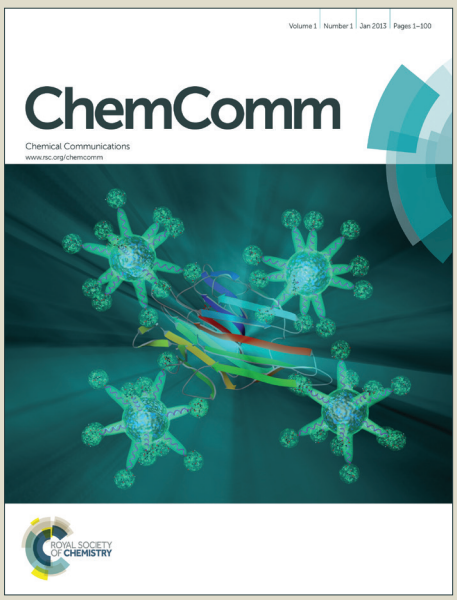
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Regioselectivity switch in chiral amine-catalysed asymmetric addition of aldehydes to reactive enals

Taichi Kano, Hiroki Maruyama, Ryu Sakamoto and Keiji Maruoka*

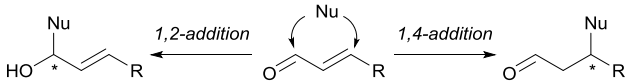
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

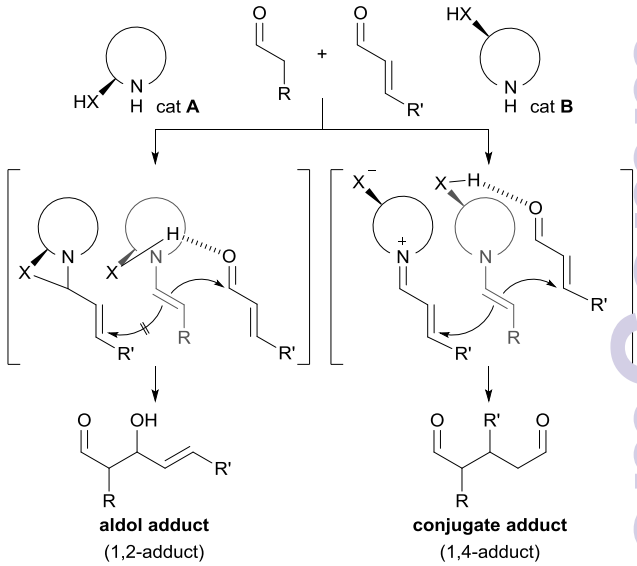
In this paper, we present a regioselectivity switch for the chiral amine-catalysed asymmetric addition of aldehydes to reactive enals to afford either aldol adducts or conjugate adducts in a stereoselective fashion. The unprecedented asymmetric aldol reaction of aldehydes with enals was realized by use of a diarylprolinol catalyst, giving synthetically useful and important chiral allylic alcohols.

The control of site selectivity in a chemical reaction is a fundamental goal with challenge in synthetic organic chemistry. In the nucleophilic addition reaction to enals, 1,2-adducts and/or 1,4-adducts are obtained depending on the nature of the nucleophile and the reaction conditions such as solvent, and the catalyst control of regioselectivity is a challenging task (Scheme 1).[1,2] In the presence of a chiral amine catalyst, enals are known to form the corresponding iminium intermediates, and a number of asymmetric 1,4-additions of various nucleophiles to such activated iminium intermediates have been developed to date.[3] The reaction of enals with aliphatic donor aldehydes, which can be activated as nucleophiles by forming enamine intermediates, also gives only 1,4-adducts.[4,5] While amine catalysts can promote the 1,2-addition (aldol reaction) of aliphatic donor aldehydes to reactive acceptor aldehydes as well as the 1,4-addition,[6] to the best of our knowledge, the aldol reaction between aliphatic donor aldehydes and enals has not been reported. We were therefore interested in a catalyst control of regioselectivity in the amine-catalysed reaction between aliphatic aldehydes and enals and developing the aldol reaction giving the synthetically useful and important chiral allylic alcohols.[7] We report here the successful realization of amine-catalysed asymmetric 1,2- and 1,4-addition of aldehydes to reactive enals using catalyst control.



Scheme 1 1,2-Addition versus 1,4-addition.

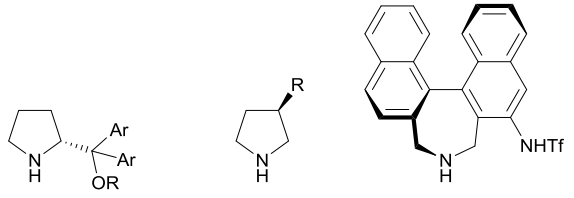
We expected that the regioselectivity between 1,2- and 1,4-addition of aldehydes to enals might be controlled by amine catalysts having different spatial arrangement of the amino group and the acidic functionality (Scheme 2).[8] In the case of the amine catalyst **A** with a proximal acid functionality (HX), the formed iminium intermediate, which is prone to undergo the 1,4-addition, would be deactivated by the neighboring acid group (HX), and consequently, 1,2-addition (aldol reaction) proceeds exclusively through the enamine intermediate with the aid of the proximal acid functionality. On the other hand, the amine catalyst **B** having a distal acid functionality (HX) can form both the enamine and iminium intermediates, thereby giving the 1,4-adduct preferentially. Additionally, the reaction between the enamine and the enal activated and oriented by the distal acidic proton likely favors the conjugate addition (1,4-addition) over the aldol reaction (1,2-addition).



Scheme 2 Control of the regioselectivity by amine organocatalysts.

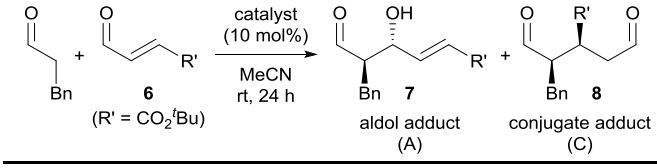
Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan. E-mail: maruoka@kuchem.kyoto-u.ac.jp;
†Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/x0xx00000x

We first examined several chiral amine catalysts in the reaction of 3-phenylpropanal with *t*-butyl 4-oxo-2-butenoate (**6**), which was chosen for the high reactivity, no possibility of forming the undesired dienamine intermediate and the synthetic utility of the resulting product.[4d,4e] With proline catalyst, neither aldol adduct **7** nor conjugate adduct **8** was obtained probably due to the decomposition of proline (Table 1, entry 1).[9] The reaction using pyrrolidine or chiral pyrrolidine (*R*)-**1**[10] gave only trace amounts of **7** and **8** along with multiple side products (entries 2 and 3). When diarylprolinol (*R*)-**2**[11], which was develped by Hayashi and exhibits efficient catalytic activity in aldol reactions, was employed as an amine catalyst having a proximal acid functionality, the aldol reaction proceeded exclusively to afford *anti*-**7** as a major diastereomer, albeit in moderate yield and stereoselectivity (entry 4). The chiral amine catalysts (*R*)-**3** and (*R*)-**4**[12] having a distal acid functionality promoted both aldol reaction and conjugate addition, and side reactions observed in the reaction using the pyrrolidine catalyst with no acidic functionality were significantly suppressed (entries 5 and 6). While **8** was obtained as the predominant product as expected, the stereoselectivity was not satisfactory. On the other hand, when the binaphthyl-modified amine catalyst (*S*)-**5**[13] having a distal acid functionality was employed, the conjugate adduct **8** was obtained predominantly in high diastereo- and enantioselectivity (entry 7).



(*R*)-**1** (Ar = Ph, R = TMS) (*R*)-**3** (R = OH) (*S*)-**5**
(*R*)-**2** (Ar = 3,5-$(CF_3)_2C_6H_3$, R = H) (*R*)-**4** (R = NHTf)

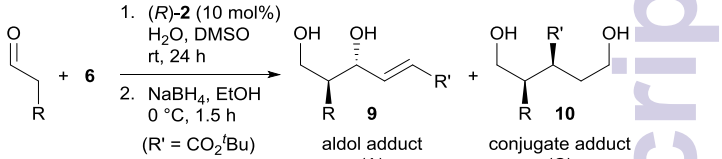
Table 1 Amine-catalysed reaction of 3-phenylpropanal with **6**[a]



Entry	Catalyst	Yield[b] (%)	A/C[c]	*anti*/*syn*[d]	ee[e] (%)
1	L-proline	nd	-	-	-
2	pyrrolidine	<5	-	-	-
3	(*R*)-**1**	<5	-	-	-
4	(*R*)-**2**	49	>20/1	2.5/1	89
5	(*R*)-**3**	19	1/10	1/20	39
6	(*R*)-**4**	45	1/2.8	1/4.3	–2
7[f]	(*S*)-**5**	62	1/6.6	1/16	98

[a] The reaction of 3-phenylpropanal (0.1 mmol) with **6** (0.3 mmol) was carried out in the presence of a catalyst (0.01 mmol) in acetonitrile (0.1 mL) at room temperature for 24 h. [b] Total yield of isolated **7** and **8**. [c] Determined by yields of isolated products. [d] The diastereoselectivity of the predominant product was determined by ^{1}H NMR. [e] The enantioselectivity of the major diastereomer was determined by HPLC using chiral column. [f] The reaction was performed at 0 °C in the presence of 5 mol% of (*S*)-**5**.

Table 2 Asymmetric aldol reaction of aldehydes with **6**[a]

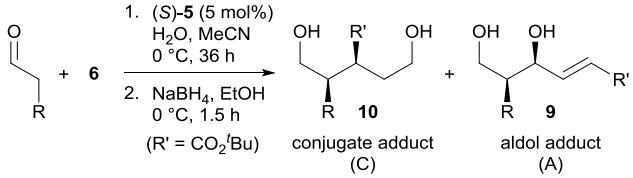


Entry	R	Yield[b] (%)	A/C[c]	*anti*/*syn*[d]	ee[e] (%)
1[f]	Bn	28	>20/1	6.2/1	96
2	Bn	76	>20/1	7.3/1	97
3	Me	99	>20/1	9.6/1	99
4	allyl	79	>20/1	9.8/1	97
5[g]	*i*-Pr	50	>20/1	6.5/1	88
6	NHCbz	65	>20/1	3.8/1	96

[a] The reaction of an aldehyde (0.1 mmol) with **6** (0.3 mmol) was carried out in the presence of (*R*)-**2** (0.01 mmol) and H_2O (0.5 mmol) in DMSO (0.1 mL) at room temperature for 24 h. [b] Yield of isolated products. [c] Determined by yields of isolated products. [d] The diastereoselectivity of **9** was determined by ^{1}H-NMR. [e] The enantioselectivity of *anti*-**9** was determined by HPLC using chiral column. [f] Performed in the absence of H_2O. [g] Performed with **5** (0.4 mmol) for 48 h.

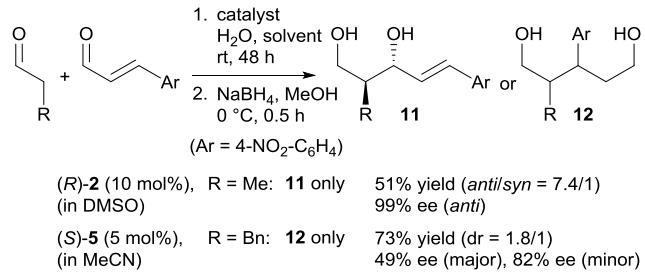
We next optimized the reaction conditions for the asymmetric aldol reaction catalysed by (*R*)-**2**. Among the solvents tested, dimethyl sulfoxide was found to be the optimal solvent in terms of both diastereo- and enantioselectivity, while the yield was low (Table 2, entry 1).[14] Fortunately, addition of water led to a significant increase in yield (entry 2). Under the optimized conditions, the reactions of several aliphatic aldehydes with **6** afforded the corresponding *anti*-aldol adducts **9** in good stereoselectivity (entries 2–5). Use of the Cbz protected aminoacetaldehyde[15] gave the *anti*-aminoalcohol derivative **9** (R = NHCbz) as a major diastereomer (entry 6). In all cases examined, the conjugate adducts were not observed. The absolute configurations of **9** were determined to be (4*R*,5*S*) by conversion to the known compound and comparison of its

Table 3 Asymmetric conjugate addition of aldehydes to **6**[a]



Entry	R	Yield[b] (%)	C/A[c]	*syn*/*anti*[d]	ee[e] (%)
1[f,g]	Bn	62	6.6/1	16/1	98
2[g]	Bn	68	8.2/1	14/1	97
3	Bn	79	8.6/1	15/1	97
4	Me	65	>20/1	8.4/1	91
5	Bu	74	7.5/1	17/1	94
6	allyl	54	>20/1	>20/1	94
7[h]	*i*-Pr	50	>20/1	>20/1	95

[a] The reaction of an aldehyde (0.1 mmol) with **6** (0.3 mmol) was carried out in the presence of (*S*)-**5** (0.005 mmol) and H_2O (0.5 mmol) in acetonitrile (0.1 mL) at 0 °C for 36 h. [b] Yield of isolated products. [c] Determined by yields of isolated products. [d] The diastereoselectivity of **10** was determined by ^{1}H-NMR. [e] The enantioselectivity of *syn*-**10** was determined by HPLC using chiral column. [f] Performed in the absence of H_2O. [g] Performed for 24 h. [h] Performed for 53 h.



Scheme 3 Regioselectivity switch in the reaction of 4-nitrocinnamaldehyde.

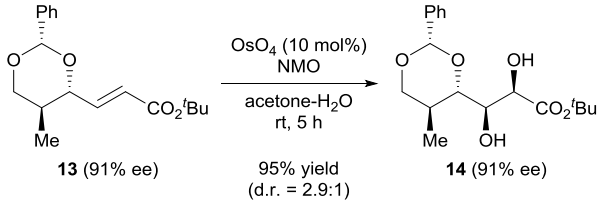
optical rotation to the literature value.[14]

The reaction conditions of the conjugate addition catalysed by (*S*)-**5** were then optimized. Solvent screening revealed that the reaction in acetonitrile afforded the highest diastereo- and enantioselectivity (Table 3, entry 1).[14] Both addition of water and a longer reaction time were effective for increasing the reaction yield (entries 2 and 3). Under the optimized conditions, the reactions of several aliphatic aldehydes with **6** gave the *syn*-conjugate adducts in good to high regio- and stereoselectivity (entries 3–7).

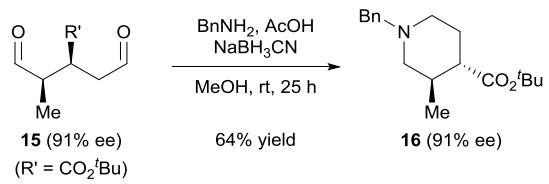
The regioselectivity switch could also be induced by changing the amine catalyst in the reaction of another enal such as 4-nitrocinnamaldehyde (Scheme 3). The reaction catalysed by (*R*)-**2** in DMSO gave the aldol adduct **11** exclusively in good stereoselectivity. On the other hand, the reaction catalysed by (*S*)-**5** in acetonitrile afforded the conjugate adduct **12** solely, albeit with moderate stereoselectivity.

The obtained aldol adduct and conjugate adducts are versatile synthetic intermediates. For instance, 5-deoxy-5-methyl-altrose derivative **14**, which serves as a building block for a macrolide synthesis,[16] was readily synthesized by dihydroxylation of **13** after protection of the aldol adduct **9** (R = Me) (Scheme 4). Dialdehyde **15** obtained by the conjugate addition could be converted to the chiral piperidine **16** by the double reductive amination without loss of optical purity (Scheme 5). The absolute configurations of **15** were determined to be (2*S*,3*R*) by single-crystal X-ray analysis of **16**·(*S*)-binaphthyl phosphoric acid salt.

Based on the observed stereochemistry, the transition state



Scheme 4 Synthesis of 5-deoxy-5-methyl-altrose derivative **14**.



Scheme 5 Synthesis of piperidine **16** by the double reductive amination.

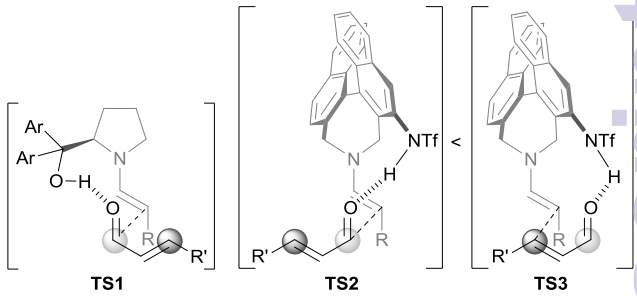
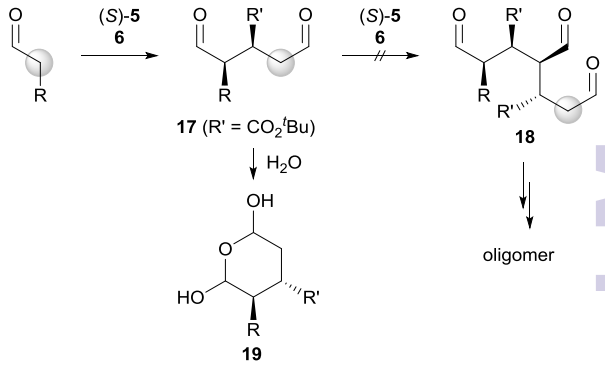


Fig. 1 Plausible transition state models.



Scheme 6 Formation of hydrate **19**.

models for both aldol reaction catalysed by (*R*)-**2** and conjugate addition catalysed by (*S*)-**5** were proposed (Fig. 1). In the case of the aldol reaction the proximal hydroxy group of (*R*)-**2** might suppress the formation of the iminium intermediate from the enal as shown in Scheme 2[17,18] and promote only the aldol reaction via **TS1**.[11a] On the other hand, (*S*)-**5** promoted both aldol reaction[12a] and conjugate addition, and the reaction rate of the conjugate addition was faster than that of the aldol reaction. The activation and orientation of the enal by the acidic proton of the triflamide group likely lead to better interaction of the α-carbon of the enamine with the β-carbon of the enal (**TS3**) than that with the carbonyl carbon (**TS2**) probably due to the unique spatial arrangement of the activation site and reaction site of the enamine intermediate.[19] Although the present conjugate addition did not exhibit a non-linear effect,[14,20] the possibility of the reaction between the enamine intermediate and the iminium intermediate cannot be ruled out completely.[21]

Since the present conjugate addition gives the non-α-branched aldehyde **17**, further conjugate addition of **17** to **6** and oligomerization seems possible (Scheme 6). However, neither the double conjugate adduct **18** nor oligomer was obtained and the conjugate adduct was isolated as the mixture of dialdehyde **17** and its hydrate **19**. This indicates that the undesired conjugate addition of **17** could be suppressed by the formation of **19** in situ.

In summary, both asymmetric 1,2- and 1,4-addtions of aldehydes to enals were realized, in which the regioselectivity could be switched by use of structurally different chiral amine catalysts. The unprecedented 1,2-addition of aldehydes to the reactive enal gave useful chiral allylic alcohols as aldol adducts.

This methodology certainly expands the synthetic utility of enamine catalysis and provides a new synthetic strategy for controlling regioselectivity in organic synthesis.

Notes and references

1 For reviews, see: (*a*) E. D. Bergman, D. Ginsburg and R. Pappo, *Org. React.*, 1959, **10**, 179; (*b*) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, 1992; (*c*) P. Knochel, N. Millot, A. Rodriguez and C. E. Tucker, *Org. React.*, 2001, **58**, 417.

2 For selected examples, see: (*a*) K. Maruoka, H. Imoto, S. Saito and H. Yamamoto, *J. Am. Chem. Soc.*, 1994, **116**, 4131; (*b*) T. Ooi, Y. Kondo and K. Maruoka, *Angew. Chem. Int. Ed.*, 1997, **36**, 1183; (*c*) W. H. Sikorski and H. J. Reich, *J. Am. Chem. Soc.*, 2001**, 123**, 6527; (*d*) J. Lv, L. Zhang, Y. Zhou, Z. Nie, S. Luo and J.-P. Cheng, *Angew. Chem. Int. Ed.*, 2011, **50**, 6610; (*e*) I. Ibrahem, G. Ma, S. Afewerki and A. Córdova, *Angew. Chem. Int. Ed.*, 2013, **52**, 878; (*f*) X. Ye, X. Sun, Z. Huang, N. Yang, Z. Su, C. Hu and Z. Song, *Org. Biomol. Chem.*, 2014, **12**, 3021.

3 For a pioneering work of asymmetric 1,4-additions via iminium catalysis, see: (*a*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001**, 123**, 4370; For reviews, see: (*b*) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416; (*c*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem. Int. Ed.*, 2008, **47**, 6138.

4 (*a*) M. T. Hechavarria Fonseca and B. List, *Angew. Chem. Int. Ed.*, 2004, **43**, 3958; (*b*) I. K. Mangion and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 3696; (*c*) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui and M. Shoji, *J. Am. Chem. Soc.*, 2005, **127**, 16028; (*d*) B.-C. Hong, M.-F. Wu, H.-C. Tseng and J.-H. Liao, *Org. Lett.*, 2006, **8**, 2217; (*e*) B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su and J.-H. Liao, *J. Org. Chem.*, 2007, **72**, 8459; (*f*) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente and S. Vera, *Angew. Chem. Int. Ed.*, 2007, **46**, 8431; (*g*) B.-C. Hong, R. Y. Nimje and J.-H. Liao, *Org. Biomol. Chem.*, 2009, **7**, 3095; (*h*) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo and M. Christmann, *Org. Lett.*, 2009, **11**, 4116; (*i*) B.-C. Hong, A. A. Sadani, R. Y. Nimje, N. S. Dange and G.-H. Lee, *Synthesis*, 2011, 1887; (*j*) B.-C. Hong, C.-S. Hsu and G.-H. Lee, *Chem. Commun.*, 2012, **48**, 2385.

5 For related amine-catalyzed 1,4-additions of aldehydes to enones, see: (*a*) P. Melchiorre and K. A. Jørgensen, *J. Org. Chem.*, 2003, **68**, 4151; (*b*) T. J. Peelen, Y. Chi and S. H. Gellman, *J. Am. Chem. Soc.*, 2005, **127**, 11598; (*c*) Y. Chi and S. H. Gellman, *Org. Lett.*, 2005, **7**, 4253; (*d*) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 18296; (*e*) M. Kikuchi, T. Inagaki and H. Nishiyama, *Synlett*, 2007, 1075.

6 For pioneering works in enamine catalysis, see: (a) U. Eder, G. Sauer and R. Wiechert, *Angew. Chem. Int. Ed.*, 1971, **10**, 496; (*b*) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615; (*c*) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; For reviews, see: (*d*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*e*) G. Guillena, C. Nájera and D. J. Ramón, *Tetrahedron: Asymmetry*, 2007, **18**, 2249; See also ref 3c.

7 The catalytic asymmetric aldol reaction between silyl enolates and enals was realized by using a chiral Lewis base as catalyst to give chiral allylic alcohols, while the enantioselectivity was not satisfactory: S. E. Denmark and S. K. Ghosh, *Angew. Chem. Int. Ed.*, 2001, **40**, 4759.

8 Tripeptide can be excellent catalysts for both 1,2-addition and 1,4-addition: (*a*) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan and H. Wennemers, *Org. Lett.*, 2005, **7**, 1101; (*b*) M. Wiesner, J. D. Revell and H. Wennemers, *Angew. Chem. Int. Ed.*, 2008, **47**, 1871.

9 Proline is known to decompose through decarboxylation in the presence of a highly electron deficient aldehydes: T. Kano, O. Tokuda, J. Takai and K. Maruoka, *Chem. Asian J.*, 2006, **1**, 210.

10 (*a*) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2005, **44**, 794; (*b*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem. Int. Ed.*, 2005, **44**, 4212.

11 (*a*) T. Urushima, Y. Yasui, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2010, **12**, 2966; (*b*) Y. Hayashi, Y. Yasui, T. Kawamura, M. Kojima and H. Ishikawa, *Angew. Chem. Int. Ed.*, 2011, **50**, 2804; (*c*) Y. Hayashi, Y. Yasui, T. Kawamura, M. Kojima and H. Ishikawa, *Synlett*, 2011, **6**, 485; (*d*) Y. Hayashi, Y. Yasui, M. Kojima, T. Kawamura and H. Ishikawa, *Chem. Commun.*, 2011, **48**, 4570; (*e*) Y. Hayashi and M. Kojima, *ChemCatChem*, 2013, **5**, 2883; (*f*) Y. Hayashi, M. Kojima, Y. Yasui, Y. Kanda and T. Mukaiyama, H. Shomura, D. Nakamura, L. Ritmaleni and T. Sato, *ChemCatChem*, 2013, **5**, 2887.

12 (*a*) H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2008, **130**, 875; (*b*) M. Pouliquen, J. Blanchet, M.-C. Lasne and J. Rouden, *Org. Lett.*, 2008, **10**, 1029; (*c*) T. Kano, Y. Hato, A. Yamamoto and K. Maruoka, *Tetrahedron*, 2008, **64**, 1197.

13 (*S*)-**5** was employed in various asymmetric 1,2-addition reactions. Aldol reaction: (*a*) T. Kano, Y. Yamaguchi, Y. Tanaka and K. Maruoka, *Angew. Chem. Int. Ed.*, 2007, **46**, 1738; (*b*) T. Kano, Y. Yamaguchi and K. Maruoka, *Chem. Eur. J.*, 2009, **15**, 6678; Mannich reaction: (*c*) T. Kano, Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408; (*d*) T. Kano, Y. Yamaguchi and K. Maruoka, *Angew. Chem. Int. Ed.*, 2009, **48**, 1838; Aminoxylation: (*e*) T. Kano, A. Yamamoto and K. Maruoka, *Tetrahedron Lett.*, 2008, **49**, 5369.

14 See the ESI† for details.

15 (a) T. Kano, R. Sakamoto, M. Akakura and K. Maruoka, *J. Am. Chem. Soc.*, 2012, **134**, 7516; (*b*) T. Kano, R. Sakamoto and K. Maruoka, *Org. Lett.*, 2014, **16**, 944.

16 G. Sabitha, A. S. Rao and J. S. Yadav, *Org. Biomol. Chem.*, 2013, **11**, 7218.

17 In the ^{1}H-NMR spectrum of the mixture of (*R*)-**2** and **6** in DMSO-d_6, the cyclic hemiaminal derived from (*R*)-**2** and **6** was detected instead of the corresponding iminium salt.

18 The acetic acid salt of (*S*)-**2** promoted the intramolecular 1,4-addition to enals, probably via the transient iminium intermediate: A. I. Gerasyuto, R. P. Hsung, N. Sydorenko and B. Slafer, *J. Org. Chem.*, 2005, **70**, 4248.

19 The reaction using the binaphthyl-modified amine catalyst with no acidic functionality instead of (*S*)-**5** gave the conjugate adduct **8** predominantly with lower enantioselectivity than (*S*)-**5**. This result suggests that the acidic functionality is not necessarily required to obtain 1,4-regioselectivity, but is still involved in the transition state of the conjugate addition.

20 The ee value of the product correlated linearly with that of the catalyst. For a review of non-linear effects in asymmetric catalysis, see: H. B. Kagan and T. O. Luukas in *Comprehensive Asymmetric Catalysis*, eds. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, Chapter 4.1.

21 Possible mechanisms for this transformation include the inverse-electron demand Diels-Alder reaction also: K. Juhl and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2003, **42**, 1498.