Communications

Dynamic Kinetic Resolutions Catalyzed by a Planar-Chiral Derivative of DMAP: Enantioselective Synthesis of Protected α-Amino Acids from Racemic Azlactones

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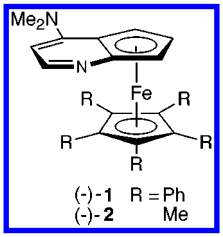
Due to the widespread occurrence of α-amino acids in biologically active compounds, the development of efficient methods for their enantioselective synthesis is a challenge of considerable practical importance.[1] To date, approaches that employ stoichiometric chiral auxiliaries have been the primary focus of attention, although several effective catalytic methods have also been reported, perhaps most notably the metal-catalyzed asymmetric hydrogenation of dehydroamino acids.[2]

One straightforward route to the synthesis of protected α-amino acids involves the ring opening of azlactones by alcohols or by water. Because of the propensity of azlactones to racemize (pK_a ~9),[3] this process is especially interesting from the standpoint of asymmetric catalysis, since a dynamic kinetic resolution (deracemization)[4] should be possible (Figure 1). Indeed, proof-of-principle for this strategy has been established using enzymes.[5]



4-(Dimethylamino)pyridine (DMAP) is an effective catalyst for the ring opening of azlactones by alcohols. We recently described the synthesis and resolution of two planar-chiral derivatives of DMAP (**1** and **2**), and we demonstrated the efficiency of enantiopure **1** as a catalyst for the kinetic resolution of secondary alcohols.[6] In this paper, we report the application of enantiopure **2** to the deracemization/ring opening of azlactones.

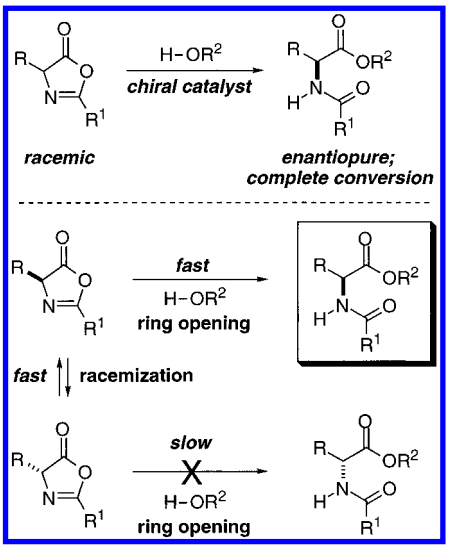
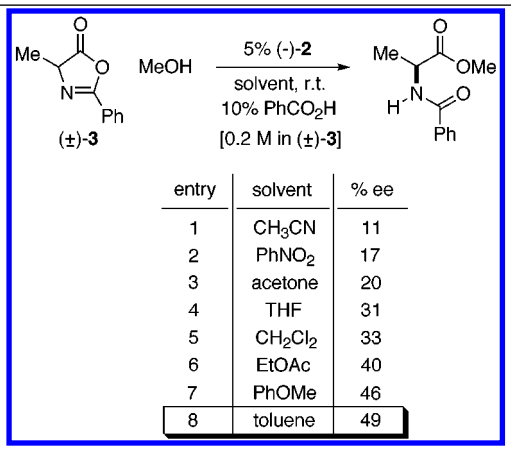


Figure 1. Dynamic kinetic resolution in the ring opening of azlactones.

Table 1. Dynamic Kinetic Resolution: Solvent Effect on Enantioselectivity



entry	solvent	% ee
1	CH_3CN	11
2	$PhNO_2$	17
3	acetone	20
4	THF	31
5	CH_2Cl_2	33
6	EtOAc	40
7	PhOMe	46
8	toluene	49

In initial studies, we determined that, like DMAP itself, planar-chiral DMAP analogue **2** catalyzes the addition of alcohols to azlactones and that racemization occurs rapidly relative to ring opening (eq 1).[7] With regard to the central issue of stereoselectivity, we investigated the methanolysis of (±)-**3**, and we established that enantiopure (−)-**2** catalyzes the dynamic kinetic resolution of this azlactone, preferentially affording the L-alanine derivative (Table 1). The level of enantioselectivity is solvent-dependent, with toluene furnishing the highest ee (entry 8, 49% ee).

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(2) (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106−112. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 1. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2.

(3) (a) de Jersey, J.; Zerner, B. *Biochemistry* **1969**, *8*, 1967−1974. (b) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918−2922. (c) Benoiton, N. L. *The Peptides*; Academic: New York, 1983; Vol. 5, Chapter 4.

(4) (a) Stecher, H.; Faber, K. *Synthesis* **1997**, 1−69. (b) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447−456. (c) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490. (d) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56.

(5) (a) Pugniere, M.; Kraicsovits, F.; Coletti-Previero, M.-A.; Previero, A. *Biotech. Lett.* **1985**, *7*, 641−646. (b) Bevinakatti, H. S.; Newadkar, R. V.; Banerji, A. A. *J. Chem. Soc., Chem. Commun.* **1990**, 1091−1092. (c) Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R.-L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252−3258. (d) Turner, N. J.; Winterman, J. R.; McCague, R.; Parratt, J. S.; Taylor, S. J. C. *Tetrahedron Lett.* **1995**, *36*, 1113−1116.

(6) (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. In press. See also: Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231.

(7) We inadvertently discovered that the presence of benzoic acid leads to ring opening of the azlactone at a faster rate and with higher enantioselectivity than in the absence of benzoic acid (with no benzoic acid: <2% ee for the ring opening of (±)-**3** with MeOH catalyzed by (−)-**2**).

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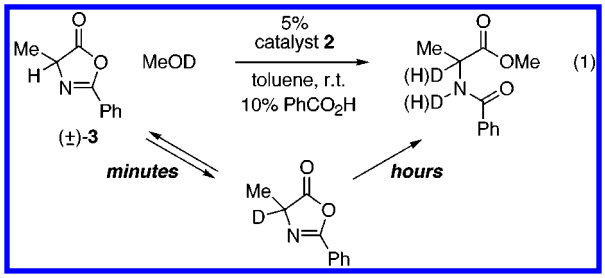
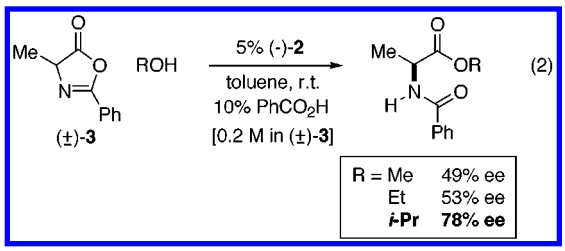


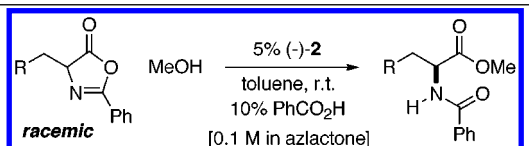
The stereoselectivity of the dynamic kinetic resolution of **3** increases as the steric demand of the alcohol increases, reaching 78% ee when *i*-PrOH is employed as the nucleophile (eq 2). Unfortunately, ring opening under these conditions is extremely slow ($t_{1/2} \sim 1$ week).



As illustrated in Table 2, our planar-chiral DMAP derivative catalyzes the dynamic kinetic resolution of a range of azlactones with fair enantioselectivity and in excellent yield.[8,9] While the observed enantiomeric excesses are modest compared with the ultimate goal of 100% ee, it is worthwhile to note that these values represent the best selectivities reported to date for the deracemization/ring opening of azlactones with nonenzymatic catalysts.[10]

Although we have not yet had the opportunity to pursue a detailed investigation of the origin of stereoselectivity in these reactions, the dependence of ee on the structure of the alcohol (eq 2) suggests that nucleophilic addition of catalyst **2** to the enantiomeric azlactones is not the stereochemistry-determining step. Elucidating which of the subsequent steps *is* critical may permit rational optimization of this promising transformation.

Table 2. Dynamic Kinetic Resolution of Azlactones



R	% ee	% yield
H	54	98
Me	44	94
$CH{=}CH_2$	61	94
i-Pr	55	95
cyclohexyl	54	93
Ph	56	94
CH_2SMe	50	94

In conclusion, we have established that chiral DMAP derivative **2** catalyzes the deracemization/ring opening of azlactones, thereby affording protected α-amino acids. This study furnishes a new benchmark for nonenzymatic enantioselective catalysis of this important process. Future investigations will focus on further optimization of this reaction, as well as on the dynamic kinetic resolution of related heterocycles. In combination with our earlier work on the asymmetric acylation of secondary alcohols, the present study provides support for the suggestion that planar-chiral DMAP derivatives may prove to be effective enantioselective catalysts for a significant subset of the reactions known to be catalyzed by DMAP.

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Supporting Information Available: Experimental procedures and compound characterization data (24 pages).

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(8) **Sample Experimental Procedure (Table 2, Entry 1).** A solution of benzoic acid (6.1 mg, 0.050 mmol) and methanol (30 μL, 0.74 mmol) in 2 mL of toluene was added to a solution of catalyst (−)-**2** (8.8 mg, 0.025 mmol) and azlactone (88 mg, 0.50 mmol) in 3 mL of toluene. The resulting purple reaction mixture was stirred at rt for 48 h. The solution was then poured directly onto a column of silica gel, and the product was purified by flash chromatography, which provided 104 mg (100%) of the desired alanine derivative. GC analysis (Chiraldex G-TA) revealed a 54% ee of protected L-alanine.

(9) **Notes.** (1) The data reported in Table 2 are the average of two runs. (2) For each substrate, ≤10% ring opening occurs in the absence of catalyst under otherwise identical conditions. (3) The ring-opened product does not racemize under the reaction conditions. (4) Higher ee is observed at lower concentration. (5) Somewhat lower rates and enantioselectivities are observed when the reactions are conducted with unpurified reagents and are exposed to oxygen and moisture. (6) The ring openings of hindered azlactones proceed with lower rates and enantioselectivities (e.g., 2-phenyl-4-isopropyloxazalone: 13% ee). (7) Carboxylic acids (achiral and chiral) other than benzoic acid provide comparable or lower ee.

(10) We are aware of only one example of catalytic, enantioselective deracemization/ring opening of azlactones with a nonenzymatic catalyst (copper complex, <15% ee): Belokon, Y. N.; Bachurina, I. B.; Tararov, V. I.; Saporovskaya, M. B. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1992**, *41*, 422−429.