

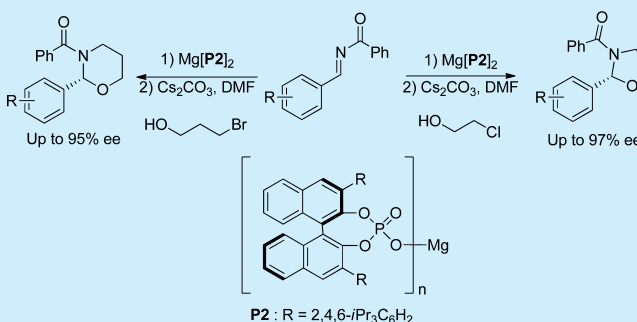
Asymmetric One-Pot Synthesis of 1,3-Oxazolidines and 1,3-Oxazinanes via Hemiaminal Intermediates

Sri Krishna Nimmagadda, Zuhui Zhang, and Jon C. Antilla*

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue, CHE205A, Tampa, Florida 33620, United States

Supporting Information

ABSTRACT: A highly efficient method for the enantioselective one-pot synthesis of 1,3-oxazolidines and 1,3-oxazinanes has been reported. The reaction proceeds via the formation of hemiaminal intermediates obtained by the enantioselective addition of respective alcohols to imines catalyzed by a chiral magnesium phosphate catalyst, followed by intramolecular cyclization under mildly basic conditions. A wide range of substrates have been converted to the respective chiral heterocyclic products in high yields and with excellent enantioselectivities using this one-pot procedure.



Chiral oxazolidines are important structural moieties that exist in many biologically active compounds.¹ The 1,3-oxazolidine ring is present in polycyclic tetrahydroisoquinoline alkaloids such as quinocarin and its analogue terazomine, both of which have antitumor activity.^{1,2} They are widely used in asymmetric synthesis³ as chiral auxiliaries^{3a} in reactions that include cyclopropanation,^{3b} Grignard reaction,^{3c} epoxidation,^{3d} 1,3-dipolar cycloadditions,^{3e} intramolecular Diels–Alder reaction,^{3f} and hydrogenation.^{3g} 1,3-Oxazolidines are also used as chiral ligands for transition metal catalysts in asymmetric catalysis.⁴ Generally, oxazolidines are prepared by the condensation of chiral 1,2-amino alcohols with aldehydes, ketones, or oxo compounds.⁴ These methods involve the use of chiral reagents and stoichiometric equivalents of catalysts. Yoon et al. described copper catalyzed aminohydroxylation of styrenes and oxyamination of olefins using an iron catalyst for the enantioselective synthesis of 1,3-oxazolidines.⁵ Recently, Jarvo et al. developed transition metal catalyzed stereospecific and stereoconvergent methods to synthesize chiral 1,3-oxazolidines.⁶ In addition, Du and co-workers reported rhodium catalyzed cycloaddition reactions of racemic butadiene monoxide with imines.⁷ Wang et al. proposed an interesting approach to synthesize benzoxazoles via organocatalytic [4 + 1] annulation, but with poor enantiocontrol.⁸ Herein, we report the chiral magnesium phosphate catalyzed asymmetric one-pot synthesis of chiral 1,3-oxazolidines with high yields and excellent enantioselectivity.

Over the past decade, chiral phosphoric acids⁹ and metal complexes of chiral phosphates¹⁰ have been used as effective catalysts in various asymmetric transformations.¹¹ In 2008, our group reported the enantioselective addition of alcohols to imines using 3,3'-9-anthryl-BINOL phosphoric acid.¹² To further expand the utility of this methodology, we envisioned the possible synthesis of chiral 1,3-oxazolidines (Figure 1) by

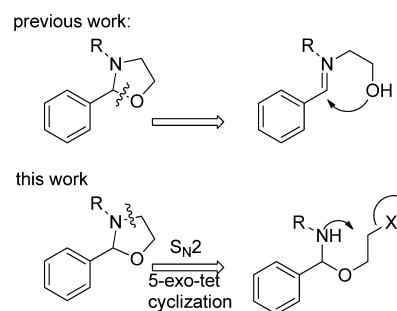


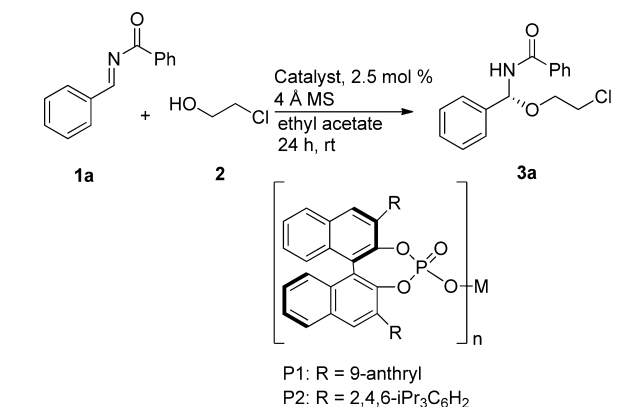
Figure 1.

cyclization through intramolecular nucleophilic substitution in 5-exo-tet fashion, in accordance with Baldwin's rules.¹³

Intrigued by the reports of Ishihara,^{10a–c} List,^{10d} and the recent results from our group on chiral BINOL phosphates,^{10e–h,k} we initiated optimization of the catalyst with the use of chiral phosphoric acids and their metal phosphate complexes as possible catalysts. Interestingly, 9-anthryl derived BINOL phosphoric acid gave a very low ee (Table 1, entry 1). This prompted us to explore alkali and alkaline-earth metal complexes of chiral phosphates. Ca[P1]₂ gave a good yield but showed very poor selectivity (Table 1, entry 2), while with Mg[P1]₂ the product is formed with high yield and enantioselectivity. We observed that a 3,3'-triisopropyl derived BINOL phosphate metal complex also gave the product in high yield and enantioselectivity. Clearly, Mg[P2]₂ has proven to be the best catalyst (Table 1, entry 5) with excellent selectivity, whereas Ca, Li, Al, Zn, Sr complexes of the 3,3'-triisopropyl

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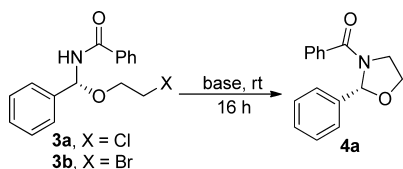
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Table 1. Optimization of Reaction Conditions^a

entry	catalyst	yield (%) ^b	ee (%) ^c
1	H[P1]	73	7
2	Ca[P1] ₂	91	10
3	Mg[P1] ₂	90	95
4	Ca[P2] ₂	70	68
5	Mg[P2] ₂	90	97
6	Li[P2] ₂	94	66
7	Al[P2] ₃	90	40
8	Zn[P2] ₂	95	74
9	Sr[P2] ₂	98	74

^aReaction conditions: **1a** (1.0 equiv), **2** (2.0 equiv), 2.5 mol % catalyst, ethyl acetate (1 mL), and 4 Å MS 40 mg/mL. ^bIsolated yield.

^cDetermined by chiral HPLC analysis.

Table 2. Optimization of Reaction Conditions for the Intramolecular Cyclization^a

entry	X	base	yield (%) ^b	ee of 3 (%) ^c	ee of 4a (%) ^c
1	Cl	K ₃ PO ₄	10	95	ND
2	Cl	DBU	0	95	ND
3	Cl	Cs ₂ CO ₃	0	95	ND
4	Br	DMAP	0	65	ND
5	Br	DBU	82	65	22
6	Br	KOtBu	86	65	57
7	Br	Cs ₂ CO ₃	90	65	65
8 ^d	Cl	KOtBu	71	95	84
9 ^{e,f}	Cl	Cs ₂ CO ₃	97	93	93

^aReaction Conditions: **3** (1.0 equiv), base (4.0 equiv), ethyl acetate.

^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dTHF used as solvent. ^eDMF used as solvent. ^fBase added at 0 °C.

derived BINOL phosphate showed moderate enantioselectivities (entries 4, 6–9).

A brief screening of bases was performed for the intramolecular cyclization of **3a**. We observed that K₃PO₄, DBU, and Cs₂CO₃ in ethyl acetate did not lead to the cyclized product **4a**. By using the more reactive substrate **3b** with bromide as the leaving group, the desired transformation was provided with bases DBU and KOtBu in good yields. But the highest enantioselectivity we observed for **3b** was 65% (Table

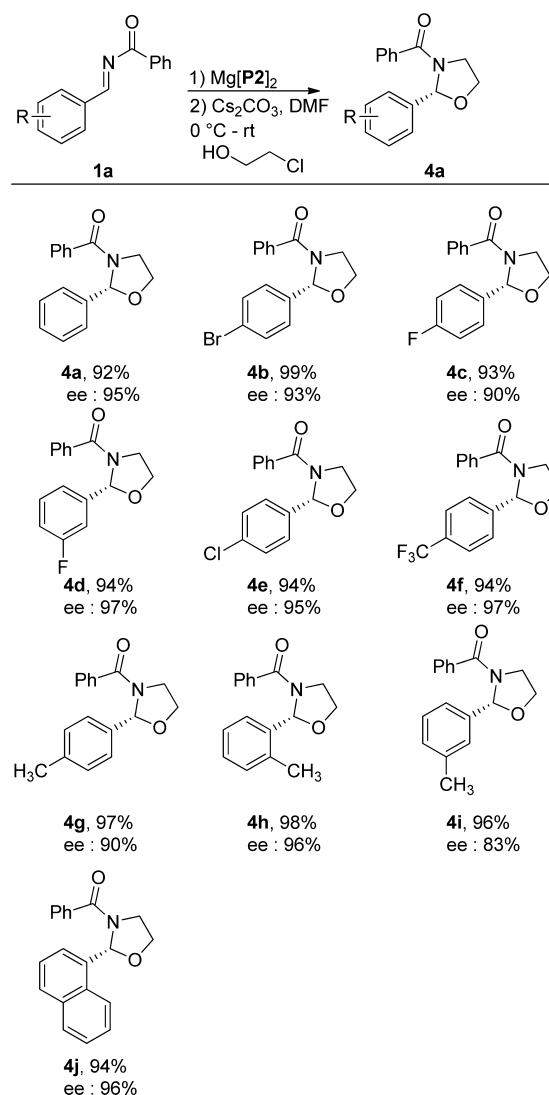


Figure 2. Catalytic asymmetric synthesis of 1,3-oxazolidines. Experimental conditions: **1a** (1.0 equiv), **2** (2.0 equiv), 2.5 mol % catalyst, ethyl acetate, and 4 Å MS 40 mg/mL. Ethyl acetate was removed before step 2, and DMF and Cs₂CO₃ (2.0 equiv) were added. All yields are isolated. The ee was determined by chiral HPLC analysis.

2, entries 5,6). Interestingly, Cs₂CO₃ gave product **4a** in high yield retaining the selectivity (Table 2, entry 7).

To our delight, optimization of solvents using **3a** with bases of varied strength furnished the desired product in good yield. With KOtBu as the base the reaction showed little loss in selectivity, whereas Cs₂CO₃ at 0 °C produced **4a** in high yield with retention of selectivity. Presumably, a strong base would also interact with the acidic proton on carbon and hence lower the selectivity of the cyclized product. Clearly, cyclization of **3a** using Cs₂CO₃ in DMF is the ideal condition for the formation of **4a** in high yield with excellent enantioselectivity (entry 9).

To further investigate the scope of this reaction in one pot, we performed the reaction from **3a** to **4a** in ethyl acetate as solvent. Unfortunately, the reaction did not proceed to completion (Table 2, entry 3). Alternatively, we tried the transformation from **1a** to **3a** in DMF using optimized conditions, but a racemic product was obtained. On the basis of these observations, after formation of **3a**, we concentrated the reaction by removing the solvent and then added DMF and

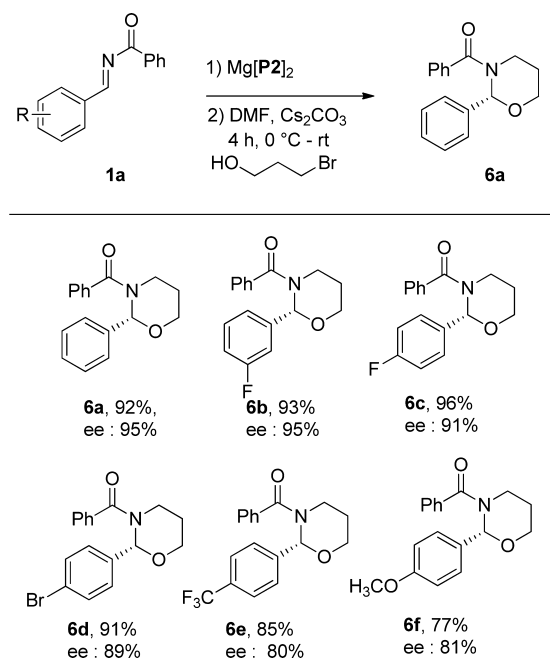


Figure 3. Catalytic asymmetric synthesis of 1,3-oxazinan-2-ones. Experimental conditions: **1a** (1.0 equiv), **5** (2.0 equiv), 5 mol % catalyst, ethyl acetate, and 4 Å MS 40 mg/mL. Ethyl acetate was removed before step 2, and DMF and Cs₂CO₃ (2.0 equiv) were added. All yields are isolated. The ee was determined by chiral HPLC analysis.

Cs₂CO₃. Compound **4a** was then obtained in one pot in high yield with excellent retention of enantioselectivity.

Under the optimized conditions, we examined a wide variety of imine substrates. The products were obtained in good yield with excellent enantioselectivities (Figure 2). The results showed that the substituents, both electron-donating and -withdrawing groups, at the *para* position on the phenyl ring of imines had little effect on the enantioselectivity. Electron-withdrawing groups at the *meta* position on the phenyl ring (**4d**) showed excellent selectivity compared to the electron-releasing methyl group (**4i**). The absolute configuration was determined by HPLC comparison of the product **3a** to the literature.¹¹

We further envisaged the possible synthesis of chiral 1,3-oxazinan-2-ones¹⁴ using the optimized methodology. The hemiaminal intermediate formed by the addition of 3-chloropropanol to **1a** was obtained with high selectivity, but after cyclization with Cs₂CO₃ a racemic product was observed. A series of experiments were conducted with 3-chloropropanol using different bases and different temperature variations which showed no effect on retaining selectivity. To our delight, the use of more reactive 3-bromopropanol favored the formation of six membered products with moderate to good enantioselectivities and high yields. Both electron-releasing and -withdrawing substituents on the phenyl ring were tolerated (Figure 3).

In summary, the one-pot synthesis of chiral 1,3-oxazolidin-2-ones and chiral 1,3-oxazinan-2-ones by 9-anthryl derived chiral BINOL magnesium phosphate catalyzed enantioselective addition of alcohol to imines followed by 5-*exo-tet* cyclization and 6-*exo-tet* cyclization of hemiaminal intermediates under mild basic conditions has been successfully achieved with high yields and excellent enantioselectivities.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental conditions, characterization data, and spectra for all compounds. This material is available for free of charge via Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jantilla@usf.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For a review on tetrahydroisoquinoline natural products, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
- (2) (a) Williams, R. M.; Glinka, T.; Flanagan, M. E.; Gallegos, R.; Coffman, H.; Pei, D. J. *Am. Chem. Soc.* **1992**, *114*, 733. (b) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268.
- (3) For selected examples, see: (a) Agami, C.; Couty, F. *Eur. J. Org. Chem.* **2004**, 677. (b) Bernardi, A.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1989**, *30*, 3733. (c) Isobe, M.; Hirose, Y.; Shimokawa, K.; Nishikawa, T.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 5499. (d) Cardani, S.; Gennari, C.; Scolastico, C.; Villa, R. *Tetrahedron* **1989**, *45*, 7397. (e) Lacoste, J.-E.; Soucy, C.; Rochon, F. D.; Breau, L. *Tetrahedron Lett.* **1998**, *39*, 9121. (f) Jung, M. E.; Street, L. J. *Heterocycles* **1988**, *27*, 45. (g) Bernardi, A.; Carugo, O.; Pasquarello, A.; Sidjimov, A.; Poli, G. *Tetrahedron* **1991**, *47*, 7357.
- (4) For review, see: Wolf, C.; Xu, H. *Chem. Commun.* **2011**, 47, 3339.
- (5) (a) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610. (b) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, 5118. (c) Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 4570. (d) Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2012**, *134*, 12370.
- (6) Shaghafi, M. B.; Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 5188.
- (7) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154.
- (8) Song, A.; Chen, X.; Song, X.; Zhang, X.; Zhang, S.; Wang, W. *Org. Lett.* **2013**, *15*, 2510.
- (9) For selected reviews, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Doyle, A. D.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Terada, M. *Chem. Commun.* **2008**, 4097. (e) Terada, M. *Synthesis* **2010**, 1929. (f) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (g) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (h) Rueping, M.; Kuenkel, A.; Atodiressei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.
- (10) (a) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Syn. Catal.* **2008**, *350*, 1776. (b) Shen, K.; Liu, X.; Cai, Y.; Lin; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 6008. (c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823. (d) Klusmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189. (e) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135. (f) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339. (g) Ingle, G. K.; Liang, Y.; Mormino, M.; Li, G.; Fronczek, F. R.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2054. (h) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188. (i) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389. (j) Shi, S.; Huang, F.; Zhu, P.; Dong, Z.; Hui, X. *Org. Lett.* **2012**, *14*, 2010. (k) Li, G.; Liang, T.; Wojtas, L.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 4628.

- (11) For a recent review, see: Yamashita, Y.; Tsubogo, T.; Kobayashi, S. *Chem. Sci.* **2012**, 3, 967.
- (12) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, 130, 12216.
- (13) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
- (14) For synthesis and biological importance of 1,3-oxazinanes, see: (a) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, 42, 4837. (b) Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, 3, 34. (c) Diness, F.; Beyer, J.; Meldal, M. *QSAR Comb. Sci.* **2004**, 23, 130. (d) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, 70, 1897. (e) Zanatta, N.; Squizani, A. M. C.; Fantinel, L.; Nachtigall, F. M.; Borchhardt, D. M.; Bonacorso, H. G.; Martins, M. A. P. *J. Brazil. Chem. Soc.* **2005**, 16, 1255. (f) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, 48, 4373. (g) D'hooghe, M.; Dekeukeleire, S.; Mollet, K.; Lategan, C.; Smith, P. J.; Chibale, K.; Kimpe, N. D. *J. Med. Chem.* **2009**, 52, 4058.