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A Highly Selective, Organocatalytic Route to Chiral Dihydro-1,2-oxazines

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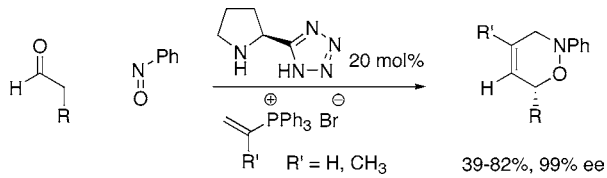
ABSTRACT



The organocatalyzed asymmetric synthesis of chiral dihydro-1,2-oxazines from achiral starting materials proceeds in moderate to excellent yields and excellent enantioselectivity. This sequential reaction gives the desired products in a single pot.

The synthesis of enantiomerically pure 1,2-oxazines represents an interesting challenge because there is a scarcity of methods for their preparation.[1] This unit is present in biologically active natural products[2] (Figure 1) and is an amino-heterocycle with potential as a medicinal scaffold, as well as scope for further elaboration.[3] Achieving an efficient and selective method for the preparation of this group is therefore a valuable goal. In general two routes to this class of molecule are used. They are the [4 + 2] cycloaddition between nitroso compounds and dienes and the ring-closing metathesis of suitable precursors. However, the reaction of nitroso compounds with dienes can suffer from poor regiocontrol and is inherently racemic without control induced by chiral substituents[4] or chiral auxiliaries.[5] Ring-closing metathesis is also useful in that regio- and stereocontrol can be imparted from chiral starting materials, although it can be somewhat protracted as a result.[6] Elegant new methods for the synthesis of tetrahydro-1,2-oxazine derivatives have been achieved with either diastereoselective[7] or enantio-

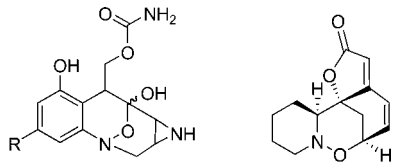


Figure 1. Natural products containing the 1,2-oxazine functionality.

(1) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149.

(2) (a) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145. (b) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (c) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (d) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594. (e) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 600. (f) Hirai, O.; Shimomura, K.; Mizota, T.; Matsumoto, S.; Mori, J.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 607. (g) Hori, Z.; Yamauchi, M.; Imanishi, T.; Parello, J.; Hanaoka, M.; Munavall, S. *Tetrahedron Lett.* **1972**, 1877.

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(4) (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (b) Streith, J.; Defoin, A. *Synlett* **1996**, 189. (c) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(5) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2003**, *32*, 582.

(6) (a) Le Flohic, A.; Meyer, C.; Cossy, J.; Desmurs, J. R. *Tetrahedron Lett.* **2003**, *44*, 8577. (b) Yang, Y. K.; Tae, J. *Synlett* **2003**, 2017. (c) Yang, Y. K.; Tae, J. *Synlett* **2003**, 1043. (d) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398.

(7) (a) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (b) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554. (c) Miyata, O.; Namba, M.; Ueda, M.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1274. (d) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.

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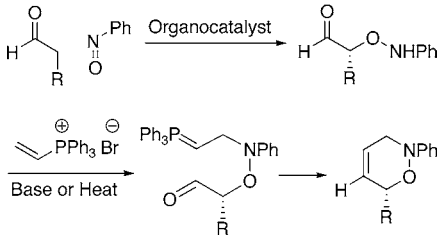
selective control.[8] Despite these notable examples, the catalytic synthesis of *chiral* nonracemic 1,2-oxazines from commercially available *achiral* starting materials is not known. Here we describe such a process: a multicomponent reaction sequence to produce dihydro-1,2-oxazines, which proceeds with excellent enantio- and regioselectivity.

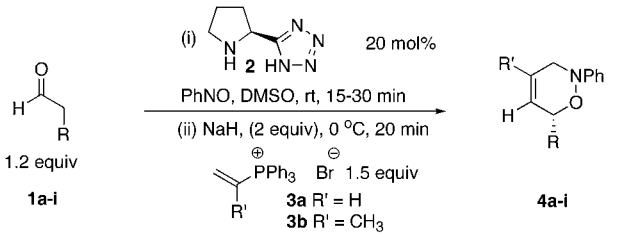
It was envisaged that α-oxyamination of an enamine intermediate with nitrosobenzene[9−12] could be followed by nucleophilic attack on a vinyl phosphonium salt, which would subsequently form a dihydro-1,2-oxazine through an intramolecular Wittig process[13] (Scheme 1).

Scheme 1. Projected Synthesis of Chiral Dihydro-1,2-oxazines



Initial work centered on conditions most appropriate for the organocatalytic α-oxyamination reaction, while remaining suitable to carry out the following steps in a single pot. We therefore chose conditions similar to those first developed by Zhong,[10] as only a small excess of aldehyde partner was required. Studies were carried out with isovaleraldehyde, owing to the good yields achieved in α-oxyamination reactions. Following α-oxyamination, attempts to effect conjugate addition based upon thermally inducing the reaction were unsuccessful, and addition through a base-mediated reaction was subsequently investigated. Pleasingly, after optimization, it was found that addition of 2 equivalents of

Table 1. Synthesis of Dihydro-1,2-oxazines Catalyzed by L-Pyrrolidinyl-tetrazole **2**



entry	aldehyde	dihydro-1,2-oxazine	yield[a] (ee)[b] %
1	**1a**	**4a**	71, (99)
2	**1b**	**4b**	50, (99)[c]
3	**1c**	**4c**	45, (99)[c]
4	**1d**	**4d**	39, (99)[c]
5	**1e**	**4e**	44, (99)
6	**1f**	**4f**	50, (99)
7	**1g**	**4g**	40, (99)
8	**1h**	**4h**	82, (99)
9	**1i**	**4i**	53, (99)[d]

[a] Isolated yields of chromatographed material. [b] The ee values were determined directly by chiral HPLC. [c] The ee was determined by chiral HPLC following N−O bond cleavage. [d] The ee was determined directly by chiral GC.

NaH gave excellent conversion (71% yield) and showed excellent enantioselectivity (99% ee).

The absolute configuration was assigned by comparison with the α-oxyamination of isovaleraldehyde with L-proline by Zhong, where the absolute configuration was determined unambiguously.[10] Pyrrolidinyl-tetrazole **2**, developed independently by our group,[14] Yamamoto,[12] and Arvidsson,[15] was found to be the optimum catalyst tested in this process.[11,16] With this information in hand, the scope of this reaction was

(8) Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764.

(9) (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (d) Casas, J.; Sunden, H.; Cordova, A. *Tetrahedron Lett.* **2004**, *45*, 6117. (e) Cheong, P. H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912. (e) Cordova, A.; Sunden, H.; Bogevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673. (f) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. (g) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966. (h) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (i) Ibrahem, I.; Casas, J.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (j) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317. (k) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. (l) Wang, W.; Wang, J.; Li, H.; Liao, L. X. *Tetrahedron Lett.* **2004**, *45*, 7235. (m) Zhong, G.; Yu, Y. P. *Org. Lett.* **2004**, *6*, 1637. (n) Zhong, G. *Chem. Commun.* **2004**, 606. (o) Engqvist, M.; Casas, J.; Sunden, H.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 2053. (p) Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1577. (q) Sunden, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3385. (r) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.

(10) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247.

(11) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374.

(12) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.

(13) Schweizer, E. E.; Hayes, J. E.; Hanawalt, E. M. *J. Org. Chem.* **1985**, *50*, 2591.

(14) (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (b) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

(15) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.

(16) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962.

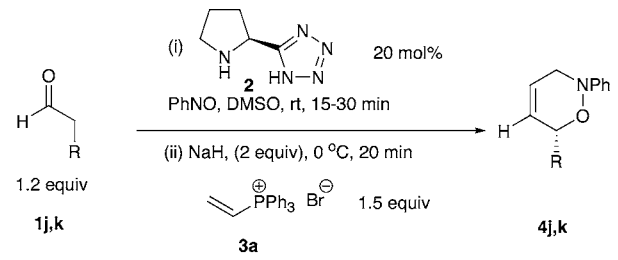
then assessed using catalyst **2** and a range of aldehydes (Table 1).

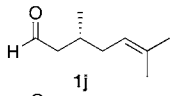
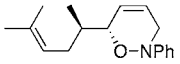
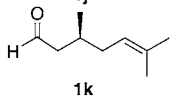
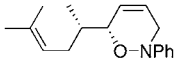
Interestingly linear aldehydes gave yields lower than those of branched derivatives. This is thought to be related to the ease of homo-aldol coupling and potential side reactions of the products. Increasing the number of equivalents of aldehyde tended to reduce the overall yield, supporting the hypothesis that aldol products may interfere with the reaction. The increasing yields observed as substitution of the aldehyde increases (39% for **4d**, 71% for **4a**, and 82% for **4h**) may also suggest homo-aldol processes are competitive, as greater substitution should disfavor homo-aldol reactions.

The reaction was then extended to the synthesis of a more substituted dihydro-1,2-oxazine. Phosphonium salt **3b** was reacted under standard conditions to give the desired dihydro-1,2-oxazine **4i** in 53% yield and 99% ee, proving that access to trisubstituted allylic alcohols could be achieved following N−O bond reduction.

Finally, we investigated the matched/mismatched effects by using citronellal as a chiral aldehyde to create dihydro-1,2-oxazines with pendant chirality. Although yields are similar, diastereoselectivity did differ with a diastereomeric ratio of 11:1 observed for the mismatched case (entry 1, Table 2). Interestingly, with L-proline as catalyst, only a trace of **4k** was observed using the matched coupling partner.

Table 2. Synthesis of Dihydro-1,2-oxazines from Citronellal

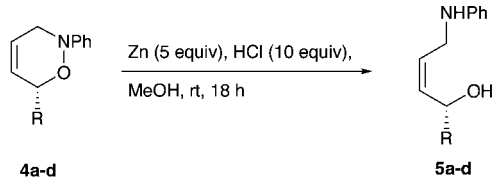


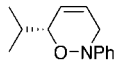
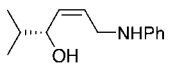
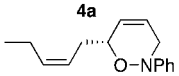
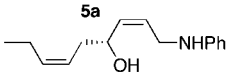
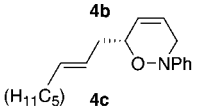
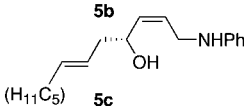
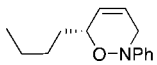
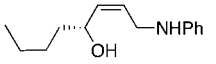
entry	aldehyde	dihydro-1,2-oxazine	yield[a] (de)[b] %
1	 1j	 4j	67, (83)
2	 1k	 4k	61, (99)

[a] Isolated yields of chromatographed material. [b] The de values were determined directly by crude ^{1}H NMR.

Cleavage of the N−O bond to liberate the free allylic alcohol was then accomplished in high yield using zinc in methanolic HCl (Table 3). Upon N−O cleavage, enantiopurity and side chain geometry were retained (entries 2 and 3).

Table 3. Synthesis of *cis*-Allylic Alcohols through N−O Cleavage



entry	dihydro-1,2-oxazine	*cis*-allylic alcohol	yield[a] (ee)[b] %
1	 4a	 5a	83, (99)
2	 4b	 5b	92, (99)
3	 4c	 5c	83, (99)
4	 4d	 5d	96, (99)

[a] Isolated yields of chromatographed material. [b] The ee values were determined directly by chiral HPLC.

In summary, a new one-pot synthesis of chiral dihydro-1,2-oxazines from achiral starting materials has been developed. The products undergo facile N−O reduction to give *cis*-allylic alcohols. We are now investigating the extension of this methodology to supply tetrasubstituted dihydro-1,2-oxazines and further synthetic applications of these dihydro-1,2-oxazines and allylic alcohols shall be reported in due course.

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Supporting Information Available: Detailed experimental procedure and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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