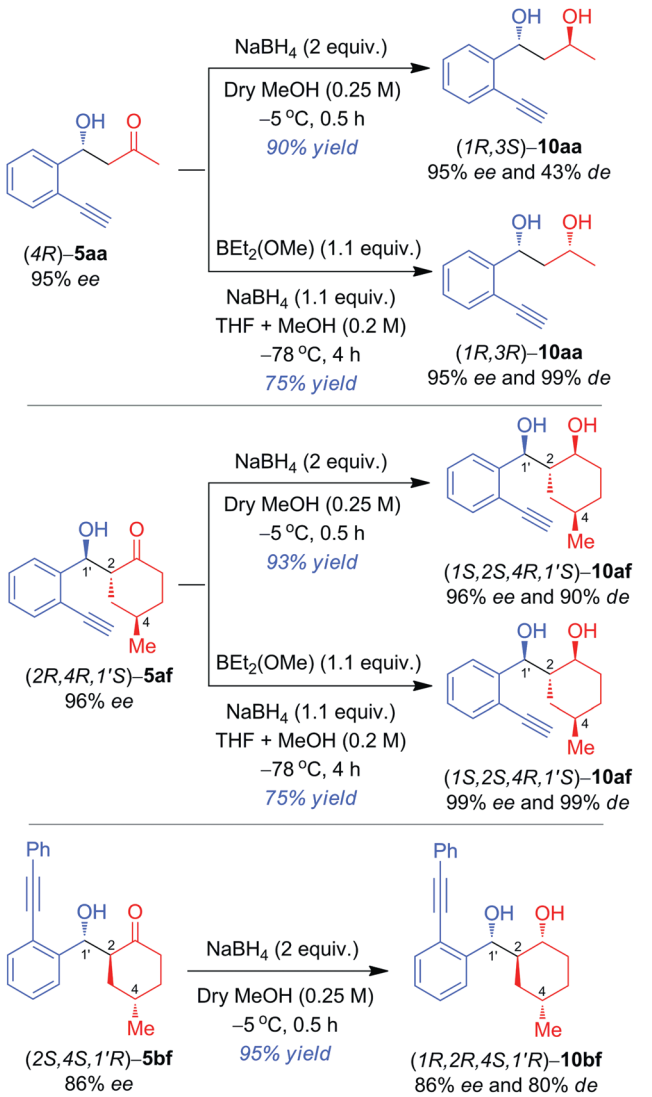
Table 4 Direct application of chiral BLA products **5aa**/**6aa** in click reactions[a]



Entry	Product	Yield[b] (%)
1	 8aaa	55
2	 8aab	55
3	 8aac	65
4[c]	 9aab	30

[a] See Experimental section. [b] Yield refers to the column purified product. [c] Reaction performed with 2 equiv. of **7b** in the presence of $CuSO_4$ (1 equiv.) and Cu powder (5 mol%) in EtOH (0.15 M) at RT for 8 h.

selective $NaBH_4$ reduction of (+)-**5aa** as shown in Scheme 5. The BLA adduct (+)-**5aa** was converted into the diol *anti*-**10aa** as major product in 90% yield with 43% de by 2 equiv. of $NaBH_4$ in dry MeOH (0.25 M) at −5 °C within 0.5 h (Scheme 5). Interestingly, the same reduction on (+)-**5aa** in the presence of 1.1 equiv. of $BEt_2(OMe)$ as Lewis acid furnished the diol *syn*-(−)-**10aa** as single product in 75% yield with 99% de and 95% ee by 1.1 equiv. of $NaBH_4$ in dry THF + MeOH (4 : 1, 0.2 M) at −78 °C for 4 h (Scheme 5). In a similar manner, highly functionalized chiral *syn*-diols (1*S*,2*S*,4*R*,1′*S*)-**10af** and (1*R*,2*R*,4*S*,1′*R*)-**10bf** were furnished in very good yields with excellent ee and de's from chiral BLA products (2*R*,4*R*,1′*S*)-**5af** (96% ee) and (2*S*,4*S*,1′*R*)-**5bf** (86% ee) respectively as shown in Scheme 5. Stereochemistry of the newly generated hydroxyl group in the major diols **10aa–10bf** from **5aa–5bf** was tentatively assigned as *syn*-selective based on the chelating action of diethylmethoxyborane[12] and cyclohexanone conformational strain. Outcome of the high stereoselectivity from the simple $NaBH_4$ reduction on **5af** and **5bf** can be readily explained *via* the approach of the hydride from the less crowded equatorial side of the hydroxyl-ketone **5af**/**5bf**. These chiral *syn*-diols **10** will be suitable starting materials for the synthesis of oxa-cyclic natural and unnatural products through Lewis acid-catalysis.[13]



Scheme 5 High-yielding stereoselective reduction of BLA products **5** to *syn*-1,3-diols **10**.

Conclusions

In summary, the organocatalytic asymmetric BLA reaction of 2-alkynylbenzaldehydes with various ketone donors was studied. In some cases, the formation of expected BLA adducts was accompanied by some novel double aldol addition products in moderate to good yields with high de and ee's. The potential of the BLA adducts has been demonstrated in the stereoselective synthesis of chiral acyclic and cyclic 1,2,3-triazole compounds **8–9** and *syn*-diols **10**. The 1,5-dihydroxy-pentan-3-one derivatives **6** can be utilized as intermediates for the development of potential HIV-1 protease inhibitors.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants J are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials

All solvents and commercially available chemicals were used as received.

Acknowledgements

This work was made possible by a grant from the Department of Science and Technology (DST), New Delhi [Grant No.: DST/SR/S1/OC-65/2008]. RM and RM thank Council of Scientific and Industrial Research (CSIR), New Delhi for their research fellowship. We thank Dr P. Raghavaiah for his help in X-ray structural analysis.

References

1 (*a*) P. Wieland and K. Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215; (*b*) N. L. Wendler, H. L. Slates and M. Tischler, *J. Am. Chem. Soc.*, 1951, **73**, 3816; (*c*) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496–497; (*d*) Z. G. Hajos and D. R. Parrish, *Ger. Offen.*, 1971, CODEN: GWXXBX DE 2102623 19710729, CAN 76:59072 (in German: pp. 42); (*e*) S. Ramachandran and M. S. Newman, *Org. Synth. Coll.*, 1973, **V**, 486; (*f*) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1612–1615; (*g*) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615–1621; (*h*) T. Bui and C. F. Barbas III, *Tetrahedron Lett.*, 2000, **41**, 6951–6954.

2 (*a*) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396; (*b*) W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386–7387; (*c*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260–5267.

3 (*a*) A. Córdova, W. Notz and C. F. Barbas III, *J. Org. Chem.*, 2002, **67**, 301–303; (*b*) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798–6799; (*c*) A. Bogevig, K. Juhl, N. Kumaragurubaran and K. A. Jorgensen, *Chem. Commun.*, 2002, 620–621; (*d*) M. Nakadai, S. Saito and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8167–8177;

(*i*) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma and E. Solcaniova, *Chem. Commun.*, 2002, 2510–2511; (*f*) T. Darbre and M. Machuqueiro, *Chem. Commun.*, 2003, 1090–1091; (*g*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475–2479; (*h*) S. Chandrasekhar, C. Narsihmulu, N. R. Reddy and S. S. Sultana, *Chem. Commun.*, 2004, 2450–2451; (*i*) J. T. Suri, D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2005, **7**, 1383–1385; (*j*) Y. Zhou and Z. Shan, *J. Org. Chem.*, 2006, **71**, 9510–9512; (*k*) J. Huang, X. Zhang and D. W. Armstrong, *Angew. Chem., Int. Ed.*, 2007, **46**, 9073–9077; (*l*) S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2007, **129**, 288–289; (*m*) S. S. V. Ramasastry, K. Albertshofer, F. Tanaka and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2007, **46**, 5572–5575; (*n*) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi and C. F. Barbas III, *Org. Lett.*, 2008, **10**, 1621–1624; (*o*) D. Enders and A. A. Narine, *J. Org. Chem.*, 2008, **73**, 7857–7870; (*p*) C. L. Chandler and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 6737–6739; (*q*) D. B. Ramachary and R. Sakthidevi, *Chem.–Eur. J.*, 2009, **15**, 4516–4522; (*r*) J. N. Moorthy and S. Saha, *Eur. J. Org. Chem.*, 2009, 739–748; (*s*) S. Saha and J. N. Moorthy, *Tetrahedron Lett.*, 2010, **51**, 912–916; (*t*) R. Pedrosa, J. M. Andrés, R. Manzano, D. Román and S. Téllez, *Org. Biomol. Chem.*, 2011, **9**, 935–940; (*u*) J. Agarwal and R. K. Peddinti, *J. Org. Chem.*, 2011, **76**, 3502–3505.

4 (*a*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 12911–12912; (*b*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 11273–11283; (*c*) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16–17; (*d*) B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842; (*e*) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, **37**, 558–569; (*f*) C. Marquez and J. O. Metzger, *Chem. Commun.*, 2006, 1539–1541; (*g*) M. B. Schmid, K. Zeitler and R. M. Gschwind, *Angew. Chem., Int. Ed.*, 2010, **49**, 4997–5003.

5 (*a*) C. Ji, Y. Peng, C. Huang, N. Wang and Y. Jiang, *Synlett*, 2005, **6**, 986–990; (*b*) D. Gryko and R. Lipinski, *Eur. J. Org. Chem.*, 2006, 3864–3876; (*c*) C. Ji, Y. Peng, C. Huang, N. Wang, Z. Luo and Y. Jiang, *J. Mol. Catal. A: Chem.*, 2006, **246**, 136–139; (*d*) S. Hu, T. Jiang, Z. Zhang, A. Zhu, B. Han, J. Song, Y. Xie and W. Li, *Tetrahedron Lett.*, 2007, **48**, 5613–5617.

6 For selected papers on asymmetric reactions from our group, see: (*a*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*b*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2008, **6**, 2488–2492; (*c*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4176–4187; (*d*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2010, **8**, 2859–2867; (*e*) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, 2010, **75**, 74–85; (*f*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259–4265; (*g*) D. B. Ramachary, Y. V. Reddy, A. Banerjee and S. Banerjee, *Org. Biomol. Chem.*, 2011, **9**, 7282–7286; (*h*) D. B. Ramachary, M. S. Prasad and R. Madhavachary, *Org. Biomol. Chem.*, 2011, **9**, 2715–2721; (*i*) D. B. Ramachary and K. Ramakumar, *Eur. J. Org. Chem.*, 2011, 2599–2605; (*j*) D. B. Ramachary, Ch. Venkaiah and P. M. Krishna, *Chem. Commun.*, 2012, **48**, 2252–2254; (*k*) D. B. Ramachary, R. Madhavachary and M. S. Prasad, *Org. Biomol. Chem.*, 2012, **10**, 0000–0000, DOI: 10.1039/c2ob07122c.

7 (*a*) L. Wang, Y. Duan, P. Stouten, G. V. De Lucca, R. M. Klabe and P. A. Kollman, *J. Comput.-Aided Mol. Des.*, 2001, **15**, 145–156; (*b*) P. K. Jadhav and F. J. Woerner, *Tetrahedron Lett.*, 1995, **36**, 6383–6386; (*c*) M. Miyashita, M. Hoshino and A. Yoshikoshi, *Chem. Lett.*, 1990, 791–794; (*d*) T. Hashimoto, M. Tori and Y. Asakawa, *Chem. Pharm. Bull.*, 1986, **34**, 1846–1849.

8 (*a*) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A. Qiao, Y.-Z. Jiang and Y.-D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262–5263; (*b*) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5755–5760; (*c*) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285–9289; (*d*) M. Raj, V. Maya, S. K. Ginotra and V. K. Singh, *Org. Lett.*, 2006, **8**, 4097–4099; (*e*) V. Maya, M. Raj and V. K. Singh, *Org. Lett.*, 2007, **9**, 2593–2595; (*f*) X.-Y. Xu, Y.-Z. Wang and L.-Z. Gong, *Org. Lett.*, 2007, **9**, 4247–4249; (*g*) J. Jiang, L. He, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *Chem. Commun.*, 2007, 736–738; (*h*) J. Jiang, L. He, S. W. Luo, L.-F. Cun and L.-Z. Gong, *Chem. Commun.*, 2008, 6609–6610; (*i*) M. Raj, V. Maya and V. K. Singh, *J. Org. Chem.*, 2009, **74**, 4289–4297.

9 X-ray crystal data of (*R*,*R*)-(+)-**6aa**: $C_{21}H_{18}O_3$; M_W = 318.37, Orthorhombic, space group *P*2(1)2(1)2(1), with *a* = 5.771(11) Å, *b* = 10.930(2) Å, *c* = 28.102(6)Å, α = 90.00°, β = 90.00°, γ = 90.00°. CCDC-804553 contains the supplementary crystallographic data for this crystal structure†.

10 (*a*) B. Rodriguez, A. Bruckmann and C. Bolm, *Chem.–Eur. J.*, 2007, **13**, 4710–4722; (*b*) J. Jiang, L. He, S.-W. Luo, L.-F. Cuna and L.-Z. Gong, *Chem. Commun.*, 2007, 736–738; (*c*) S. Luo, H. Xu, J. Li, L. Zhang, X. Mi, X. Zheng and J.-P. Cheng, *Tetrahedron*, 2007, **63**, 11307–11314; (*d*) X.-W. Liu, T. N. Le, Y. Lu, Y. Xiao, J. Ma and X. Li, *Org. Biomol. Chem.*, 2008, **6**, 3997–4003; (*e*) S. S. Chimni, S. Singh and D. Mahajan, *Tetrahedron: Asymmetry*, 2008, **19**, 2276–2284; (*f*) X. Companyo, G. Valero, L. Crovetto, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 6564–6568.

11 (*a*) V. Haridas, S. Sahu and P. Venugopalan, *Tetrahedron*, 2011, **67**, 727–733; (*b*) M. Yano, C. C. Tong, M. E. Light, F. P. Schmidtchen and P. A. Gale, *Org. Biomol. Chem.*, 2010, **8**, 4356–4363; (*c*) R. Rajesh, G. Periyasami and R. Raghunathan, *Tetrahedron Lett.*, 2010, **51**, 1896–1898; (*d*) H.-C. Hung, C.-W. Cheng, I.-T. Ho and W.-S. Chung, *Tetrahedron Lett.*, 2009, **50**, 302–305; (*e*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (*f*) V. Haridas, K. Lal, Y. K. Sharma and S. Upreti, *Org. Lett.*, 2008, **10**, 1645–1647; (*g*) A. Dondoni and A. Marra, *J. Org. Chem.*, 2006, **71**, 7546–7557; (*h*) J. H. V. Maarseveen, W. S. Horne and M. R. Ghadiri, *Org. Lett.*, 2005, **7**, 4503–4506; (*i*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (*j*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.

12 (*a*) M. T. Crimmins and P. Siliphaivanh, *Org. Lett.*, 2003, **5**, 4641–4644; (*b*) K. M. Chen, G. E. Hardtmann, K. Prasad, O. Repic and M. J. Shapiro, *Tetrahedron Lett.*, 1987, **28**, 155–158.

13 (*a*) B. Alcaide, P. Almendros and J. M. Alonso, *Org. Biomol. Chem.*, 2011, **9**, 4405–4416; (*b*) P. Patel and C. V. Ramana, *Org. Biomol. Chem.*, 2011, **9**, 7327–7334; (*c*) P. N. Liu, F. H. Su, T. B. Wen, H. H.-Y. Sung, I. D. Williams and G. Jia, *Chem.–Eur. J.*, 2010, **16**, 7889–7897; (*d*) C. V. Ramana, B. Induvadana, B. Srinivas, K. Yadagiri, M. N. Deshmukh and R. G. Gonnade, *Tetrahedron*, 2009, **65**, 9819–9832; (*e*) C. V. Ramana, R. Mallik and G. Sahoo, *Tetrahedron Lett.*, 2009, **50**, 4844–4847; (*f*) C. V. Ramana, R. Mallik and R. G. Gonnade, *Tetrahedron*, 2008, **64**, 219–233; (*g*) C. V. Ramana, P. Patel and R. G. Gonnade, *Tetrahedron Lett.*, 2007, **48**, 4771–4774; (*h*) B. Koo and F. E. McDonald, *Org. Lett.*, 2007, **9**, 1737–1740; (*i*) C. V. Ramana, R. Mallik, R. G. Gonnade and M. K. Gurjar, *Tetrahedron Lett.*, 2006, **47**, 3649–3652; (*j*) K. Malleswara Rao, M. Bhanuchandra and A. K. Sahoo, *J. Org. Chem.*, 2010, **75**, 2247–2258.