Synthesis of Phenylcyclopropane-Based Secondary Amine Catalysts and Their Applications in Enamine Catalysis

Aika Takeshima,[†] Taichi Kano*,[†] and Keiji Maruoka*,[†,‡,§]

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

[‡]Department of Organocatalytic Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606-8501, Japan

[§]School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China

Supporting Information Placeholder
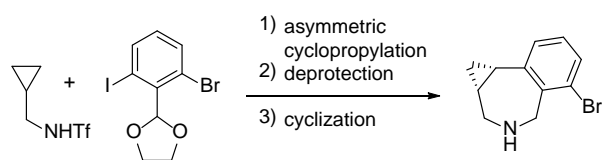
ABSTRACT: A novel chiral motif based on a phenylcyclopropane scaffold has been designed and a facile synthetic route to the key-intermediate for the synthesis of phenylcyclopropane-based chiral secondary amines has been developed. Newly synthesized chiral amines function as effective catalysts for several asymmetric reactions through enamine intermediates.

In asymmetric catalysis, the design of novel chiral motif is highly important for the development of new chiral ligands or catalysts providing unprecedented reactivity and selectivity. Among them, the axially chiral binaphthyl structure has been widely applied to chiral ligands such as BINAP, BINOL or various catalysts.[1] We have previously designed binaphthyl-based secondary amine catalysts (*S*)-**1** and (*S*)-**2** containing an acid functional group at the 3-position for enamine catalysis (Figure 1).[2–4] These catalysts have been successfully utilized in several asymmetric reactions, and have shown unique reactivity and selectivity in comparison with commonly used proline and its derivatives. 3-Mono-substituted binaphthyl-based secondary amine structures were also found in amine organocatalysts (*S*)-**3** and (*S*)-**4**.[5] In spite of their utility, however, the applications of binaphthyl-based amines in asymmetric reactions are still rare due to their synthetic inefficiency. Since the axially chiral binaphthyl dicarboxylic acid (*S*)-**5** is not readily available, the binaphthyl-based secondary amine (*S*)-**6** as a key-intermediate for our catalysts is less accessible.[6] In connection with our interest in asymmetric reactions promoted by chiral secondary amines, we have developed a novel chiral motif (*S*,*R*)-**7** based on a phenylcyclopropane scaffold that can be prepared through scalable processes using readily available and inexpensive reagents (Scheme 1). In designing this motif, the one naphthalene moiety of the previous binaphthyl-based amine is replaced with a cyclopropane ring as it is considered to be an isostere of olefin in medicinal chemistry.[7] The modular nature of this motif allows quick access to several secondary amine catalysts. This new family of catalysts opens up opportunities for the exploration of new reactions and also the development of highly effective catalysts for known reactions. We report herein the simple

and efficient synthesis of phenylcyclopropane-based secondary amine catalysts and their applications to the asymmetric reactions through enamine intermediates.

Kano & Maruoka (ref 2)   Kano & Maruoka (ref 3)   Lu (ref 5)
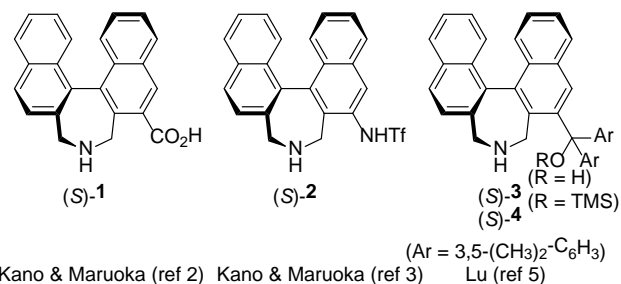
Figure 1. Binaphthyl-based organocatalysts.

Scheme 1. Design of a Novel Chiral Secondary Amine Motif
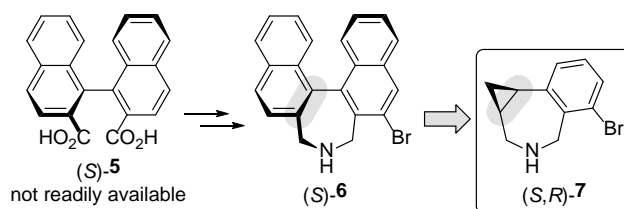
Synthesis of chiral secondary amine **7** commenced with the preparation of acetal **9** by treatment of 2-bromo-6-iodobenzaldehyde (**8**)[8] with ethylene glycol in the presence of *p*-toluenesulfonic acid monohydrate. The palladium-catalyzed

asymmetric cyclopropylation of the obtained **9** with *N*-cyclopropylmethyl triflamide **10** gave the desired phenylcyclopropane (*R*,*S*)-**12** in excellent enantioselectivity, albeit with moderate yield.[9] Removal of trifluoromethanesulfonyl group and subsequent acidic work-up provided the cyclic imine, which was reduced with NaBH₄ to the cyclic amine (*R*,*S*)-**7** (Scheme 2).

**Scheme 2. Synthesis of Chiral Secondary Amine (*R*,*S*)-7**
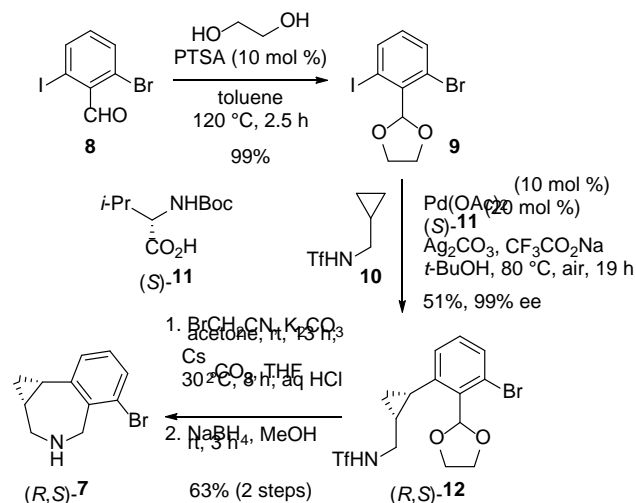
With the key-intermediate (*R*,*S*)-**7** in hand several chiral secondary amine catalysts could be synthesized after the protection of the amino group by benzyloxycarbonyl (Cbz) group (Scheme 3). After the palladium-catalyzed amination of (*R*,*S*)-**13** with benzophenone imine,[10] treatment with Tf₂O and deprotection afforded trifluoromethanesulfonamide (*R*,*S*)-**14** in 77% yield. The chiral amino alcohol (*R*,*S*)-**15** was prepared by treatment of lithiated (*R*,*S*)-**13** with benzophenone and subsequent deprotection. Treatment of (*R*,*S*)-**15** with trimethylsilyl triflate gave the chiral amine (*R*,*S*)-**16**. Finally, the chiral amine catalyst (*R*,*S*)-**17** was synthesized through debromination of (*R*,*S*)-**13**.

Scheme 3. Synthesis of a Series of Phenylcyclopropane-Based Secondary Amine Catalysts[a]
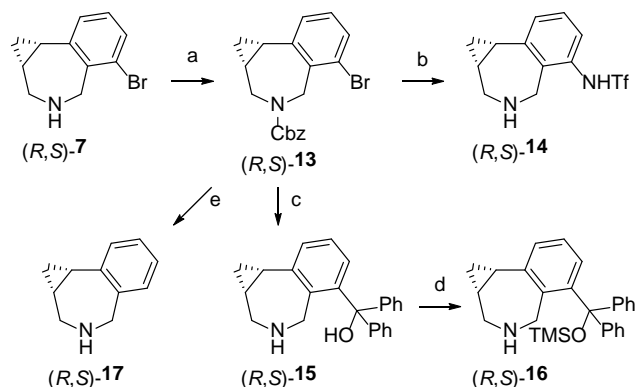
[a]Reagents and conditions: (a) Cbz-Cl, Et₃N, THF, rt (99%); (b) (i) benzophenone imine, Pd₂(dba)₃, BINAP, NaOt-Bu, toluene, reflux, then 1N HCl, THF, reflux; (ii) Tf₂O, *N,N*-dimethylaniline, CH₂Cl₂, rt; (iii) H₂, Pd/C, MeOH, 40 °C (77% for three steps); (c) (i) BuLi, THF, –78 °C; benzophenone, 0 °C (59%); (ii) H₂, Pd(OH)₂, MeOH, rt (81%); (d) TMSOTf, Et₃N, CH₂Cl₂, rt (92%); (e) H₂, Pd(OH)₂, Et₃N, THF, rt (64%).
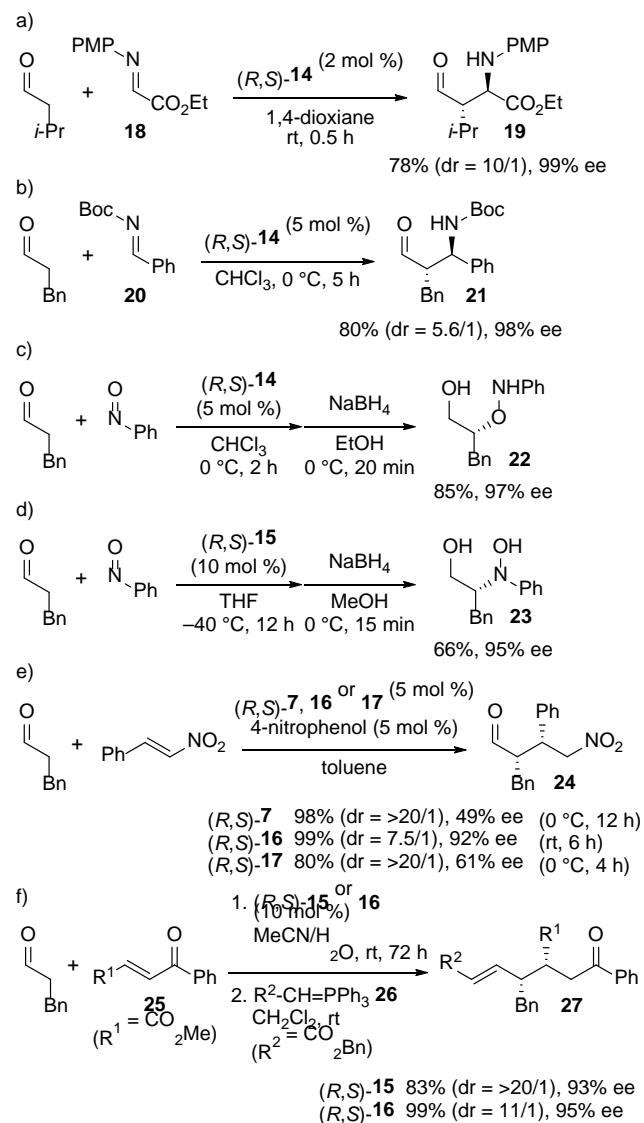
The absolute configurations of chiral amino sulfonamide **14** were determined by X-ray crystal structure analysis of HCl salt of **14** (Figure 2). It was found that the spatial relationship between two nitrogen atoms of **14** closely resembles that of the binaphthyl-based amino sulfonamide catalyst (*R*)-**2**.[11,12]
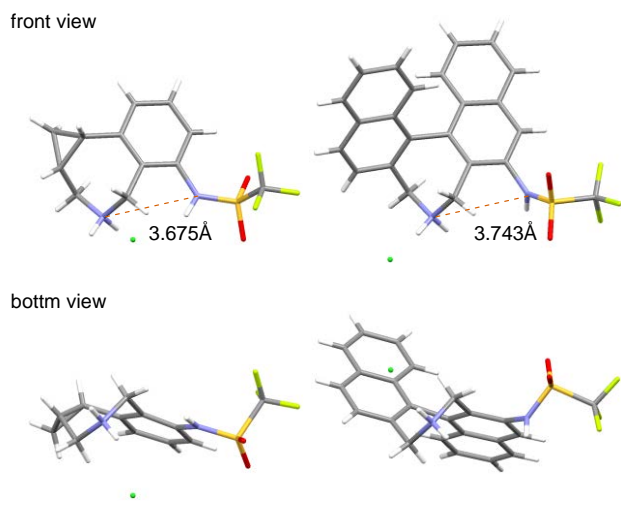

Figure 2. X-ray crystal structures of (*R*,*S*)-**14**·HCl salt and (*R*)-**2**·HCl salt.

Proline and its derivatives are known to promote the *syn*-selective Mannich reaction of aldehydes with imines.[13] On the other hand, the newly synthesized (*R*,*S*)-**14** was found to effectively catalyze the *anti*-selective Mannich reaction between isovaleraldehyde and an α-imino ester **18** to give the corresponding *anti*-Mannich adduct **19** with excellent enantioselectivity (Scheme 4a).[3a,13f,13g] The Mannich reaction using *N*-Boc-protected imine **20** also gave the unusual *anti*-adduct **21** in good yield with high enantioselectivity (Scheme 4b).[3b] Since the phenylcyclopropane-based amino sulfonamide catalyst (*R*,*S*)-**14** behaves similarly to the binaphthyl-based catalyst (*R*)-**2**, utility of the phenylcyclopropane scaffold as a novel chiral motif has been evaluated in several other amine-catalyzed reactions. We found that (*R*,*S*)-**14** was an effective catalyst for the asymmetric aminoxylation of 3-phenylpropanal with nitrosobenzene, and in-situ reduction of the product with NaBH₄ gave 1,2-diol derivative **22** in excellent enantioselectivity (Scheme 4c).[14,15] On the other hand, use of chiral amino alcohol (*R*,*S*)-**15** as catalyst afforded the optically enriched hydroxyamination product **23** exclusively from the same set of reactants (Scheme 4d).[16,17] Several chiral amine catalysts were applied to the conjugate addition of 3-phenylpropanal to nitrostyrene, and (*R*,*S*)-**16** bearing a bulky diphenyl(trimethylsiloxy)methyl group provided the corresponding conjugate adduct **24** in good yield with high enantioselectivity (Scheme 4e).[5,18] Additionally, (*R*,*S*)-**16** proved to be an appropriate catalyst for the conjugate addition to enone **25**, giving ketone **27** with satisfactory yield and stereoselectivity after olefination of the resulting conjugate adduct with **26** (Scheme 4f).[19]

Scheme 4. Asymmetric Reactions Catalyzed by Phenylcyclopropane-Based Amines

a)

i-Pr (aldehyde) + **18** (PMP-N=CH-CO$_2$Et) → (R,S)-**14** (2 mol %), 1,4-dioxane, rt, 0.5 h → **19** (O, HN-PMP, i-Pr, CO$_2$Et)
78% (dr = 10/1), 99% ee

b)

Bn (aldehyde) + **20** (Boc-N=CH-Ph) → (R,S)-**14** (5 mol %), CHCl$_3$, 0 °C, 5 h → **21** (O, HN-Boc, Bn, Ph)
80% (dr = 5.6/1), 98% ee

c)

Bn (aldehyde) + (O=N-Ph nitrone) → (R,S)-**14** (5 mol %), CHCl$_3$, 0 °C, 2 h; NaBH$_4$, EtOH, 0 °C, 20 min → **22** (OH, NHPh, O, Bn)
85%, 97% ee

d)

Bn (aldehyde) + (O=N-Ph nitrone) → (R,S)-**15** (10 mol %), THF, −40 °C, 12 h; NaBH$_4$, MeOH, 0 °C, 15 min → **23** (OH, OH, N-Ph, Bn)
66%, 95% ee

e)

Bn (aldehyde) + Ph-CH=CH-NO$_2$ → (R,S)-**7**, **16** or **17** (5 mol %), 4-nitrophenol (5 mol %), toluene → **24** (O, Ph, NO$_2$, Bn)

(R,S)-**7**   98% (dr = >20/1), 49% ee   (0 °C, 12 h)
(R,S)-**16** 99% (dr = 7.5/1), 92% ee   (rt, 6 h)
(R,S)-**17** 80% (dr = >20/1), 61% ee   (0 °C, 4 h)

f)

Bn (aldehyde) + **25** (R^1-CH=CH-C(O)-Ph, R^1 = CO$_2$Me) → 1. (R,S)-**15** or **16** (10 mol %), MeCN/H$_2$O, rt, 72 h; 2. R^2-CH=PPh$_3$ **26** (R^2 = CO$_2$Bn), CH$_2$Cl$_2$, rt → **27** (R^2, R^1, O, Ph, Bn)

(R,S)-**15** 83% (dr = >20/1), 93% ee
(R,S)-**16** 99% (dr = 11/1), 95% ee

Possible transition state models for the amine-catalyzed Mannich reactions are proposed as shown in Figure 3. In the case of the proline-catalyzed reaction, the *syn*-isomer is obtained through the s-*trans*-enamine (Figure 3, **TS1**). While both s-*trans*-enamine and s-*cis*-enamine might be formed in the reaction catalyzed by (S)-**2**, only s-*cis*-enamine can react with the imine that is activated by the distal acidic proton of the triflamide of (S)-**2**, giving the unusual *anti*-isomer predominantly (Figure 3, **TS2**). On the basis of the observed stereochemical outcome, the reaction catalyzed by (R,S)-**14**, which is a pseudo-enantiomer of (S)-**2**, would proceed through a similar transition state **TS3**, thus affording the *anti*-product.
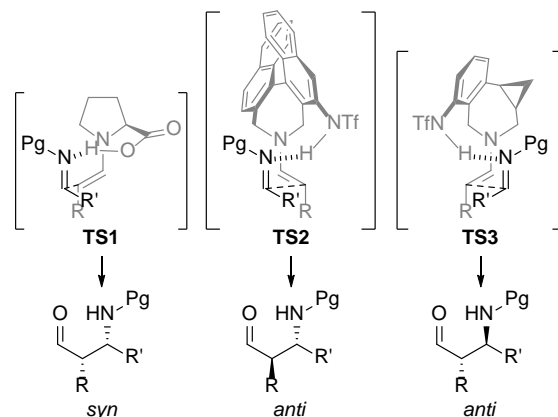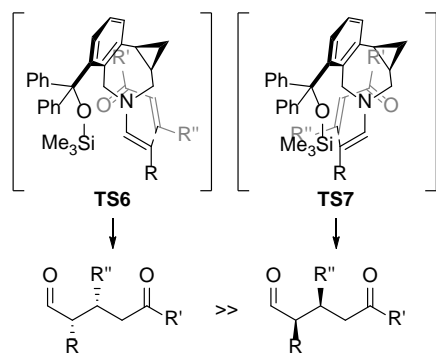

Figure 3. Proposed transition state models for the amine-catalyzed Mannich reactions.

Possible transition state models for the amine-catalyzed aminoxylation and hydroxyamination are also proposed as shown in Figure 4. In the case of the aminoxylation catalyzed by (R,S)-**14**, the observed stereochemistry was rationalized by the transition state model in which nitrosobenzene approaches the *Re* face of the s-*cis*-enamine, as directed by the highly acidic triflamide group (**TS4**). The present aminoxylation might proceed through the acid-base complexation between the triflamide group and the nitroso group that makes the oxygen atom of nitrosobenzene more reactive. On the other hand, the less acidic hydroxy group of (R,S)-**15** directs and activates nitrosobenzene by hydrogen bonding with the oxygen atom of the nitroso group to give the hydroxyamination product with the *R* configuration (**TS5**). In the absence of the highly acidic functionality such as triflamide group, the nitrogen atom of nitrosobenzene is basically more reactive than the oxygen atom because of the higher electronegativity of oxygen atom. We assumed that the acidity of the hydroxy group of (R,S)-**15** is not enough to form the acid-base complex and the hydroxyamination would proceed instead through **TS5** utilizing hydrogen bonding.
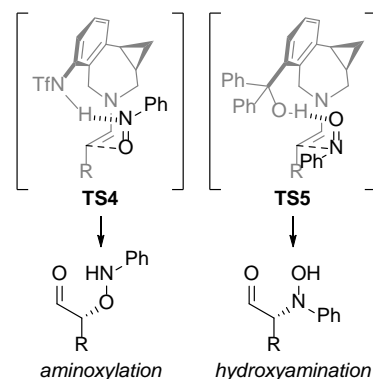
Figure 4. Proposed transition state models for the amine-catalyzed aminoxylation and hydroxyamination.

The newly developed amine catalysts having no α-substituent can generate both s-*trans* and s-*cis*-enamine intermediates as shown in Figure 5. The conjugate addition catalyzed by (R,S)-**16** seems to proceed through **TS6** because of the greater steric repulsion between the catalyst cyclopropane moiety and the acyl group of electron-deficient olefin in **TS7** compared to that in **TS6**.

Figure 5. Proposed transition state models for the amine-catalyzed conjugate addition.

In summary, we have developed chiral secondary amine catalysts based on a phenylcyclopropane scaffold as a novel chiral motif. The new design of amine catalysts enabled us to synthesize various types of amine organocatalysts in an efficient way. Research is currently underway to explore the advantages of these phenylcyclopropane-based secondary amines in asymmetric catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: maruoka@kuchem.kyoto-u.ac.jp kano@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Catalytic Asymmetric Synthesis; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Asymmetric Organocatalysis; Berkessel, A.; Gröger H.; Wiley-VCH, Weinheim, 2005. (c) Enantioselective Organocatalysis, Dalko, P. I. ed.; Wiley-VCH, Weinheim, 2007.

(2) (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3055. (b) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem.–Asian. J.* **2006**, *1*, 210.

(3) (a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (b) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1738. (c) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1838. (d) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem.–Eur. J.* **2009**, *15*, 6678. (e) Kano, T.; Noishiki, A.; Sakamoto, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10626. (f) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516. (g) Kano, T.; Sakamoto, R.; Yamaguchi, Y.; Itoh, K.; Maruoka, K. *Chem. Commun.* **2013**, *49*, 1118. (h) Kano, T.; Sakamoto, R.; Maruoka, K. *Chem. Commun.* **2014**, *50*, 942. (i) Kano, T.; Sakamoto, R.; Maruoka, K. *Org. Lett.* **2014**, *16*, 944.

(4) A similar biphenyl-based amine catalyst has also been developed, see: (a) Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130. (b) Kano, T.; Song, S.; Kubota, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 1191. (c) Kano, T.; Song, S.; Maruoka, K. *Chem. Commun.* **2012**, *48*, 7037.

(5) Liang, D.-C.; Luo, R.-S.; Yin, L.-H.; Chan, A. S. C.; Lu, G. *Org. Biomol. Chem.* **2012**, *10*, 3071.

(6) Kano, T.; Takeda, M.; Sakamoto, R.; Maruoka, K. *J. Org. Chem.* **2014**, *79*, 4240. See also ref 2b.

(7) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712.

(8) Boga, S. B.; Alhassan, A. B.; Hesk, D. *Tetrahedron Lett.* **2014**, *55*, 4442.

(9) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042.

(10) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(11) Kano, T.; Yamamoto, A.; Shirozu, F.; Maruoka, K. *Synthesis* **2009**, 1557.

(12) The crystal structure of (*S*)-**2** is inverted to (*R*)-**2** for ease of comparison.

(13) (a) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (b) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677. (c) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (d) Córdova, A. *Chem.–Eur. J.* **2004**, *10*, 1987. (e) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 609. See also: (f) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (g) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040.

(14) (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112. (e) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5374.

(15) Kano, T.; Yamamoto, A.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 5369. See also ref 11.

(16) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046.

(17) (a) Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054. (b) Macharia, J.; Wambua, V.; Hong, Y.; Harris, L.; Hirschi, J. S.; Evans, G. B.; Vetticatt, M. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 8756.

(18) For selected examples of amine-catalyzed conjugate additions of aldehydes to nitroalkenes, see: (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (b) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (c) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1369. (d) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (e) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (f) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545. (g) Chi, Y.; Guo, L.; Kopf, N.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608. (h) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1871. (i) Garcia-Garcia, P.; Ladepeche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719. (j) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem, Int. Ed.* **2008**, *47*, 4722. (k) Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, L. A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018. (l) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6. (m) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50. See also: (n) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

(19) (a) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10*, 5425. (b) Kan, S. B. J.; Maruyama, H.; Akakura, M.; Kano, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 9487.