Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2015, **6**, 3550

Enantioselective synthesis of bicyclo[3.n.1]alkanes by chiral phosphoric acid-catalyzed desymmetrizing Michael cyclizations†

Alan R. Burns,‡[ab] Amaël G. E. Madec,‡[b] Darryl W. Low,[a] Iain D. Roy[a] and Hon Wai Lam*[ab]

Received 2nd March 2015
Accepted 12th April 2015

DOI: 10.1039/c5sc00753d

www.rsc.org/chemicalscience

2,2-Disubstituted cyclic 1,3-diketones containing a tethered electron-deficient alkene undergo chiral phosphoric acid-catalyzed desymmetrizing Michael cyclizations to give bridged bicyclic products in high enantioselectivities. Both bicyclo[3.2.1]octanes and bicyclo[3.3.1]nonanes are accessible using this methodology.

Bicyclo[3.n.1]alkanes appear in numerous biologically active natural products (selected examples are shown in Fig. 1) and have widespread applications in organic synthesis.[1,2] Although many creative approaches for the synthesis of these structures have been devised,[1,2] the preparation of enantiomerically enriched chiral bicyclo[3.n.1]alkanes by asymmetric catalysis currently represents only a small fraction of these methods.[3,4] In view of the present level of development, increasing the number of available catalytic enantioselective reactions to access these compounds is an important area of research. Herein, we report a new approach for the enantioselective synthesis of bicyclo[3.2.1]octanes and bicyclo[3.3.1]nonanes by chiral phosphoric acid-catalyzed Michael cyclizations of 1,3-diones onto tethered electron-deficient alkenes. These reactions give products containing three new stereogenic centers, including an all-carbon quaternary center, resulting from the formal enantioselective, desymmetrizing enolization of 2,2-disubstituted cyclic 1,3-diketones. In addition, these reactions further demonstrate the ability of chiral phosphoric acids to promote transformations of unactivated ketones by enolization, which has so far been relatively underexplored.[5]

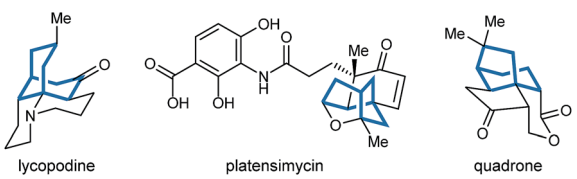
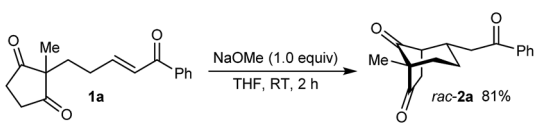
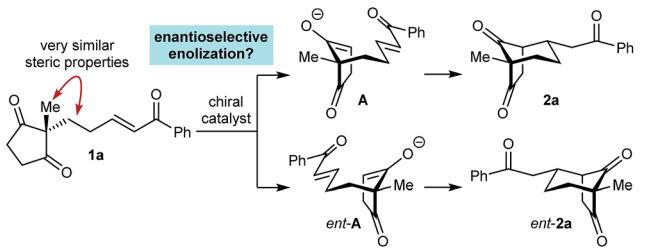


Fig. 1 Natural products containing bicyclo[3.n.1]alkanes.



(1)

As part of our interest in the catalytic enantioselective desymmetrization of 2,2-disubstituted cyclic 1,3-diketones,[6] we observed that enone dione **1a** can undergo an intramolecular Michael addition to form the chiral bicyclo[3.2.1]octane *rac*-**2a** under basic conditions.[7] For example, treatment of **1a** with NaOMe in THF at room temperature gave *rac*-**2a** in 81% yield (eqn (1)). Following this result, the development of a catalytic enantioselective variant captured our interest. However, a challenging feature of this reaction that differentiates it from the significant majority of catalytic enantioselective Michael reactions described previously[8] is that stereogenicity is first generated in the *enolization step*, rather than the carbon–carbon bond-forming step (Scheme 1).[9] Therefore, any chiral catalyst employed has to, at first glance, facilitate the enantioselective, desymmetrizing enolization[10] of a 2,2-disubstituted cyclic 1,3-



Scheme 1 Asymmetric induction in the formation of **2a**.

[a]*EaStCHEM, School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, David Brewster Road, Edinburgh, EH9 3FJ, UK.*

[b]*School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK. E-mail: hon.lam@nottingham.ac.uk*

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data for **2d**, **3a**, **6e**, and **6f**. CCDC 1045000–1045003. See DOI: 10.1039/c5sc00753d

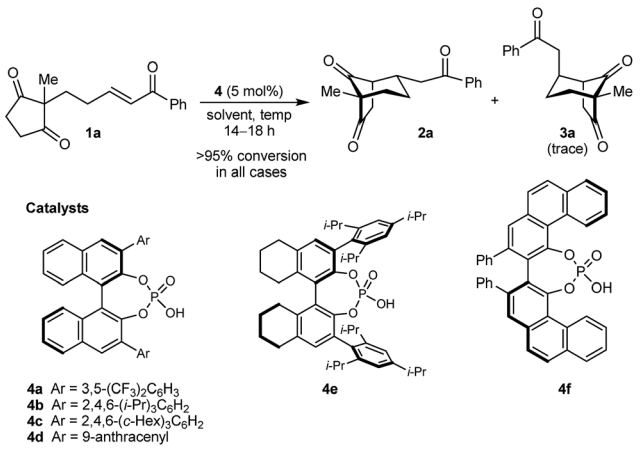
‡ These authors contributed equally.

diketone. Due to the two substituents at the prochiral 2-position (methyl *versus* primary alkyl) possessing very similar steric properties, this task appeared to be far from trivial.

We hypothesized that a solution to this challenge could be obtained under conditions where enolization of **1a** is reversible, potentially enabling rapid interconversion of the enolates **A** and *ent*-**A**. Under such Curtin–Hammett conditions,[11] carbon–carbon bond formation could then be the enantiodetermining step. Furthermore, it appeared likely that chiral catalysts capable of binding to both the enolate oxygen atom and the enone carbonyl group would increase the energy difference between diastereomeric transition states, thus maximizing the prospects of achieving high enantioselectivities.

In the last ten years, chiral Brønsted acids, such as phosphoric acids, have emerged as extremely versatile catalysts for a diverse range of transformations.[12–14] In many cases, both the Lewis acidity of the hydroxyl group and the Lewis basicity of the phosphoryl group of the catalyst play key roles in the simultaneous activation of electrophile–nucleophile pairs.[13] We were therefore hopeful that chiral phosphoric acids would be suitable bifunctional catalysts for the enantioselective cyclization of **1a**, and this indeed turned out to be the case (Table 1).[15] For example, heating **1a** in the presence of various BINOL-derived phosphoric acids **4a–4d** (5 mol%) in toluene at 80 °C for 14–18 h led to complete consumption of **1a** to form bicyclo[3.2.1]octane **2a** as the major product (Table 1, entries 1–4).[16] Small traces of a diastereomeric product **3a**,[16] in which the phenyl ketone-containing substituent occupies an axial position, were detected by TLC analysis, but the exact diastereomeric ratios could not be determined by ^{1}H NMR analysis due to overlapping signals. Furthermore, promising enantioselectivities were obtained with phosphoric acids **4b–4d** containing sterically more hindered aryl groups at the 3,3′-positions (entries 2–4). Catalysts **4b** and **4c**, possessing 2,4,6-trisubstituted aryl groups, gave the best results (entries 2 and 3). Switching to the H_8-BINOL scaffold in catalyst **4e** was detrimental (entry 5, compare with entry 2), while the vaulted biaryl-derived phosphoric acid **4f** gave a low enantioselectivity (entry 6). Due to its commercial availability and relative ease of synthesis compared with **4c**, phosphoric acid **4b** (TRIP) was selected for further investigations. Changing the solvent to cyclohexane[17] and lowering the reaction temperature to 50 °C gave marginally superior results (entries 7 and 8).

Table 1 Evaluation of catalysts and reaction conditions for the Michael cyclization of **1a**[a]



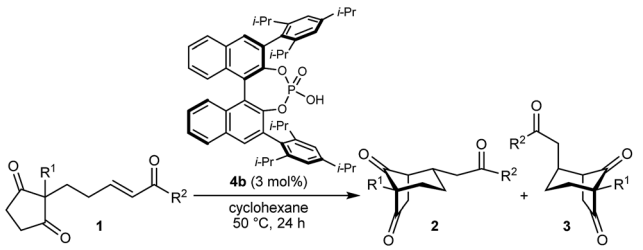
Entry	Catalyst	Solvent	Temp. (°C)	ee[b] of **2a** (%)
1	**4a**	Toluene	80	28
2	**4b**	Toluene	80	89
3	**4c**	Toluene	80	90
4	**4d**	Toluene	80	76
5	**4e**	Toluene	80	74
6	**4f**	Toluene	80	17
7	**4b**	Cyclohexane	80	90
8	**4b**	Cyclohexane	50	91

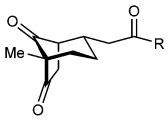
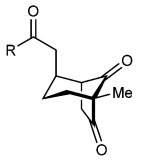
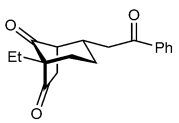
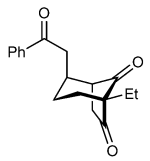
[a] Reactions were conducted using 0.05 mmol of **1a**. Complete consumption of **1a** was observed in all cases by ^{1}H NMR analysis. [b] Determined by HPLC on a chiral stationary phase.

With an effective catalyst and solvent identified, the scope of the reaction with respect to the preparation of bicyclo[3.2.1]-octanes was investigated (Table 2). The catalyst loading of **4b** could be decreased from 5 mol% to 3 mol% without detriment, and the reactions were complete after 24 h. Under these conditions, a range of enone diones **1a–1k** underwent Michael cyclizations to give products **2a–2k** in generally high yields and with good to high enantioselectivities (86–95% ee).[16] The process is compatible with electron-donating (entries 2 and 3) or electron-withdrawing aryl groups (4 and 5) on the enone carbonyl, as well as 2-naphthyl (entries 6 and 7) or *tert*-butyl groups (entry 8). Additional Lewis basic heteroatoms in heteroarene substituents such as 2-pyridyl, 2-furyl, or 2-thienyl groups were also tolerated (entries 9–11). Finally, replacement of the methyl group at the 2-position of the cyclic 1,3-diketone with an ethyl group did not affect the efficiency of the reaction (entry 12). In some cases, the reactions were highly diastereoselective, and only one product was detected (entries 2, 3, 6–8, 11, and 12). Although small but appreciable quantities of the minor diastereomeric products **3** were also formed in other cases, these were readily separated from the major isomers, the yields of which remained high (entries 1, 4, 5, 9, and 10). The enantiomeric excesses of the minor product were comparable to those of the major product in some cases (entries 1, 4, and 10), but were lower for substrates containing a 3-chlorophenyl or 2-pyridyl group attached to the enone carbonyl (entries 5 and 9). The process is also amenable to being conducted on a gram-scale. For example, the cyclization of **1f** (1.00 g, 3.12 mmol) using 1.6 mol% of phosphoric acid **4b** gave **2f** as the only observable diastereomer in 84% yield and 90% ee after 90 h (entry 7).

The synthesis of bicyclo[3.3.1]nonanes **6** with good enantioselectivities is also possible using this methodology (Table 3). As with the corresponding bicyclo[3.2.1]octanes, many of these reactions also resulted in diastereomeric products (Table 3, entries 1, 4–9, and 11–13). In general, the enantiomeric excess of the major products were slightly lower compared with those of the bicyclo[3.2.1] octanes **2** (see Table 2), though interestingly, the minor diastereomers **7** were usually formed in higher enantioselectivities. The process remained broadly tolerant of

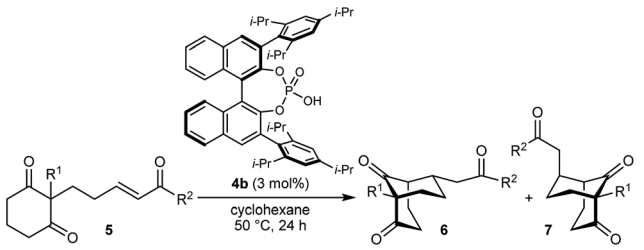
Table 2 Enantioselective Michael cyclizations to give bicyclo[3.2.1]-octanes[a]

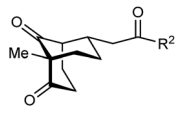
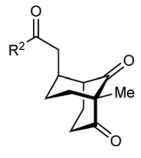
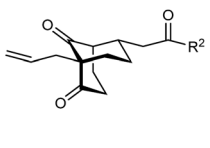
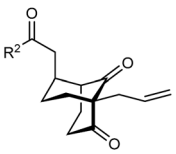
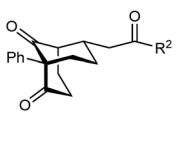
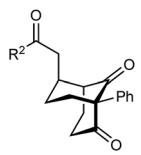
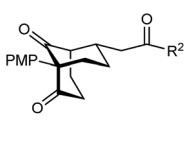
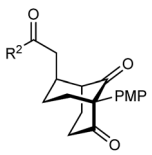


Entry	R^1	R^2	Major product **2**	Minor product **3**
				
1	Me	Ph	**2a** 93%, 91% ee	**3a** 7%, 87% ee
2		4-MeC_6H_4	**2b** 91%, 92% ee	**3b** —[b]
3		4-$MeOC_6H_4$	**2c** 92%, 91% ee	**3c** —[b]
4		4-ClC_6H_4	**2d** 80%, 94% ee	**3d** 11%, 85% ee
5		3-ClC_6H_4	**2e** 79%, 86% ee	**3e** 13%, 66% ee
6		2-Naphthyl	**2f** 97%, 91% ee	**3f** —[b]
7[c]		2-Naphthyl	**2f** 84%, 90% ee	**3f** —[b]
8		*t*-Bu	**2g** 96%, 95% ee	**3g** —[b]
9[d]		2-Pyridyl	**2h** 76%, 87% ee	**3h** 20%, 29% ee
10		2-Furyl	**2i** 80%, 88% ee	**3i** 17%, 90% ee
11		2-Thienyl	**2j** 97%, 92% ee	**3j** —[b]
				
12	Et	Ph	**2k** 95%, 93% ee	**3k** —[b]

[a] The reactions were performed with **1a–k** (0.20 mmol) in cyclohexane (2 mL). Yields are of pure isolated single diastereomers. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] The minor product was not detected. [c] Conducted using **1f** (1.00 g, 3.12 mmol) and 1.6 mol% of **4b** in cyclohexane/toluene (4 : 1) at 50 °C for 90 h. [d] The reaction was conducted in toluene.

Table 3 Enantioselective Michael cyclizations to give bicyclo[3.3.1]-nonanes[a]



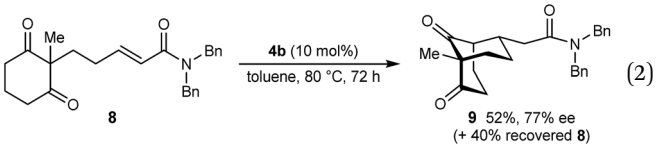
Entry	R^1	R^2	Major product **6**	Minor product **7**
				
1	Me	Ph	**6a** 77%, 82% ee	**7a** 14%, 94% ee
2		4-MeC_6H_4	**6b** 95%, 86% ee	**7b** —[b]
3		4-$MeOC_6H_4$	**6c** 94%, 87% ee	**7c** —[b]
4		4-FC_6H_4	**6d** 82%, 86% ee	**7d** 13%, 86% ee
5		4-ClC_6H_4	**6e** 73%, 87% ee	**7e** 19%, 96% ee
6[c]		4-$NO_2C_6H_4$	**6f** 85%, 72% ee	**7f** 15%, 88% ee
7[d]		3-$CF_3C_6H_4$	**6g** 68%, 86% ee	**7g** 21%, 94% ee
8		2-$MeOC_6H_4$	**6h** 60%, 83% ee	**7h** 24%, 93% ee
9		2-ClC_6H_4	**6i** 75%, 92% ee	**7i** 20%, 85% ee
10		2-Naphthyl	**6j** 96%, 87% ee	**7j** —[b]
11		2-Pyridyl	**6k** 75%, 82% ee	**7k** 19%, 46% ee
12		CH_2CH_2OBn	**6l** 35%, 92% ee	**7l** 24%, 80% ee
				
13	Allyl	Ph	**6m** 89%, 86% ee	**7m** 6%, 94% ee
14		4-ClC_6H_4	**6n** 94%, 88% ee	**7n** —[b]
				
15	Ph	Ph	**6o** 68%, 94% ee	**7o** —[b]
16		2-Thienyl	**6p** 50%, 97% ee	**7p** —[b]
				
17	PMP	Ph	**6q** 63%, 94% ee	**7q** —[b]
18		2-Thienyl	**6r** 49%, 92% ee	**7r** —[b]

[a] The reactions were performed with **5a–5r** (0.20 mmol) in cyclohexane (2 mL). Yields are of pure isolated single diastereomers. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] The minor product was not detected. [c] The reaction was conducted in toluene. [d] The reaction was conducted in cyclohexane (4 mL). PMP = *para*-methoxyphenyl.

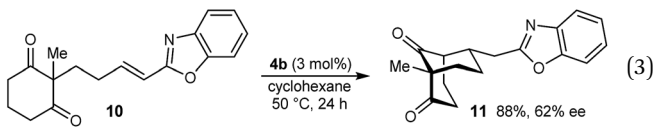
different (hetero)arenes at the enone carbonyl group, including *ortho*-substituted phenyl groups (entries 8 and 9). A 4-nitrophenyl ketone led to a more modest enantioselectivity for the major product (entry 6). The reaction was also compatible with an alkyl substituent at the enone carbonyl group that possesses enolizable protons; the cyclization of **5l** gave products **6l** and **7l** in 59% combined yield (entry 12). Again, variation of the substituent at the 2-position of the 1,3-diketone was possible, with allyl (entries 13 and 14), phenyl (entries 15 and 16), and *para*-methoxyphenyl groups (entries 17 and 18) providing good results. In particular, aryl substituents at the 2-position had a beneficial effect on the enantioselectivity compared with the corresponding methyl-substituted analogues. For example, **6o**

and **6q** were obtained in significantly higher enantioselectivity (94% ee, entries 15 and 17) compared with **6a** (82% ee, entry 1).

The process is not limited to α,β-unsaturated ketones as the Michael acceptor. For example, substrate **8**, containing an α,β-unsaturated amide, successfully underwent cyclization to give bicyclo[3.3.1]nonane **9** in 52% yield and 77% ee, with the starting material being recovered in 40% yield (eqn (2)). Due to the lower reactivity of **8** compared with α,β-unsaturated ketones, a higher catalyst loading, temperature, and reaction time were required for reasonable results. Interestingly, the benzyl ester analogue of **8**, in which the alkene is expected to be more electrophilic than in **8**, was unreactive towards chiral phosphoric acid-catalyzed Michael cyclizations. This observation suggests that in addition to the electrophilicity of the electron-deficient alkene, the Lewis basicity of the oxygen atom of the α,β-unsaturated carbonyl (to facilitate binding of the chiral phosphoric acid) is also important for reactivity. Furthermore, the 2-alkenylbenzoxazole-containing substrate **10** also underwent cyclization in a good yield (eqn (3)) although the enantioselectivity of this reaction was modest (62% ee).[18]



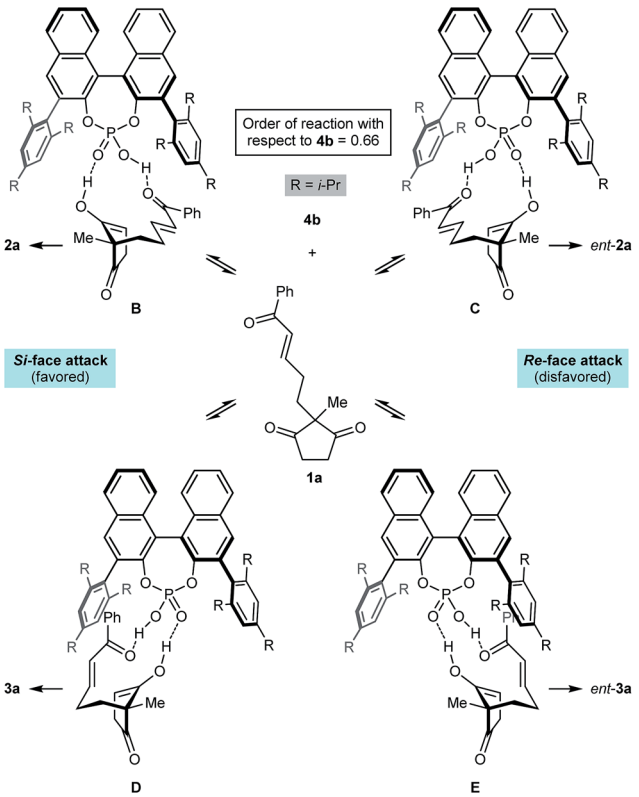
(2)



(3)

Scheme 2 presents a working hypothesis for the mode of action of the chiral phosphoric acid **4b**, using substrate **1a** for illustration. We propose that the catalyst promotes reversible keto-enol tautomerization of **1a**,[5] and is able to simultaneously bind the carbonyl group of the electrophilic enone and the hydroxyl group of the nucleophilic enol. The formation of the enantiomers **2a** and *ent*-**2a** of the major product can be explained by chair-like conformations **B** and **C**, respectively, in which the enone occupies a pseudoequatorial position. The preferential formation of **2a** is consistent with cyclization through conformation **B** being favored, in which the enol attacks the *Si*-face of the alkene.[19] The formation of the two enantiomers **3a** and *ent*-**3a** of the minor product can be explained by conformations **D** and **E**, where the enone occupies a pseudoaxial position. Again, attack of the *Si*-face of the alkene is favored (conformation **D**), leading to the preferential formation of **3a**.[19] This model is similar to one proposed by List and co-workers to explain the mode of enantioinduction in asymmetric chiral phosphoric acid-catalyzed Fischer indolizations.[20]

Preliminary kinetic studies were also performed on the cyclization of **5d** into **6d** and **7d** in toluene-d8 using different concentrations of catalyst **4b**. From these experiments, the order of the reaction with respect to **4b** was calculated to be



Scheme 2 Proposed mode of action of catalyst **4b**.

0.66.[21] This non-integer value confirms the mechanism of the reaction is indeed complex, and may involve a series of equilibria as presented in Scheme 2. The complexity of the mechanism was further confirmed by a reaction in which the enantiomeric excess of **2j** was measured during the course of the cyclization; the ee of **2j** was not constant throughout, and increased from 70% ee after 1 h (15% conversion) to 90% ee after 24 h (75% conversion).[21,22] Rationalization of these observations awaits the results of further studies.

In summary, the enantioselective synthesis of bicyclo[3.2.1]-octanes and bicyclo[3.3.1]nonanes has been achieved by the chiral phosphoric acid-catalyzed Michael cyclizations of enone diones. These reactions involve the unusual enantioselective desymmetrization of 2,2-disubstituted cyclic 1,3-diketones, in which the bifunctional activation of the substrate by the catalyst is likely to be critical for success. This work further demonstrates the utility of chiral Brønsted acids in the enantioselective preparation of stereochemically complex structures, and investigation of these catalysts in other desymmetrization processes are likely to result in further advances in future. These studies, along with further mechanistic experiments, are topics for future study in our group.

Acknowledgements

We thank the EPSRC (Leadership Fellowship to H.W.L.), AstraZeneca, Pfizer, the University of Edinburgh, and the University of Nottingham for financial support. We thank Dr William Lewis (University of Nottingham) for X-ray

crystallography, and Jorge Solana González for assistance in the preparation of substrates.

Notes and references

1 For reviews of bicyclo[3.n.1]alkanes, see: (*a*) M. Presset, Y. Coquerel and J. Rodriguez, *Chem. Rev.*, 2013, **113**, 525–595; (*b*) M. Ruiz, P. Lopez-Alvarado, G. Giorgi and J. C. Menendez, *Chem. Soc. Rev.*, 2011, **40**, 3445–3454; (*c*) E. Butkus, *Synlett*, 2001, 1827–1835; (*d*) M.-H. Filippini and J. Rodriguez, *Chem. Rev.*, 1999, **99**, 27–76.

2 For a review of the synthesis of bridge-containing compounds in general, see: W. Zhao, *Chem. Rev.*, 2010, **110**, 1706–1745.

3 M. Presset, Y. Coquerel and J. Rodriguez, *ChemCatChem*, 2012, **4**, 172–174.

4 For examples, see: (*a*) N. Itagaki, M. Kimura, T. Sugahara and Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4185–4188; (*b*) C. G. Bashore, M. G. Vetelino, M. C. Wirtz, P. R. Brooks, H. N. Frost, R. E. McDermott, D. C. Whritenour, J. A. Ragan, J. L. Rutherford, T. W. Makowski, S. J. Brenek and J. W. Coe, *Org. Lett.*, 2006, **8**, 5947–5950; (*c*) C.-L. Cao, X.-L. Sun, Y.-B. Kang and Y. Tang, *Org. Lett.*, 2007, **9**, 4151–4154; (*d*) M. Movassaghi and B. Chen, *Angew. Chem., Int. Ed.*, 2007, **46**, 565–568; (*e*) M. L. Grachan, M. T. Tudge and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2008, **47**, 1469–1472; (*f*) B. M. Trost, P. J. McDougall, O. Hartmann and P. T. Wathen, *J. Am. Chem. Soc.*, 2008, **130**, 14960–14961; (*g*) M. Rueping, A. Kuenkel, F. Tato and J. W. Bats, *Angew. Chem., Int. Ed.*, 2009, **48**, 3699–3702; (*h*) C.-L. Cao, Y.-Y. Zhou, J. Zhou, X.-L. Sun, Y. Tang, Y.-X. Li, G.-Y. Li and J. Sun, *Chem.–Eur. J.*, 2009, **15**, 11384–11389; (*i*) M. Rueping, A. Kuenkel and R. Fröhlich, *Chem. –Eur. J.*, 2010, **16**, 4173–4176; (*j*) D. Ding, C.-G. Zhao, Q. Guo and H. Arman, *Tetrahedron*, 2010, **66**, 4423–4427; (*k*) C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu and X.-P. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 9585–9588; (*l*) C.-H. Wei, S. Mannathan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 10592–10595; (*m*) W. Raimondi, M. d. M. Sanchez Duque, S. Goudedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne and J. Rodriguez, *Synthesis*, 2013, **45**, 1659–1666; (*n*) M. Tsakos, M. R. J. Elsegood and C. G. Kokotos, *Chem. Commun.*, 2013, **49**, 2219–2221; (*o*) A. Lefranc, L. Guénée, S. Goncalves-Contal and A. Alexakis, *Synlett*, 2014, **25**, 2947–2952; (*p*) A. Lefranc, L. Gremaud and A. Alexakis, *Org. Lett.*, 2014, **16**, 5242–5245; (*q*) A. D. Gammack Yamagata, S. Datta, K. E. Jackson, L. Stegbauer, R. S. Paton and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2015, **54**, 4899–4903.

5 For examples of transformations of unactivated ketones by chiral phosphoric acid-catalyzed enolization, see: (*a*) K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka and T. Akiyama, *Angew. Chem., Int. Ed.*, 2009, **48**, 9652–9654; (*b*) G. Pousse, F. L. Cavelier, L. Humphreys, J. Rouden and J. Blanchet, *Org. Lett.*, 2010, **12**, 3582–3585; (*c*) I. Felker, G. Pupo, P. Kraft and B. List, *Angew. Chem., Int. Ed.*, 2015, **54**, 1960–1964; (*d*) X. Yang and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3205–3208.

6 (*a*) D. W. Low, G. Pattison, M. D. Wieczysty, G. H. Churchill and H. W. Lam, *Org. Lett.*, 2012, **14**, 2548–2551; (*b*) A. R. Burns, J. Solana González and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 10827–10831; (*c*) B. M. Partridge, J. Solana González and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 6523–6527.

7 For the racemic synthesis of compounds similar to **2a**, see: (*a*) S. Danishefsky, G. Koppel and R. Levine, *Tetrahedron Lett.*, 1968, **9**, 2257–2260; (*b*) Y. Wang, A. Jaunet, P. Geoffroy and M. Miesch, *Org. Lett.*, 2013, **15**, 6198–6201; (*c*) D.-H. Jhuo, B.-C. Hong, C.-W. Chang and G.-H. Lee, *Org. Lett.*, 2014, **16**, 2724–2727.

8 For selected reviews covering catalytic asymmetric Michael reactions, see: (*a*) C. Schneider and F. Abels, *Org. Biomol. Chem.*, 2014, **12**, 3531–3543; (*b*) M. M. Heravi, P. Hajiabbasi and H. Hamidi, *Curr. Org. Chem.*, 2014, **18**, 489–511; (*c*) Y. Zhang and W. Wang, *Catal. Sci. Technol.*, 2012, **2**, 42–53; (*d*) J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis*, 2007, **2007**, 1279–1300; (*e*) S. C. Jha and N. N. Joshi, *ARKIVOC*, 2002, **vii**, 167–196.

9 During the final preparation of this manuscript, the synthesis of 2-azabicyclo[3.3.1]nonanes by catalytic enantioselective desymmetrizing Michael cyclizations was reported see ref. 4q.

10 For reviews of asymmetric deprotonations, including enolizations, see: (*a*) N. S. Simpkins and M. D. Weller, in *Stereochemical Aspects of Organolithium Compounds*, Verlag Helvetica Chimica Acta, 2010, pp. 1–52; (*b*) K. W. Henderson and W. J. Kerr, *Chem. –Eur. J.*, 2001, **7**, 3430–3437; (*c*) P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439–1458; (*d*) P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1–26; (*e*) N. S. Simpkins, *Chem. Soc. Rev.*, 1990, **19**, 335–354.

11 J. I. Seeman, *Chem. Rev.*, 1983, **83**, 83–134.

12 For seminal reports of the use of chiral phosphoric acids as catalysts in asymmetric synthesis, see: (*a*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568; (*b*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357.

13 For selected reviews, see: (*a*) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999–1010; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (*c*) M. Terada, *Chem. Commun.*, 2008, 4097–4112; (*d*) D. Kampen, C. M. Reisinger and B. List, in *Asymmetric Organocatalysis*, ed. B. List, 2009, pp. 395–456; (*e*) M. Terada, *Synthesis*, 2010, 1929–1982; (*f*) M. Terada, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 101–119; (*g*) A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276; (*h*) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539–4549; (*i*) M. Terada, *Curr. Org. Chem.*, 2011, **15**, 2227–2256; (*j*) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156–1171; (*k*) P. Nagorny, Z. Sun and G. A. Winschel, *Synlett*, 2013, **24**, 661–665; (*l*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047–9153.

14 For enantioselective desymmetrizations of dicarbonyl compounds by preferential nucleophilic addition to one carbonyl group, catalyzed by chiral phosphoric acids or their derivatives, see ref. 5a and: (*a*) K. Higuchi, S. Suzuki, R. Ueda, N. Oshima, E. Kobayashi, M. Tayu and T. Kawasaki, *Org. Lett.*, 2015, **17**, 154–157; (*b*) J.-B. Gualtierotti, D. Pasche, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2014, **53**, 9926–9930; (*c*) J. Wilent and K. S. Petersen, *J. Org. Chem.*, 2014, **79**, 2303–2307; (*d*) M. Yang, Y.-M. Zhao, S.-Y. Zhang, Y.-Q. Tu and F.-M. Zhang, *Chem. –Asian J.*, 2011, **6**, 1344–1347; (*e*) V. N. Wakchaure and B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 4136–4139.

15 For examples of enantioselective Michael additions of ketones catalyzed (or co-catalyzed) by chiral phosphoric acids, see ref. 5b and: (*a*) T. Akiyama, T. Katoh and K. Mori, *Angew. Chem., Int. Ed.*, 2009, **48**, 4226–4228; (*b*) M. Yamanaka, M. Hoshino, T. Katoh, K. Mori and T. Akiyama, *Eur. J. Org. Chem.*, 2012, 4508–4514; (*c*) L. Liu, D. Wu, X. Li, S. Wang, H. Li, J. Li and W. Wang, *Chem. Commun.*, 2012, **48**, 1692–1694.

16 The relative and absolute stereochemistries of the products described herein were assigned by analogy to those of products **2d**, **3a**, **6e**, and **6f**, which were determined by X-ray crystallography. See the ESI.†

17 Although the substrate and phosphoric acid **4b** are poorly soluble in cyclohexane at room temperature, the reaction mixtures become homogeneous upon heating to 50 °C.

18 For catalytic enantioselective conjugate additions of carbon-centered nucleophiles to 2-alkenylazaarenes, see: (*a*) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh and M. F. A. Adamo, *Angew. Chem.*, 2009, **121**, 9506–9509; (*b*) G. Pattison, G. Piraux and H. W. Lam, *J. Am. Chem. Soc.*, 2010, **132**, 14373–14375; (*c*) A. Saxena and H. W. Lam, *Chem. Sci.*, 2011, **2**, 2326–2331; (*d*) T. Akiyama, T. Katoh and K. Mori, *Angew. Chem., Int. Ed.*, 2009, **48**, 4226–4228; (*e*) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh and M. Lautens, *Angew. Chem., Int. Ed.*, 2013, **52**, 9755–9758; (*f*) I. D. Roy, A. R. Burns, G. Pattison, B. Michel, A. J. Parker and H. W. Lam, *Chem. Commun.*, 2014, **50**, 2865–2868; (*g*) D. Best and H. W. Lam, *J. Org. Chem.*, 2014, **79**, 831–845.

19 However, the precise manner in which the catalyst **4b** favors *Si*-face attack is not readily explained at the present time.

20 S. Müller, M. J. Webber and B. List, *J. Am. Chem. Soc.*, 2011, **133**, 18534–18537.

21 See ESI for full details.†

22 This experiment was conducted in toluene rather than cyclohexane to ensure complete homogeneity of the reaction mixture.