Asymmetric Catalysis

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An Asymmetric Diels–Alder Reaction Catalyzed by Chiral Phosphate Magnesium Complexes: Highly Enantioselective Synthesis of Chiral Spirooxindoles**

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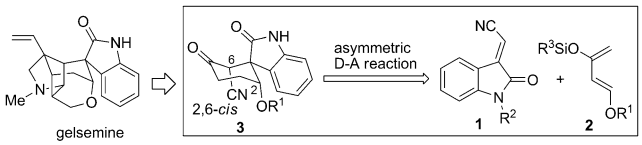
Asymmetric Diels–Alder (D-A) cycloadditions are one of the most powerful reactions for constructing chiral six-membered ring structures, which are prevalent in both natural products and biologically interesting compounds.[1] Despite a number of accomplishments in this area since the first D-A reaction was discovered in 1928, the development of highly efficient catalytic asymmetric D-A reactions is a continuous challenge to organic chemists.[2]

Recently, Ishihara et al. pioneered the asymmetric catalysis of chiral alkaline-metal phosphates.[3,4a] Soon after, our group and others found that chiral alkaline-earth-metal phosphates are effective catalysts for several important organic transformations.[4] Chiral alkaline-earth-metal phosphates are chemically neutral compounds, unlike many other catalyst and organocatalysts systems. In addition to their chemical stability, mild Lewis acidity, and non-toxic characteristics, chiral alkaline-earth-metal phosphates are clearly promising environmentally friendly catalysts. Therefore, the exploration of new applications for this catalytic system could be highly desirable and potentially important, if significant new reactions are developed that are amenable to selective catalysis with such complexes.

Chiral spirocylic oxindoles have been of particular interest to synthetic chemists in the past years, as they are the core structure of many important natural products and the spirocyclic oxindoles themselves are pharmaceutically interesting compounds.[5] One such compound is Gelsemine (Scheme 1), which contains a chiral spiro[cyclohexane-1,3′-oxindoline] as the core structure. There are several elegant and successful examples for the total synthesis of Gelsemine.[6] However, efficient methods for synthesizing this kind of six-membered spirooxindole by a catalytic asymmetric route are rare. In 1998, Overman et al. developed an interesting intramolecular asymmetric Heck coupling for forming this type of spirocyclic structure.[7] Recently, several excellent methods were reported for the synthesis of six-membered spirooxindoles by cascade reactions based on asymmetric organocatalysis. However, those spirooxindole products exclusively feature 2,6-*trans* substituted groups.[8] We proposed that a direct asymmetric D-A reaction between oxindole dieneophile **1** and Danishefsky's type **2** diene (Scheme 1) could provide rapid access to the 2,6-*cis*, six-membered spirooxindole **3**.[9] We expected to activate dienenophile **1** with chiral phosphate complexes of type **P** to introduce high enantioselectivities for this D-A reaction (**I**, Figure 1).



Scheme 1. Direct asymmetric D-A cycloaddition to a core structure of gelsemine.

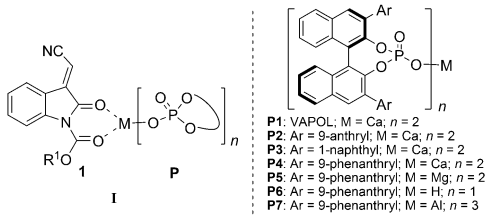


Figure 1. A proposed activation model with chiral alkaline-earth-metal phosphates. VAPOL = (*S*)-2,2′-diphenyl-(4-biphenanthrol).

We initiated our study by screening various chiral calcium phosphate catalysts (5 mol%) in hexanes for the asymmetric D-A reaction (ratio of **1a**/**2a** = 1:1.2). To our delight, the reaction smoothly gave the desired adduct **3a** in moderate to good yields (68–86%; Table 1, entries 1–4); however, extremely low enantioselectivities were obtained (1–24% *ee*). Subsequent evaluation of solvent effects with catalyst **P4** improved the *ee* to 52% when chloroform was used as the solvent (entry 7). Fortunately, the *ee* further increased to 76% and only a single diastereoisomer was obtained (99:1 d.r.; entry 8) when we turned our attention to magnesium phosphate catalyst **P5**.

We rescreened some common organic solvents with **P5** and found that chloroform still gave superior enantioselectivity (Table 1, entries 8–14), whereas several non-polar

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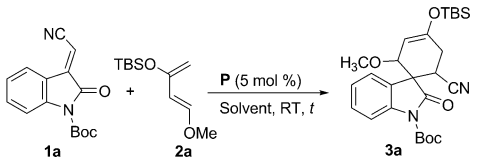
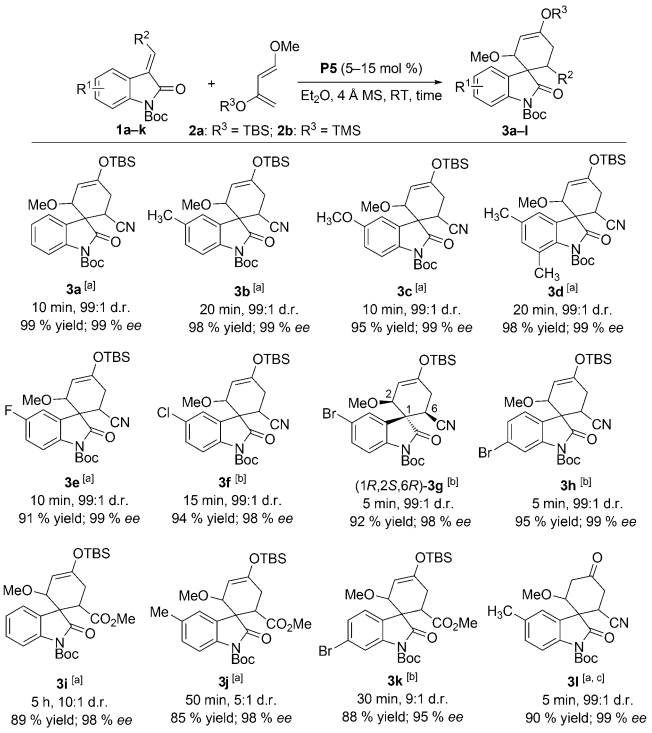
Table 1: Optimization of reaction conditions.



Entry	Catalyst	Solvent	*t*	Yield [%][a]	d.r.[a]	*ee* [%][b]
1	**P1**	hexanes	18 h	86	7:1	2
2	**P2**	hexanes	18 h	68	4:1	1
3	**P3**	hexanes	18 h	71	4:1	1
4	**P4**	hexanes	18 h	81	5:1	24
5	**P4**	toluene	18 h	83	4:1	0
6	**P4**	CH_2Cl_2	18 h	99	99:1	4
7	**P4**	$CHCl_3$	18 h	65	99:1	52
8	**P5**	$CHCl_3$	18 h	75	99:1	76
9	**P5**	toluene	18 h	75	4:1	−10
10	**P5**	CH_2Cl_2	18 h	98	99:1	0
11	**P5**	hexanes	18 h	73	5:1	−40
12	**P5**	CCl_4	18 h	93	20:1	3
13	**P5**	THF	18 h	99	3:1	13
14	**P5**	Et_2O	3 h	94	6:1	−24
15	**P6**	$CHCl_3$	18 h	99	2:1	0
16	**P5**[c]	$CHCl_3$	5 min	99	99:1	−90
17	**P5**[c]	hexanes	30 min	99	99:1	−96
18	**P5**[c]	**Et_2O**	**10 min**	**99**[d]	**99:1**	**−99**

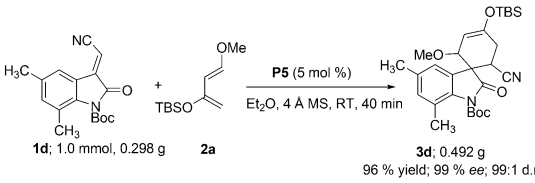
[a] Yield and d.r. were determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC analysis on a chiral stationary phase. [c] With 4 Å MS as an additive [d] Yield of isolated product.



Scheme 2. Substrate scope. The d.r. was determined by ^{1}H NMR analysis of the crude reaction mixture after the removal of ether. Yields are of isolated products. Enantioselectivity was determined by HPLC analysis on a chiral stationary phase. [a] Catalyst loading was 5 mol%. [b] Catalyst loading was 10 mol%. [c] TMS was removed after the D-A reaction; see the Supporting Information for details.

solvents were found to give moderate *ee* values, but with reversed optical rotation (entries 9, 11, and 14). Interestingly, a control experiment showed that the corresponding phosphoric acid **P6** afforded only racemic **3a** (entry 15). To our surprise, the activated 4 Å molecular sieves (MS) turned out to be an effective additive for this asymmetric D-A reaction (entries 16–18). In chloroform, full conversion was observed within less than 5 min, and the *ee* increased to 90% (entry 16).[10] Hexanes with 4 Å MS also provided enhanced stereoselectivity (96% *ee*, 99:1 d.r.; entry 17). Eventually, the best enantioselectivity was obtained when using ether as the solvent. Up to 99% *ee* and a quantitative yield of the desired cycloaddition product **3a** were obtained within 10 min (entry 18).

A series of experiments was performed to investigate the substrate scope for the asymmetric D-A reaction under the optimized reaction conditions. The results are summarized in Scheme 2. The reactions of oxindoles **1**, which bear electron-donating groups on the phenyl ring, afforded optically pure D-A cycloaddition products in nearly quantitative yields (95–99% yields, 99% *ee*, and 99/1 d.r.; **3a**–**3d**, Scheme 2). However, when there is an electron-withdrawing group such as a chlorine substituent on the phenyl ring, the *ee* decreased.[11] We assume that this is caused by a fast background reaction, as an electron-withdrawing group could render the dienenophile more reactive. Therefore, to suppress this negative effect the catalyst loading was increased to 10 mol%; as a result, the enantioselectivity improved to 98% (**3f**; Scheme 2). Under the same conditions, the reaction of other substrates with bromine also gave the corresponding spirooxindoles with high enantioselectivities (98% *ee*, **3g**; 99% *ee*, **3h**; Scheme 2). The D-A reaction could also be scaled up to 1.0 mmol with unchanged enantio- and diastereoselectivity [Eq. (1)].

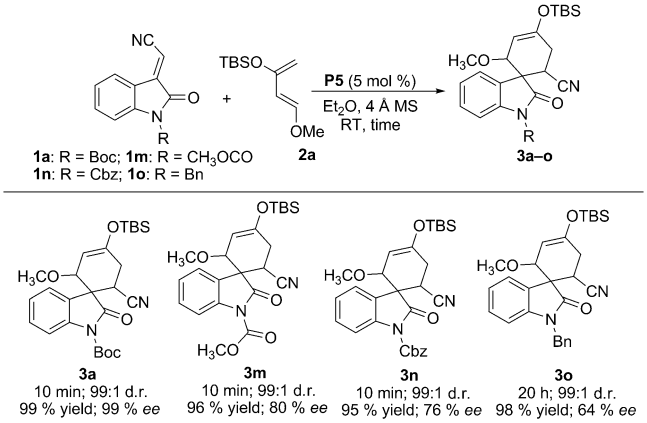


(1)

The chiral **P5**-catalyzed D-A reaction is quite general. Both cyano-substituted and the synthetically useful ester-substituted spirooxindoles were synthesized. As shown in Scheme 2, high yields and *ee* values were obtained for chiral spirooxindoles **3l**–**3k** (95–98% *ee*). Moreover, variation of the protecting group from *tert*-butyldimethylsilyl (TBS) to the smaller trimethylsilyl (TMS) has no effect on the reactivity or stereoselectivity (**3l**; 99% *ee*, 99:1 d.r.; Scheme 2). This asymmetric D-A reaction could be scaled up to 1.0 mmol of substrate without loss of yield or stereoselectivity [Eq. (1)]. Finally, the absolute configuration of the D-A adduct was determined to be 1*R*,2*S*, and 6*R* by single crystal X-ray

diffraction of **3g** (Scheme 5; for details, see the Supporting Information).

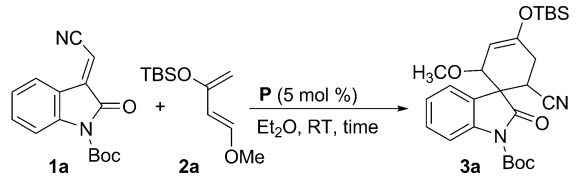
To obtain insight into the mechanism of the asymmetric D-A reaction, we prepared oxindole dienenophiles with different nitrogen protecting groups (**1a**–**1p**; Scheme 3).



Scheme 3. Substrate scope with variation of protecting groups. The d.r. was determined by ^{1}H NMR analysis of the crude reaction mixture. Yields are of isolated products. Enantioselectivity was determined by HPLC analysis on a chiral stationary phase. Bn = benzyl, Cbz = carboxybenzyl.

These experiments showed that the protecting group has a significant effect on this reaction; oxindoles with carbonyl-based protecting groups resulted in higher *ee* values than that of **1o**, a substrate with a benzyl group. These results suggest that the chiral magnesium phosphate catalyst may coordinate to the amide to induce enantioselectivity. While it is feasible that the Mg^{2+} would chelate with the carbonyl groups of the imide, a rigid six-membered-ring transition state would provide higher stereoselectivities (**I**, Figure 1).

Molecular sieves (MS) proved to be indispensable for obtaining high enantioselectivity in the reaction. Therefore, it is necessary to elucidate their role. Although the exact mechanism is not clear at this time, it is possible that metal cation exchange may happen in the presence of MS. If such an exchange really occurs, we assume that the active catalyst could be aluminum phosphate, as it is well known that MS consists of aluminosilicate minerals. However, in absence of 4 Å MS, aluminum phosphate **P7** produced low yield and stereoseletivity (31 % *ee* and 7:1 d.r.) in the D-A reaction. Chiral aluminum phosphate catalyst **P7** was also effective in this reaction in the presence of activated 4 Å MS (activated by flame-drying under vacuum; > 99 % yield, 98 % *ee*, and > 99:1 d.r.; Scheme 4a). Whereas, when in the presence of activated 4 Å MS, the D-A reaction catalyzed by **P5** gives quantitative yield and 99 % *ee*, when catalyzed by **P5** in the presence of unactivated 4 Å MS, the same reaction proceeded very sluggishly and afforded a much lower yield and low *ee* in 3 h (68 % yield, 10 % *ee*, 3.4:1 d.r.; Scheme 4b). In another experiment, **P5** and activated 4 Å MS were suspended in ether with stirring for 10 min, after that the MS were removed by filtration. The filtrate, containing **P5**, was then used to

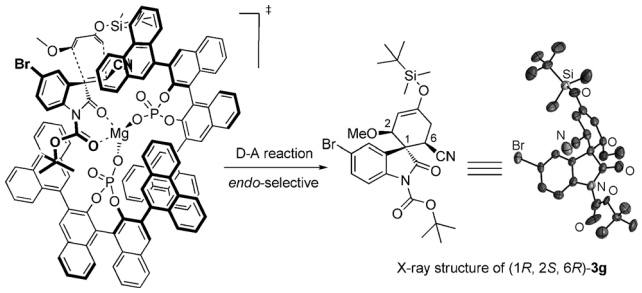


a) **P7** without 4 Å MS: 2 h; 7:1 d.r.; 81 % yield; 31 % *ee* *vs.* **P7** with activated 4 Å MS: 30 min; > 99:1 d.r.; > 99 % yield; 98 % *ee*

b) **P5** with unactivated 4 Å MS: 3 h; 3.4:1 d.r.; 68 % yield; 10 % *ee* *vs.* **P5** with activated 4 Å MS: 10 min; 99:1 d.r.; 99 % yield; 99 % *ee*

c) **P5** was stirred with activated 4 Å MS in Et_2O for 10 min, then 4 Å MS were filtered off. The filtrate with **P5** was used for the D-A reation; 10 min; 99:1 d.r., 99 % yield, 99 % *ee*.

Scheme 4. Studies on the function of molecular sieves in the asymmetric D-A reaction.



Scheme 5. Proposed transition state for the Mg phosphate catalyzed asymmetric D-A reaction.

catalyze another D-A reaction; as expected, the same results were obtained (Scheme 4c). This experiment may indicate that, once the hydrates from the magnesium complexes are removed, MS do not need to be present in the reaction.[12] Therefore, based on the above facts, it is possible that the function of MS is to remove water coordinated to magnesium. The hydrates decrease the Lewis acidity of the magnesium cations in the Mg phosphate through coordination, and change the conformation of the Mg^{II} intermediate from tetrahedral to octahedral.[13] As a result, lower reactivity and even reversed stereoselectivity were observed.

Based on the above results, a possible transition state can be proposed for the asymmetric D-A reaction catalyzed by chiral magnesium phosphate (Scheme 5). In the presence of Mg^{II} phosphate, the imide group of the oxindole coordinates with Mg^{2+} to form a tetrahedral intermediate in which the top face of the C=C bond is blocked by the 9-phenylanthryl group, while leaving the bottom open for the diene **2** to form *endo* adduct **3g**. On the other hand, the *tert*-butoxycarbonyl (Boc) group holds one of the other 9-phenylanthryl groups in position by steric hindrance. These facts could explain the stereoselectivity outcomes of the asymmetric D-A reaction catalyzed by **P5**.

In conclusion, we have developed a mild, environmentally friendly asymmetric D-A reaction catalyzed by a chiral

magnesium phosphate. This asymmetric D-A reaction provides direct access to six-membered ring spirooxindoles, which are found in the core structure of Gelsemine, as well as other compounds of pharmaceutical interest. A transition state is also proposed to account for the outcome of the D-A reaction, as well as the crucial function of the MS additive. Further studies on the mechanism and the extension of this method and its synthetic utility are in progress, and will be reported in due course.

Experimental Section

4 Å MS (50 mg) were added to a screw-cap reaction tube and flame dried in situ. Then substrate **1a** (6.8 mg, 0.025 mmol) and catalyst **P5** (1.8 mg, 5 mol%) were added, followed by the addition of anhydrous ether (1 mL). The resulting mixture was stirred at room temperature for 10 min. Then **2a** (7.2 μL, 0.03 mmol) was added via a syringe. The yellow color of the solution disappeared in about 1–2 min. The reaction was stirred for 10 min and then the solvent was removed under vacuum to give the crude product; the d.r. was determined from this crude mixture by ^{1}H NMR spectroscopy. The crude product was purified by flash chromatography (hexanes/ethyl acetate = 7:1) to give the pure D-A product **3a** (12.0 mg; 99% yield, 99:1 d.r., 99% *ee*). $[\alpha]_D^{20} = +53.8$ ($c = 0.565$, $CHCl_3$). HPLC analysis: Chiralcel AD-H (hexanes/*i*PrOH = 98:2, 1.0 mL min^{-1}), $t_{r\text{-major}}$ 6.6 min, $t_{r\text{-minor}}$ 11.0 min.

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[1] For reviews, see: a) D. A. Evans, J. S. Johnson in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, p. 1177; b) F. Fringuelli, A. Taticchi, *the Diels–Alder Reaction: Selected Practical Methods*, Wiley, New York, **2002**; c) K. Maruoka in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, p. 467; d) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019; e) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; f) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742–1773; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

[2] Selected recent examples of asymmetric D-A reactions: for metal catalysis, see: a) Y. Sudo, D. Shirasaki, S. Harada, A. Nishida, *J. Am. Chem. Soc.* **2008**, *130*, 12588–12589; b) A. Sakakura, R. Kondo, Y. Matsumura, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 17762–17764; c) C. Schotes, A. Mezzetti, *J. Am. Chem. Soc.* **2010**, *132*, 3652–3653; d) K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5625–5627; e) C. Schotes, M. Althaus, R. Aardoom, A. Mezzetti, *J. Am. Chem. Soc.* **2012**, *134*, 1331–1343; for organocatalysis, see: f) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422–2423; g) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 6736–6739; *Angew. Chem. Int. Ed.* **2008**, *47*, 6634–6637; h) C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem.* **2008**, *120*, 9376–9379; *Angew. Chem. Int. Ed.* **2008**, *47*, 9236–9239; i) L. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332–7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199; j) J. N. Payette, H. Yamamoto, *Angew. Chem.* **2009**, *121*, 8204–8206; *Angew. Chem. Int. Ed.* **2009**, *48*, 8060–8062; k) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607; l) Z. Jia, H. Jiang, J. Li, B. Gschwend, Q. Li, X. Yin, J. Grouleff, Y. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061; m) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem.* **2011**, *123*, 8797–8800; *Angew. Chem. Int. Ed.* **2011**, *50*, 8638–8641; n) B. Tan, G. Hernandez-Torres, C. F. Barbas, *J. Am. Chem. Soc.* **2011**, *133*, 12354–12357; o) Y.-K. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212–15218; p) N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto, M. Terada, *J. Am. Chem. Soc.* **2011**, *133*, 19294–19297; q) Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang, L.-Z. Gong, *J. Am. Chem. Soc.* **2012**, *134*, 6532–6535; r) J. Guin, C. Rabalakos, B. List, *Angew. Chem.* **2012**, *124*, 8989–8993; *Angew. Chem. Int. Ed.* **2012**, *51*, 8859–8863.

[3] For reviews on chiral alkaline earth metal catalysis, see: a) Y. Yamashita, T. Tsubogo, S. Kobayashi, *Chem. Sci.* **2012**, *3*, 967–975; b) A. Parra, S. Reboredo, A. M. Martín Castro, J. Alemán, *Org. Biomol. Chem.* **2012**, *10*, 5001–5020; c) S. Kobayashi, Y. Yamashita, *Acc. Chem. Res.* **2010**, *44*, 58–71; d) M. Hatano, K. Ishihara, *Synthesis* **2010**, 3785–3801; e) U. Kazmaier, *Angew. Chem.* **2009**, *121*, 5902–5904; *Angew. Chem. Int. Ed.* **2009**, *48*, 5790–5792.

[4] For pioneering work, see: a) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911–3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826; for our recent work, see: b) Z. Zhang, W. Zheng, J. C. Antilla, *Angew. Chem.* **2011**, *123*, 1167–1170; *Angew. Chem. Int. Ed.* **2011**, *50*, 1135–1138; c) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339–3341; for work from other groups, see: d) F. Lalli, C. Drouet, H. Liu, G. Masson, J. Zhu, *Org. Lett.* **2011**, *13*, 94–97; e) M. Rueping, T. Bootwicha, S. Kambutong, E. Sugiono, *Chem. Asian J.* **2012**, *7*, 1195–1198; for the earliest study on a hetero-D-A reaction catalyzed by a chiral Yb^{III} binol phosphate, see: f) T. Hanamoto, H. Furuno, Y. Sufimoto, J. Inanaga, *Synlett* **1997**, 79–80; for pioneering work on chiral Ag binol phosphate catalysis, see: g) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499.

[5] For a review, see: a) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758–766; b) S. S. Girija, Y. D. Zelalem, *Chem. Rev.* **2012**, 112, 6104–6155; for selected reports, see: c) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155; d) M. M. C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086; e) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130–10131; f) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758; g) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825; h) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735–740; i) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 1255–1257; j) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328–15333; k) B. Tan, N. R. Candeias, C. F. Barbas, *Nat. Chem.* **2011**, *3*, 473–477; l) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 9290–9293; *Angew. Chem. Int. Ed.* **2011**, *50*, 9124–9127; m) N. V. Hanhan, N. R. Ball-Jones, N. T. Tran, A. K. Franz, *Angew. Chem.* **2012**, *124*, 1013–1016; *Angew. Chem. Int. Ed.* **2012**, *51*, 989–992; n) T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem.* **2012**, *124*, 2498–2501; *Angew. Chem. Int. Ed.* **2012**, *51*, 2448–2451; o) J. Dugal-Tessier, E. A. O'Bryan,

T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 5047 – 5051; *Angew. Chem. Int. Ed.* **2012**, *51*, 4963 – 4967.

[6] For a review of the total synthesis of gelsemine, see: a) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38 – 53; *Angew. Chem. Int. Ed.* **2003**, *42*, 36 – 51; for recent examples, see: b) W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18046 – 18053; c) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18054 – 18065; d) X. Zhou, T. Xiao, Y. Iwama, Y. Qin, *Angew. Chem.* **2012**, *124*, 4993 – 4996; *Angew. Chem. Int. Ed.* **2012**, *51*, 4909 – 4912.

[7] A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6488 – 6499.

[8] a) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336 – 7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200 – 7203; b) Q. Wei, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 1008 – 1011; c) K. Jiang, Z.-J. Jia, S. Chen, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852 – 2856; d) Y.-B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao, X.-W. Wang, *Org. Lett.* **2011**, *13*, 4866 – 4869.

[9] The excellent work on the asymmetric D-A reaction by Barbas et al. inspired us to believe that this proposal would be practical, see Ref. [2n].

[10] This phenomenon was also observed by others; for selected examples, see: a) G. Desimoni, G. Faita, A. Gamba Invernizzi, P. Righetti, *Tetrahedron* **1997**, *53*, 7671 – 7688; b) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 5483 – 5488, and references therein.

[11] A 78% *ee* was obtained. This result is not listed in Scheme 2.

[12] We thank one of the reviewers for suggesting this experiment to us.

[13] It is well known that Mg^{2+} tends towards an octahedral coordination with oxygen ligands such as water.

