ORGANIC LETTERS

2011
Vol. 13, No. 3
356−358

Dynamic Kinetic Resolution of Azlactones Catalyzed by Chiral Brønsted Acids

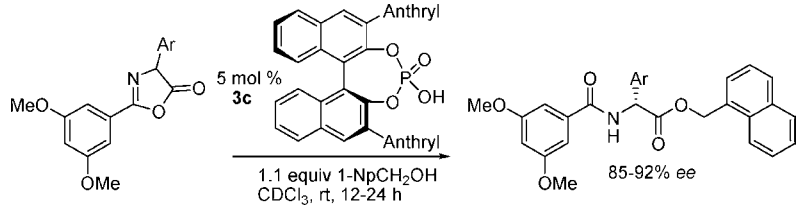
Guojian Lu and Vladimir B. Birman*

Department of Chemistry, Washington University, Campus Box 1134, One Brookings Drive, St. Louis, Missouri 63130, United States

birman@wustl.edu

Received November 11, 2010

ABSTRACT



Chiral Brønsted acids have been shown for the first time to catalyze the dynamic kinetic resolution of azlactones. 3,3′-Bis-(9-anthryl)-BINOL phosphoric acid 3c is particularly effective in the case of 4-aryl-substituted substrates, producing 85−92% ee's.

Chiral Brønsted acid catalysis has been successfully applied to a variety of enantioselective transformations.[1] To the best of our knowledge, however, it has never been used to promote asymmetric acylation reactions. Here, we report the first example of such a transformation: enantioselective alcoholysis of azlactones resulting in their Dynamic Kinetic Resolution (DKR).[2]

To date, the DKR of azlactones (±)-**1**[3] has been achieved using enzymatic,[4] Lewis acid,[5a] Lewis base,[5b,f] and bifunctional catalysis.[5d,e]

In the course of our recent studies on this reaction[5f] using enantioselective acyl transfer catalyst BTM (benzotetramisole),[6] we became aware of the importance of adding benzoic acid as a cocatalyst, as was first noted by Fu et al.[5b] We surmised that the presence of this proton source was necessary to activate the substrate toward the nucleophilic attack by BTM (see Figure 1, Path A, wherein Nu* = BTM, AH = $PhCO_2H$).[7] No appreciable reaction was observed when benzoic acid was used by itself, in the absence of BTM. We hypothesized, however, that a strong chiral Brønsted acid (A*H; see Figure 1, Path B) might be able to activate azlactones enough to promote their *direct* alcoholysis without the intermediacy of a nucleophilic catalyst.

To test this mechanistically different alternative method, we reacted 2,5-diphenylazlactone (±)-**1a** with benzyl alcohol in the presence of (*R*)-BINOL phosphoric acid **3a** (pK_a = 1.14).[8] The reaction proceeded smoothly to give the expected ester **2a**, albeit in essentially racemic form (2% ee). Encouraged by this result, we undertook a survey of several 3,3′-

(1) For 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. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (f) Terada, M. *Synthesis* **2010**, 1929.

(2) For a recent review of dynamic kinetic resolution, see: Pelissier, H. *Tetrahedron* **2008**, *64*, 1563.

(3) For a review of azlactone chemistry, see: Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432.

(4) For enzymatic methods, see: Brown, S. A.; Parker, M.-C.; Turner, N. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1687, and references cited therein.

(5) Nonenzymatic methods: (a) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723. (b) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154. (c) Xie, L.; Hua, W.; Chan, A. S. C.; Leung, Y.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 4715. (d) Berkessel, A.; Cleeman, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807. (e) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409. (f) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.

(6) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.

(7) Activation of the azlactone carbonyl via double hydrogen bonding has been utilized in the bifunctional catalyst design (ref 5d and e).

(8) Calculated value available through SciFinder.

10.1021/ol102736t
Published on Web 12/22/2010

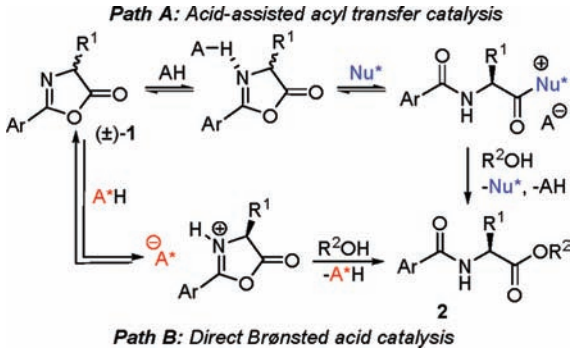
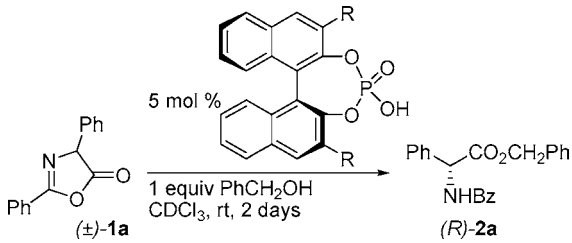


Figure 1. Two modes of catalysis in alcoholysis of azlactones employing Brønsted acids.

disubstituted derivatives of BINOL phosphoric acid (Table 1). 3,3′-Bis-(9-anthryl) analogue **3c** gave the highest enantioselectivity among common catalysts examined and thus was selected for further studies (Table 1, entry 3 vs entries 2 and 4−7). An attempt to improve its performance by further elaboration of its 9-anthryl substituents proved to be counterproductive (entry 8).

Table 1. Catalyst Screening

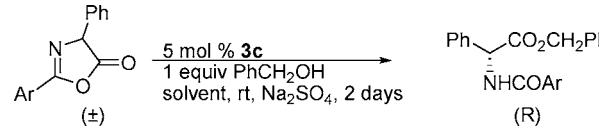


entry	R	% conv(NMR)	% ee
1	H (**3a**)	60	2
2	Phenyl (**3b**)	96	9
3	9-Anthryl (**3c**)	91	63
4	9-Phenanthryl (**3d**)	71	34
5	3,5-$(CF_3)_2C_6H_3$ (**3e**)	65	25
6	$SiPh_3$ (**3f**)	32	48
7	2,4,6-(*i*-Pr)$_3C_6H_2$ (**3g**)	39	34
8	10-Ph-anthryl (**3h**)	67	25

Variation of the C2-aryl group on the substrate was explored next. *Para*-substituents were found to have only a small effect on the enantioselectivity (Table 2, entries 1−3). On the other hand, the 3,5-dimethoxyphenyl group (entry 4) led to a substantial improvement.[9] A survey of solvents (entries 4−9) indicated that chloroform initially chosen to facilitate NMR studies was, in fact, optimal.

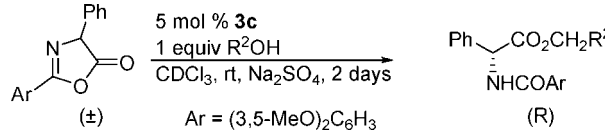
Next, we examined the effect of the of alcohol's structure on enantioselectivity (Table 3). Ultimately, 1-naphthylmethanol and 1-pyrenylmethanol were selected as optimal (entries 10 and 12). It should be noted, however, that acceptable levels of enantioselectivity could also be achieved with nonbenzylic primary alcohols of comparable steric bulk (entries 3 and 4).

Table 2. Variation of the C2-Substituent and Solvent



entry	Ar	solvent	% conv(NMR)	% ee
1	Phenyl	$CDCl_3$	91	63
2	4−Cl-C_6H_4	$CDCl_3$	84	61
3	4-OMe-C_6H_4	$CDCl_3$	91	66
4	3,5-$(OMe)_2C_6H_3$	$CDCl_3$	72	77
5	3,5-$(OMe)_2C_6H_3$	CD_2Cl_2	68	74
6	3,5-$(OMe)_2C_6H_3$	C_6D_6	59	54
7	3,5-$(OMe)_2C_6H_3$	PhMe-d_8	63	56
8	3,5-$(OMe)_2C_6H_3$	THF	35	ND
9	3,5-$(OMe)_2C_6H_3$	EtOAc	32	ND

Table 3. Variation of the Alcohol



entry	R^2OH	% conv(NMR)	% ee
1	MeOH	76	68
2	*i*-PrOH	53	71
3	*i*-$PrCH_2OH$	80	78
4	*t*-$BuCH_2OH$	82	81
5	CH_2=$CHCH_2OH$	71	75
6	$PhCH_2OH$	72	77
7	4−Br-$C_6H_4CH_2OH$	95	81
8	4-OMe-$C_6H_4CH_2OH$	86	76
9	$C_6F_5CH_2OH$	65	78
10	1-Naphthyl-CH_2OH	90	91
11	2-Naphthyl-CH_2OH	94	86
12	1-Pyrenyl-CH_2OH	100	90

In the course of the studies described above, we observed that the activity of catalyst **3c** prepared in our laboratory according to literature protocols[10] varied considerably from one batch to the next. Re-examination of recent literature reports indicated that BINOL phosphoric acids, after conventional purification by chromatography, should be washed with hydrochloric acid, presumably to remove metal cations

(9) It is noteworthy that the 3,5-dimethoxyphenyl group also proved to be optimal in a recent study of an enantioselective aldol-like reaction of azlactones catalyzed by BINOL-phosphoric acids: Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430.

(10) (a) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

absorbed from silica gel.[11] Indeed, treatment of freshly purified catalyst **3c** with 4 M HCl led to a remarkable

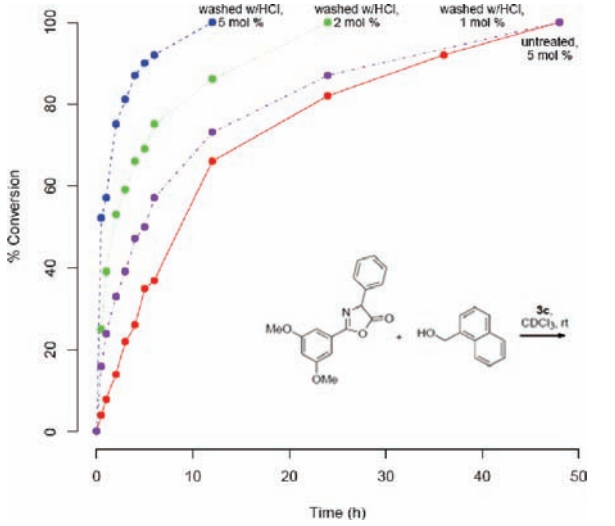


Figure 2. Influence of acid treatment on catalyst's activity.

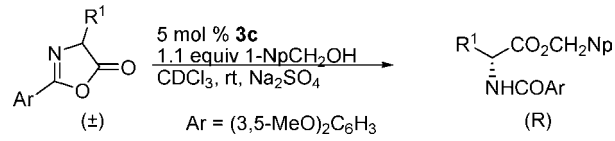
increase in its activity (Figure 2). The enantioselectivity was not affected significantly by the acid treatment (Table 4, entries 1 and 2). Lowering the reaction temperature to −20 °C did not lead to any improvement (entry 3). Lower catalyst loadings of the acid-washed catalyst, down to 1 mol %, were still effective and also produced essentially the same ee values (±1%)[12] (Figure 2). However, for the sake of consistency and experimental convenience, a 5 mol % loading continued to be used for the rest of this study.

Having thus optimized the basic parameters of the new DKR protocol, we applied it to a series of representative substrates. Substituted 4-aryl-azlactones gave rise to the corresponding α-arylglycine derivatives in 86−93% ee and 81−90% yields (Table 4, entries 4−10). *Ortho*-substitution on the C4 aryl group of the substrates led to some decrease in the reaction rate (entries 7−9). In contrast, 4-alkyl-substituted substrates produced only modest ee's (entries 11−15). Intriguingly, the DKR of 4-methyl-azlactone resulted in *opposite* enantioselectivities depending on whether acid-washed or untreated catalyst **3c** was used (entries 11 and 12), which may reflect competition between Brønsted acid and Lewis acid modes of catalysis.[11c] Furthermore,

(11) (a) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840. (b) Cheon, C.-H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823.

(12) See Supporting Information.

Table 4. Variation of C4-Substituent[a]



entry	R^1	time (h)	% yield	% ee
1[b]	Phenyl	48	90	91
2[c]	Phenyl	6	89	89
3[d]	Phenyl	20	87	89
4	4-ClC_6H_4	12	88	85
5	4-$MeOC_6H_4$	12	86	88
6	3-$MeOC_6H_4$	12	82	92
7	2-ClC_6H_4	24	88	91
8	2-$MeOC_6H_4$	24	86	89
9	1-Naphthyl	24	86	91
10	2-Naphthyl	12	86	85
11	Methyl	12	88	−8[e]
12[b]	Methyl	48	88	39
13[f]	Methyl	12	85	59
14	Isopropyl	12	84	50
15[f]	Isopropyl	12	83	29

[a] *General conditions:* 0.1 mmol of substrate, 0.11 mmol of 1-naphthylmethanol, 0.005 mmol of *acid-washed* catalyst **3c**, 50 mg of Na_2SO_4, 1 mL of $CDCl_3$, rt, unless specified otherwise. [b] Untreated catalyst **3c** was used. [c] Stopped at 95% conversion. [d] Carried out at −20 °C. [e] (*S*)-Enantiomer was major in this case. [f] Carried out using *acid-washed* catalyst **3g**.

catalyst **3g** proved to be more enantioselective than **3c** in the case of this substrate, under otherwise identical conditions (entry 13).

In conclusion, we have developed a new method for the DKR of azlactones. It is especially suited for the C4-aryl-substituted substrates, thus complementing most previously available enzymatic[4] and nonenzymatic[5] protocols. In contrast to our previously disclosed BTM-catalyzed protocol,[5f] it works well for substrates bearing *ortho*-substituted aryl groups at C4. It is also noteworthy that our study demonstrates for the first time the utility of Brønsted acid catalysis in asymmetric acylation reactions. Further exploration of its potential is currently under investigation.

Acknowledgment. We thank the National Science Foundation for partial financial support of this study (CHE 1012979).

Supporting Information Available: Experimental procedures and NMR spectra. These materials are available free of charge via the Internet at http://pubs.acs.org.

OL102736T