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# Enantioselective Synthesis of Fused Heterocycles with Contiguous Stereogenic Centers by Chiral Phosphoric Acid Catalyzed Symmetry Breaking

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**Described herein is a highly enantioselective synthesis of fused piperidine and pyrrolidine derivatives with all-carbon**
10 **stereogenic centers. The enantioselective reductive amination from *Cs*-symmetric 1,3-dione derivatives proceeded in a highly stereoselective manner by taking advantage of the desymmetrization approach to afford fused heterocycles with contiguous stereogenic centers in good to excellent**
15 **enantioselectivities (up to 98% ee).**

Fused polycycles with all-carbon quaternary centers, *e.g.,* Hajos-Parrish[1] and Wieland-Miescher ketones,[2] are important intermediates in the total synthesis of natural products.[3] In this regard, much effort has been devoted to the development
20 of a novel method for the construction of these types of skeletons.

Desymmetrization is an important tool for the construction of such kinds of congested frameworks under catalytic conditions.[4] In the 1970s, Wiechert and co-workers,[1a] and
25 Hajos and Parrish[1b] reported an (*S*)-proline-catalyzed asymmetric aldol reaction that furnished chiral cyclohexenones in excellent optical yield (93% ee). The renaissance of organocatalysis in the early 2000s opened doors to novel types of amine organocatalysts (L-
30 prolinamide,[5] β-amino acid derivatives,[6] bimorpholine·TfOH salt,[7] tripeptide,[8] primary amine,[9] cyclohexane diamine[10]), which realized excellent enantioselectivity in the asymmetric aldol reaction. Both chiral amine derivatives (covalent bond control) and chiral Brønsted acids (non-covalent bond control)
35 are viable catalytic systems in the reaction. We reported a highly enantioselective synthesis of chiral fused cyclohexenones by chiral phosphoric acid catalyzed desymmetrization of 1,3-dione.[11,12] These processes, although useful, mostly focused on the intramolecular aldol-type
40 reaction; one exception was the work of Scheidt, in which the enantioselective synthesis of fused β-lactones by a chiral NHC-catalyzed nucleophilic addition/ester formation sequence was involved.[13] A corresponding reaction involving reductive amination would be a promising tool for the
45 construction of fused polyheterocycles. Nevertheless, to the best of our knowledge, there is no precedent for the stereoselective construction of all-carbon quaternary centers by the symmetry breaking strategy based on the asymmetric imine formation (reductive amination).
50 We report herein a desymmetrization-type asymmetric reductive amination for the stereoselective construction of

fused polyheterocycles with contiguous stereogenic centers. In this process, an all-carbon quaternary center at the ring junction and its adjacent tertiary stereogenic center were well
55 controlled to afford fused piperidine and pyrrolidine derivatives with good to excellent enantioselectivities (up to 98% ee).
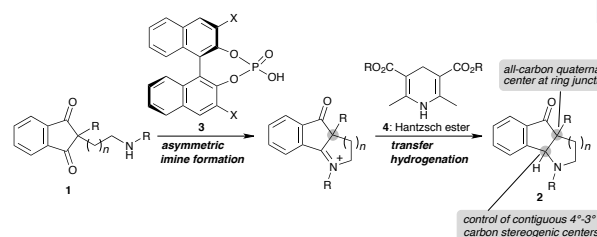


60 **Scheme 1.** Construction of fused heterocycles with contiguous stereogenic centers by symmetry breaking strategy.

An initial examination was conducted by using aldehyde **5** derived from 1,3-indandione, a precursor of planned secondary amine **1**, as the starting material in order to
65 streamline the tuning of the amine moiety. When a mixture of **5a**, *p*-anisidine, Hantzsch ester **4** (R = *t*-Bu), and activated molecular sieves 4Å was heated to 50 °C in the presence of 10 mol% of **3a** [X = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$],[14] the sequential reductive amination reaction proceeded to afford **2aa** in low chemical
70 yield in the racemic form (20%, 2% ee). In order to take advantage of the hydrogen bond between the catalyst and the hydroxy moiety, several hydroxyanilines were examined. Although desired adduct **2ab** was not obtained with *p*-hydroxyaniline, moderate but promising selectivity was
75 observed in the case of *m*-hydroxyaniline (50% ee). Interestingly, the reductive amination/*N,O*-acetal formation sequence occurred instead of the expected sequential reductive amination to give acetal **6** with contiguous
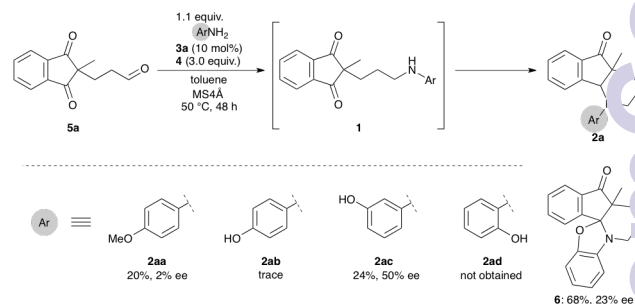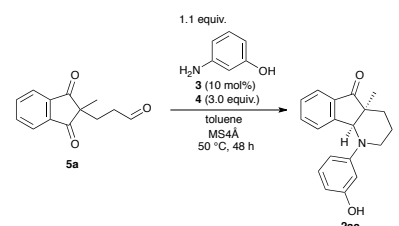


**Fig. 1** Examination of the amine moiety.

quaternary stereogenic centers by use of *o*-hydroxyaniline, although the selectivity was low (23% ee).[15,16]

Inspired by the results, we set out to screen the appropriate catalyst by use of *m*-hydroxyaniline (Table 1). Entry 1 shows the result with **3a**. The use of catalyst **3b** with 2,6-($i$-Pr)$_2$C$_6$H$_4$ groups at 3,3'-positions resulted in moderate selectivity (57% ee, entry 2). The enantioselectivity was increased to 68% ee when **3c** having a cyclohexyl (Cy) group instead of an *i*-Pr group was used (entry 3). Catalysts with an electron-withdrawing group, such as **3d** (X = 4-NO$_2$C$_6$H$_4$) and **3e** (X = 2,4-(CF$_3$)$_2$C$_6$H$_3$), slightly improved the chemical yields (33% and 37%, respectively), but the selectivity dropped to less than 20% ee (entries 4 and 5). Fortunately, **3f** with 9-anthryl groups exhibited good catalytic activity from the viewpoint of both chemical yield and enantioselectivity; **2ac** was obtained in 50% yield with 77% ee (entry 6). Although the enantioselectivity was slightly improved by use of molecular sieves 3Å in place of molecular sieves 4Å, lowering the reaction temperature to 0 °C was the most effective way to increase the enantioselectivity. Desired compound **2ac** was obtained in 93% ee, albeit in the decreased chemical yield (34%, entry 8).[17]

**Table 1** Screening for catalysts and reaction conditions.[a]



| entry | catalyst (X) | yield (%) | ee (%)[b] |
|---|---|---|---|
| 1 | 2,4,6-($i$-Pr)$_3$C$_6$H$_2$ (**3a**) | 24 | 50 |
| 2 | 2,6-($i$-Pr)$_3$C$_6$H$_3$ (**3b**) | 19 | 57 |
| 3 | 2,4,6-Cy$_3$C$_6$H$_2$ (**3c**) | 30 | 68 |
| 4 | 4-NO$_2$C$_6$H$_4$ (**3d**) | 33 | 6 |
| 5 | 2,4-(CF$_3$)$_2$C$_6$H$_3$ (**3e**) | 37 | 19 |
| 6 | 9-anthryl (**3f**) | 50 | 77 |
| 7[c] | 9-anthryl (**3f**) | 56 | 79 |
| 8[c, d] | 9-anthryl (**3f**) | 34 | 93 |

[a] Unless otherwise noted, all reactions were performed with 0.10 mmol of aldehyde **5a**, 0.30 mmol of **4**, 0.11 mmol of *m*-hydroxyaniline, and 10 mol% of **3** in toluene (2.0 mL) at 50 °C. [b] Enantiomeric excess was determined with a chiral stationary phase. [c] MS3Å was employed instead of MS4Å. [d] At 0 °C.

With the optimum reaction conditions in hand, we subjected secondary amine **1a** to the optimum reaction conditions as planned. Gratifyingly, the desired reaction proceeded smoothly to afford **2ac** in higher chemical yield without sacrificing enantioselectivity (87%, 94% ee). Although the precise reason for the dramatic improvement of the chemical yield has yet to be clarified, the formation of a pyridinium salt between phosphoric acid and Hantzsch pyridine might be responsible for the decrease of the catalytic activity.[18]

The substrate scope of this reaction is illustrated in Figure 2. Examination of the substituent at 2-position suggested that the reactivity was strongly influenced by the steric bulkiness of the substituent. Although Et-substituted product **2b** was obtained with 83% ee, an elevated temperature (50 °C) was required to realize the moderate chemical yield (52%). A bulkier benzyl substrate afforded adduct **2c** in only 18% yield, albeit with good enantioselectivity (79% ee). No desired adduct **2d** was obtained in the case of the Ph-substituted substrate even if the reaction was performed at 80 °C. On the other hand, the substituent on the aromatic ring did not have a detrimental effect on both chemical yield and enantioselectivity; 5,6-dichloro-substituted analogue **2e** was obtained in 87% yield with 98% ee.

Further investigation suggested that this methodology was also applicable to the stereoselective synthesis of a 5-5 fused skeleton by simple modification of the catalyst (**3c**: X = 2,4,6-Cy$_3$C$_6$H$_2$). Contrary to the 5-6 fused system, the 5-membered ring formation reaction proceeded smoothly to afford the corresponding adducts (**7a–d**) in moderate to good chemical yields with good to excellent enantioselectivities (86–92% ee).

The absolute configuration of **2ac** was unambiguously established by single-crystal X-ray analysis of the corresponding *p*-bromobenzoate (See SI for details),[19] and those of others shown in Table 1 and Figure 2 were surmised by analogy.
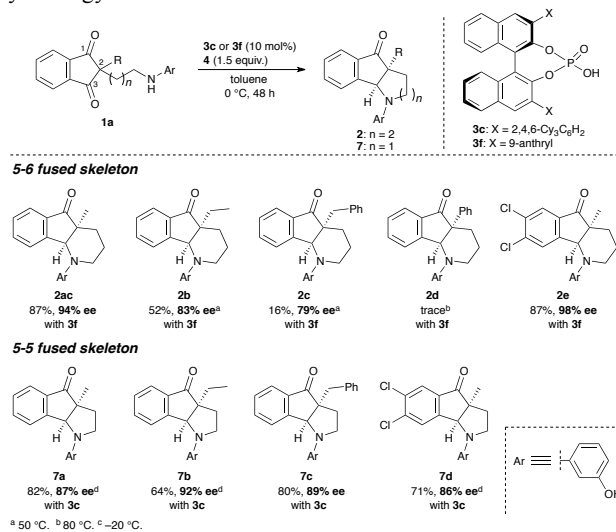


**Fig. 2** Substrate scope of intramolecular reductive amination.

The hydrogen bond between the catalyst and the substrate (*m*-hydroxyphenyl moiety) is expected to be responsible for both of the high reactivity and the high selectivity, as observed in the chiral phosphoric acid catalyzed asymmetric reactions reported so far (Scheme 2).[20] The sequential reductive amination with masked aniline (*m*-anisidine) resulted in a low chemical yield and a considerably low selectivity (23%, 8% ee at 50 °C; cf. 56%, 79% ee in **2ac**). This result suggests that the desired desymmetrization-type asymmetric reductive amination proceeded via a medium-sized cyclic transition state in which hydrogen bonding between the phenolic O–H moiety and phosphoryl oxygen, and activation of the carbonyl group by a Brønsted acid were involved.
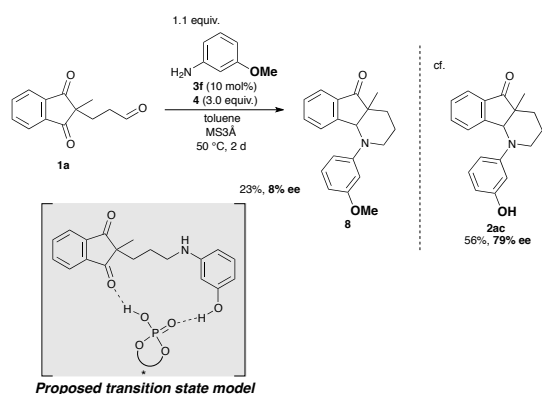
**Scheme 2.** Importance of bifunctionality of the chiral phosphoric acid and the proposed transition state model.

In summary, we have developed a highly enantioselective synthesis of fused piperidine and pyrrolidine derivatives with all-carbon stereogenic centers by chiral phosphoric acid catalyzed symmetry breaking. Using this method, several important substructures, such as 5-6 and 5-5 fused polyheterocycles with contiguous stereogenic centers, were synthesized with good to excellent enantioselectivities (up to 98% ee). Further investigations of its application to natural product synthesis are under way in our laboratory.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data for all new compounds. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1   (a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; (b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; (c) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Poland, W. Sciamanna, M. A. Scott, P. A. Wehrli, *J. Org. Chem.* **1975**, *40*, 675; (d) Z. G. Hajos, D. R. Parrish, *Org. Synth.* **1985**, *63*, 26..

2   For the synthesis of Wieland – Miescher ketone: (e) P. Wieland, K. Miescher, *Helv. Chim. Acta* **1950**, *33*, 2215; (f) J. Gutzwiller, A. Buchschacher, A. Furst, *Synthesis* **1977**, 167; (g) S. Ramachandran, M. S. Newman, *Org. Synth.* **1961**, *41*, 38.

3   For selected references, see: a) E. J. Corey, M. Ohno, R. B. Mitra, P. A. Vatakencherry, *J. Am. Chem. Soc.* **1964**, *86*, 478; (b) E. J. Corey, M. Ohno, R. B. Mitra, R. A. Vatakencherry, *J. Am. Chem. Soc.* **1964**, *86*, 478; (c) J. E. McMurry, S. J. Isser, *J. Am. Chem. Soc.* **1972**, *94*, 7132; (d) R. C. A. Isaacs, R. M. J. Di Grandi, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 3938; (e) L. A. Paquette, T.-Z. Wang, M. R. Sivik, *J. Am. Chem. Soc.* **1994**, *116*, 11323; (f) D. M. Coltart, S. J. Danishefsky, *Org. Lett.* **2003**, *5*, 1289; (f) T. J. Reddy, G. Bordeau, L. Trimble, *Org. Lett.* **2006**, *8*, 5585; (g) S. Yamashita, K. Iso, M.

Hirama, *Org. Lett.* **2008**, *10*, 3413; (h) Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1400; (i) M. Enomoto, A. Morita, S. Kuwahara, *Angew. Chem. Int. Ed.* **2012**, *51*, 12833; (j)Y. Tang, J.-T. Liu, P. Chen, M. G. Lv, Z. Z. Wang, Y.-K. Huang, *J. Org. Chem.* **2014**, *79*, 11729.

4   For reviews of catalytic enantioselective desymmetrization, see: (a) R. S. Ward, *Chem. Soc. Rev.* **1990**, *19*, 1; (b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; (c) K. Mikami, A. Yoshida, *J. Synth. Org. Chem., Jpn.* **2002**, *60*, 732; (d) Rovis, T. In New Frontiers in Asymmetric Catalysis; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2007; p 275.

5   (a) X.-M. Zhang, M. Wang, Y.-Q. Tu, C.-A. Fan, Y.-J. Jiang, S.-Y. Zhang, F.-M. Zhang, *Synlett* **2008**, 2831; (b) G. Guillena, C. Nájera, F. Viózquez, *Synlett* **2008**, 3031; (c) D. B. Ramachary, M. Kishor, *J. Org. Chem.* **2007**, *72*, 5056; (d) D. Almazi, D. A. Alonso, A.-N. BAlaguer, C. Nájera, *Adv. Synth. Catal.* **2009**, *351*, 1123; (e) B. Bradshaw, G. Etxebarria-Jardi, J. Bonjoch, S. F. Viozquez, G. Guillena, C. Nájera, *Adv. Synth. Catal.* **2009**, *351*, 2482; (f) B. Brradshow, G. Etxebarria-Jardi, . Bonjoch, *J. Am. Chem. Soc.* **2010**, *132*, 5966; (g) R. Pedrosa, J. M. Andrés, R. Manzano, C. Pérez-López, *Tetrahedron Lett.* **2013**, *54*, 3101.

6   (a) S. G. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun.* **2005**, 3802; (b) S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith, J. E. Thompson, *Org. Biomol. Chem.* **2007**, *5*, 3190.

7   (a) K. Kriis, T. Kanger, M. Laars, T. Kailas, A.-M. Müürisepp, M. Pehk, M. Lopp, *Synlett* **2006**, 1699; (b) M. Limbach, *Tetrahedron Lett.* **2006**, *47*, 3843; (c) T. Kanger, K. Kriis, M. Laars, T. Kailas, A.-M. Müürisepp, T. Pehk, M. Lopp, *J. Org. Chem.* **2007**, *72*, 5168.

8   V. D'Elia, H. Zwicknagl, O. Reiser, *J. Org. Chem.* **2008**, *73*, 3262.

9   (a) C. Xu, L. Zhang, P. Zhou, S. Luo, J.-P. Cheng, *Synthesis*, **2013**, *45*, 1939; (b) C. Xu, L. Zhang, P. Zhou, S. Luo, *J. Org. Chem.* **2014**, *79*, 11517.

10  Á. L. Fuentes de Arriba, D. G. Seisdedos, L. Simón, V. Alcázar, C. Raposo, J. R. Morán, *J. Org. Chem.* **2010**, *75*, 8303.

11  For recent reviews on chiral phosphoric acid catalysis, see: T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; (b) M. Terada, *Synthesis* **2010**, 1929; (c) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047. For seminal works of chiral phosphoric acid, see: (d) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; (e) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.

12  K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem. Int. Ed.* **2009**, *48*, 9652.

13  E. M. Phillips, J. M. Roberts, K. A. Scheidt, *Org. Lett.* **2010**, *12*, 283.

14  For pioneering works of chiral phosphoric acid catalyzed transfer hydrogenation, see: (a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; (b) S. Hoffmann, J. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; (c) R. I. Storner, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

15  Our group has recently developed chiral Brønsted acid catalyzed transfer hydrogenation of imines using benzothiazoline derivatives as hydrogen donor, see: (a) C, Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180; (b) C. Zhu, T. Akiyama, *Adv. Synth. Catal.* **2010**, *352*, 1846; (c) C. Zhu, T. Akiyama, *Synlett* **2011**, 1251; (d) A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem., Int. Ed.* **2011**, *50*, 8180; (e) K. Saito, T. Akiyama, *Chem. Commun.* **2012**, *48*, 4573; (f) C. Zhu, T. Akiyama, *Tetrahedron Lett.* **2012**, *53*, 416; (g) T. Sakamoto, K. Mori, T. Akiyama, *Org. Lett.* **2012**, *14*, 3312; (h) T. Sakamoto, K. Horiguchi, K. Saito, K. Mori, T. Akiyama, *Asian. J. Org. Chem.* **2013**, *2*, 943; (i) K. Saito, K. Horiguchi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Eur. J.* **2014**, *20*, 7616. See also: (j) D. Enders, J. X. Liebich, G. Raabe, G. *Chem. Eur. J.* **2010**, *16*, 9763; (k) C. Zhu, J. R. Falck, *ChemCatChem* **2011**, *3*, 1850; (k) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388.

16  The reaction with benzothiazoline[15] failed. The main product was benzylamine **10**, which was produced by the acid hydrolysis of **4** followed by the reductive amination of the resulting aldehyde with *m*-hydroxyaniline.
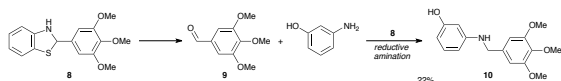
17 It is worthy to note that **2ac** was obtained in a diastereomerically pure form (only *cis*-fused compound was obtained) even when various catalysts were employed. This result clearly indicates that complete substrate control was attained in the reduction of the iminium species.

18 The use of Hantzsch pyridine **11** (10 mol%) together with the optimum reaction conditions resulted in a decrease of the chemical yield but with almost complete retention of the enantioselectivity (63%, 92% ee).
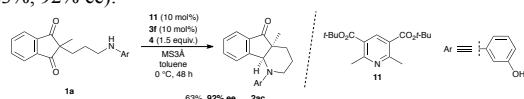
19 The structure of **2ac** was unambiguously established by single-crystal X-ray analysis. CCDC-1063974 contains the supplementary crystallographic data of **s6**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request.

20 For theoretical studies on chiral phosphoric acid catalysis, see: (a) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756; (b) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741; (c) M. Yamanaka, T. Hirata, *J. Org. Chem.* **2009**, *74*, 3266; (d) T. Akiyama, H. Morita, P. Bachu, K. Mori, M. Yamanaka, T. Hirata, *Tetrahedron* **2009**, *65*, 4950; (e) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; (f) F.-Q. Shi, B.-A Song, *Org. Biomol. Chem.* **2009**, *7*, 1292; (g) N. Nan Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 15301; (h) T. Marcelli, P. Hammar, F. Himo, *Adv. Synth. Catal.* **2009**, *351*, 525; (i) L. Simón, J. M. Goodman, *J. Org. Chem.* **2010**, *75*, 589; (j) S. Xu, Z. Wang, Y. Li, X. Zhang, H. Wang, K. Ding, *Chem. Eur. J.* **2010**, *16*, 3021; (k) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2010**, *49*, 8666; (l) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 13504; (m) L. Simón, J. M. Goodman, *J. Org. Chem.* **2011**, *76*, 1775; (n) F. Shi, S.-W. Luo, Z.-L. Tao, L. He, J. Yu, S.-J. Tu, L.-Z. Gong, *Org. Lett.* **2011**, *13*, 4680; (o) M. N. Grayson, S. C. Pellegrinet, J. M. Goodman, *J. Am. Chem. Soc.* **2012**, *134*, 2716; (p) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970; (q) H. Wang, P. Jain, J. C. Antilla, K. N. Houk, *J. Org. Chem.* **2013**, *78*, 1208; (r) Y. Shibata, M. Yamanaka, *J. Org. Chem.* **2013**, *78*, 3731; (s) G. Jindal, R. B. *J. Org. Chem.* **2014**, *79*, 7600; (t) K. Kanomata, Y. Toda, Y. Shibata, M. Yamanaka, S. Tsuzuki, I. D. Gridnev, M. Terada, *Chem. Sci.* **2014**, *5*, 3515; (u) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383.