Enantioselective Construction of Quaternary Stereocenters: Rearrangements of *O*-Acylated Azlactones Catalyzed by a Planar-Chiral Derivative of 4-(Pyrrolidino)pyridine

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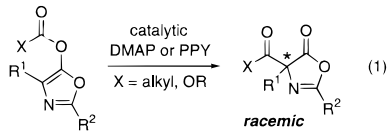
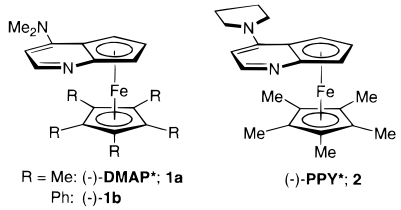
The development of catalytic enantioselective carbon−carbon bond-forming reactions, particularly those that produce quaternary stereocenters, is one of the most difficult challenges in stereoselective organic synthesis.[1,2] In 1970, Steglich reported that 4-(dimethylamino)pyridine (DMAP) and 4-(pyrrolidino)pyridine (PPY) catalyze the rearrangement of *O*-acylated azlactones to their *C*-acylated isomers, thereby generating both a new carbon−carbon bond and a new quaternary stereocenter (eq 1).[3,4] The products



(1)

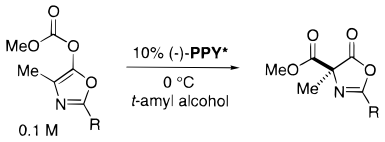
of this rearrangement process represent useful building blocks for synthetic organic chemistry, since nucleophiles react preferentially at the azlactone carbonyl group to provide protected α-alkylated α-amino acids.[5−8] To the best of our knowledge, there have been no reports of either diastereoselective or enantioselective variants of this nucleophile-catalyzed rearrangement reaction.

Several years ago, we initiated a research program directed at the development of planar-chiral derivatives of DMAP (e.g., **1a**,**b**) as enantioselective nucleophilic catalysts. To date, we have



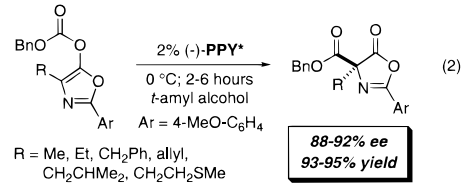
described the effectiveness of these complexes in the kinetic resolution of secondary alcohols[9] and in the deracemization/ring-opening of azlactones.[10,11] In view of Steglich's discovery that the rearrangement of *O*-acylated azlactones is subject to catalysis by 4-(dialkylamino)pyridines (eq 1), we set our sights on

Table 1. Dependence of Enantioselectivity on the 2-Substituent of the *O*-Acylated Azlactone



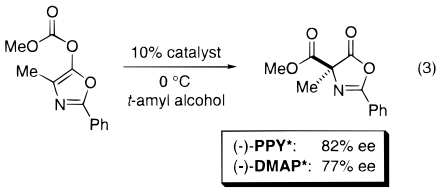
Entry	R	% ee
1	Me	54
2	*t*-Bu	42
3	2-furyl	70
4	Ph	82
5	4-Cl-C_6H_4	84
6	4-MeO-C_6H_4	84

achieving *enantioselective* rearrangements with planar-chiral derivatives of 4-(dialkylamino)pyridines. In this communication, we report the realization of this objective through the use of a new catalyst, PPY* (eq 2).



(2)

Our initial investigation into asymmetric Steglich rearrangements focused on the use of previously reported DMAP* as the chiral catalyst.[9,12] In the meantime, however, we developed a related new catalyst, PPY*,[13] which we have discovered affords a greater reaction rate and higher enantioselectivity in this rearrangement as compared with DMAP* (eq 3).[14,15]



(3)

An optimization study exploring the dependence of enantioselectivity on the 2-substituent of the *O*-acylated azlactone reveals

(1) For a recent review, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388−401. See also: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(2) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446.

(3) Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, 4727−4730.

(4) For reviews of the chemistry of 4-(dialkylamino)pyridines, see: (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069−2076. (c) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129−161.

(5) For a review of the chemistry of azlactones, see: Rao, Y. S.; Filler, R. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Chapter 3.

(6) For a brief overview of the synthesis and the significance of α-alkylated α-amino acids, see: Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227 and references therein.

(7) To the best of our knowledge, only one catalytic enantioselective method for the synthesis of α-alkylated α-amino acids has been reported (palladium-catalyzed allylic alkylation): Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635−2637.

(8) For an approach to the synthesis of enantiopure α-alkylated α-amino acids that relies upon ring-opening of racemic azlactones with 1 equiv of an enantiomerically pure amine, followed by separation of the resulting diastereomers, see: Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 563−580.

(9) (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. *J. Org. Chem.* **1998**, *63*, 2794−2795.

(10) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155.

(11) For recent work by others on chiral derivatives of 4-(dialkylamino)-pyridines, see: (a) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170. (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584−2585; **1996**, *118*, 1809−1810.

(12) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231.

(13) For the preparation of enantiopure PPY*, see the Supporting Information.

(14) (a) At room temperature, the corresponding reactions catalyzed by (−)-PPY* and (−)-DMAP* provide the rearranged product in 76% and 71% ee, respectively. (b) The use of solvents other than *tert*-amyl alcohol (e.g., CH_2Cl_2, THF, toluene, and Et_2O) leads to lower enantioselectivity. (c) The rate of rearrangement with PPY* as the catalyst is ∼4−5 times greater than that with DMAP*. (d) Catalyst **1b** is inferior to PPY* and to DMAP* in terms of both rate and enantioselectivity.

(15) Parallel observations regarding relative reactivity have been reported for the achiral parent compounds (i.e., PPY displays greater activity than DMAP in the rearrangement of *O*-acylated azlactones). See ref 4a.

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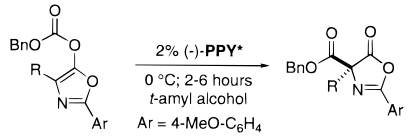
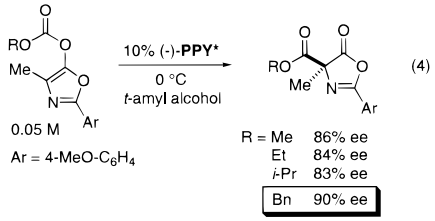
Table 2. Enantioselective Rearrangements of *O*-Acylated Azlactones Catalyzed by (−)-PPY*



R	% ee	% yield
Me	91	94
Et	90	93
CH_2Ph	90	93
allyl	91	93
CH_2CHMe_2	92	95
CH_2CH_2SMe	88	94

that alkyl (Table 1, entries 1 and 2) and heteroaryl (entry 3) groups provide lower selectivity than do aryl substituents (entries 4−6). Although the stereoselection appears to be relatively insensitive to substitution on the aromatic ring (entries 4−6), the reaction rate is affected more significantly, with use of the 4-methoxy group leading to the most rapid rearrangement.[16]

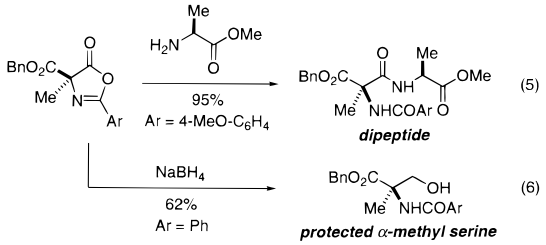
Further improvement in enantioselectivity can be gained through appropriate choice of the migrating acyl group (eq 4).



(4)

Although little variation in ee is observed for a range of simple aliphatic substituents, use of the benzyl derivative leads to appreciably enhanced stereoselection.

Under these optimized conditions, (−)-PPY* catalyzes the rearrangement of an array of *O*-acylated azlactones with high enantioselectivity and in excellent yield (2% catalyst; *tert*-amyl alcohol, 0 °C, 2−6 h; Table 2).[17,18] The utility of these rearrangement products is illustrated by their conversion to dipeptide and α-methylserine derivatives (eqs 5 and 6).[6,19,20]



(5)

(6)

(16) This electronic effect is consistent with carbon−carbon bond formation being the turnover-limiting step (vide infra).

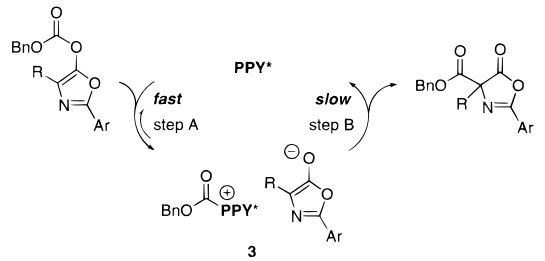
(17) General procedure: A pink, 0 °C solution of (−)-PPY* (3.8 mg, 0.010 mmol) in *tert*-amyl alcohol (4.0 mL) is added by cannula to a 0 °C solution of the *O*-acylated azlactone (0.50 mmol) in *tert*-amyl alcohol (6.0 mL), resulting in a deep-blue or purple solution. After the pink color of the catalyst has returned (2−6 h), the reaction mixture is passed through a plug of silica (EtOAc as the eluant) to remove the catalyst (the catalyst can be recovered by then flushing the silica with 10% NEt_3/90% EtOAc). The solvents are evaporated, and the product is purified by flash chromatography.

(18) The absolute configuration of the rearranged product for R = CH_2Ph (Table 2) was determined through an X-ray crystallographic study of an amide derived from ring-opening of the rearranged product with an enantiopure amine (see Supporting Information for details). The absolute configurations of the other reactions products were assigned by analogy.

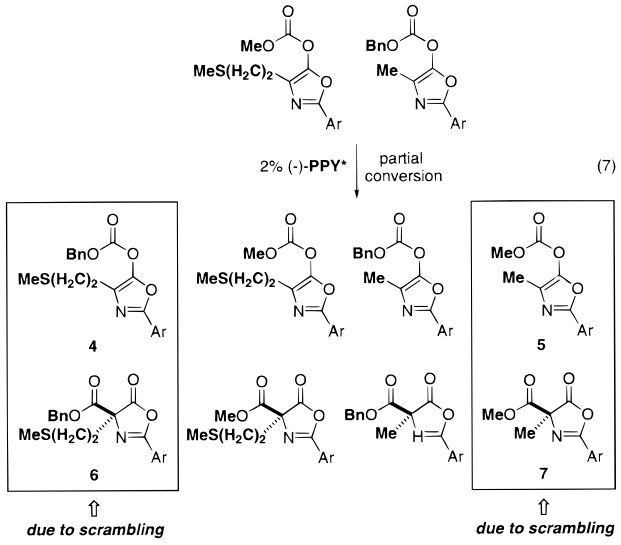
(19) For a discussion of the synthesis and the significance of α-methylserine, see: Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405−7406.

(20) The absolute configuration of the α-methylserine derivative illustrated in eq 6 was correlated with a literature compound (Leplawy, M. T.; Olma, A. *Polish J. Chem.* **1979**, *53*, 353−367); see Supporting Information for details. See also ref 18.

Scheme 1



Preliminary studies indicate that, under the typical reaction conditions, the rate of rearrangement is zero-order in substrate and independent of concentration. This observation is consistent with the pathway outlined in Scheme 1, wherein the resting state of the system is ion pair **3**. The crossover experiment illustrated in eq 7 suggests that reaction of the *O*-acylated azlactone with PPY* (Scheme 1, step A) is reversible (thereby forming scrambled "starting materials" **4** and **5**) and that the counterions of the ion pair can exchange (thereby forming **4**−**7**). Our demonstration that the rearranged products are configurationally stable under the reaction conditions provides evidence that step B of Scheme 1 is irreversible.



(7)

In summary, we have described synthetic and mechanistic studies of a new method for the enantioselective construction of quaternary stereocenters, the nucleophile-catalyzed rearrangement of *O*-acylated azlactones. Using a new planar-chiral catalyst, PPY*, we can effect this carbon−carbon bond-forming reaction, which furnishes protected α-alkylated α-amino acids, with high levels of enantioselectivity. Further investigations of the scope and the mechanism of this process are underway.

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Supporting Information Available: Experimental procedures and compound characterization data (67 pages). See any current masthead page for ordering information and Web access instructions.

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