Benzotetramisole-Catalyzed Dynamic Kinetic Resolution of Azlactones
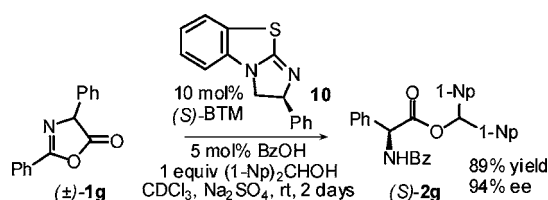
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ABSTRACT

Enantioselective acyl transfer catalyst benzotetramisole (BTM) has been found to promote dynamic kinetic resolution of azlactones providing di(1-naphthyl)methyl esters of α-amino acids with up to 96% ee.

Dynamic kinetic resolution (DKR)[1] of azlactones[2] by way of their enantioselective alcoholysis (Figure 1) provides an attractive approach to the asymmetric synthesis of α-amino acid derivatives. Enzymatic variant of this transformation,[3] while often successful, suffers from one inherent drawback: since enzymes are available in only one enantiomeric form, the reversal of enantioselectivity in a given reaction requires identification of a different enzyme, which is not always a trivial matter. Therefore, the development of nonenzymatic alternatives is of significant practical interest. Several mechanistically different approaches to activating azlactones toward alcoholysis have been employed. In 1997, Seebach et al. reported a Lewis acid-catalyzed version of this reaction using Ti(IV) TADDOLate **3** producing moderate ee's (up to 68%).[4] Promising levels of enantioselectivity (up to 78% ee) were achieved by Fu et al. in 1998 using enantioselective acyl transfer catalyst **4** (Figure 2). However, the reaction was
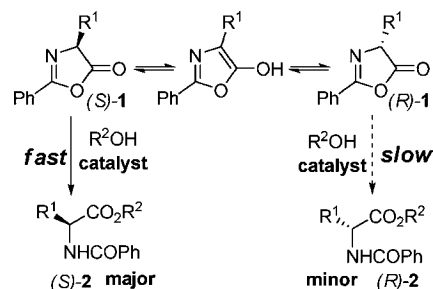

Figure 1. Dynamic kinetic resolution of azlactones.

extremely slow (50% conversion/1 week).[5] Low enantiose-lectivities (<39% ee) were reported by Hua et al. in 1999 using a combination of a chiral diketopiperazine, *cyclo*-[(*S*)-His-(*S*)-Phe] **5**, with diisopropyl L-tartrate, presumed to activate azlactones via hydrogen bonding.[6] More recently (2005–2008), encouraging results have been obtained by Berkessel et al.[7] and Connon et al.[8] using bifunctional catalysts **6** (72–95% ee) and **7** (78–88% ee), respectively.

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

(2) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432.

(3) See, e.g., (a) Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R. L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252. (b) Brown, S. A.; Parker, M.-C.; Turner, N. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1687, and references cited therein.

(4) (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Mastsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539. (b) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723.

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

(6) Xie, L.; Hua, W.; Chan, A. S. C.; Leung, Y.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 4715.
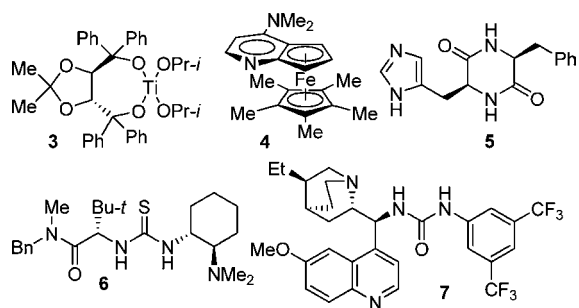
Figure 2. Catalysts previously employed for the DKR of azlactones.

Surprisingly, apart from Fu's seminal study, there have been no other reported attempts to achieve DKR of azlactones using enantioselective acyl transfer catalysis. Over the past several years, our group has developed amidine-based catalysts **8–11** (Figure 3), which display high enantioselectivity in the acylation of several classes of alcohols and oxazolidinones.[9] Recently, Shiina et al.[10] have demonstrated the utility of BTM **10** in the kinetic resolution (KR) of α-arylpropionic acids via enantioselective alcoholysis of their mixed anhydrides. We have found that HBTM **11** is also effective in the KR of α-aryloxy- and arylthioalkanoic acids via their symmetrical anhydrides.[11] These results have encouraged us to re-examine the possibility of DKR of azlactones via the acyl transfer mechanism.
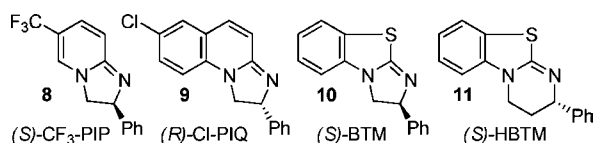

Figure 3. Amidine-based catalysts used in this study.

An equimolar combination of HBTM and benzoic acid was found to promote the methanolysis of substrate (±)-**1a** without any appreciable enantioselectivity (Table 1, entry 1). Switching to benzyl alcohol resulted in a modest *ee* (entry 2). The reaction with diarylcarbinols was extremely slow (entries 3 and 4). After these disappointing first results, we

were pleased to discover that BTM is much more effective in this reaction. Encouraging results were obtained even using methanol (entry 5); however, the bulky di(1-naphthyl)methanol[10,11] was required to bring the enantiomeric excess to a respectable 85% (entry 11). A single recrystallization from ethyl acetate produced completely enantiopure material (>99.5% ee). The earlier imidazoline-based catalysts, **8** and **9**, proved to be competent but less active and less enantioselective than BTM (entries 12–14).
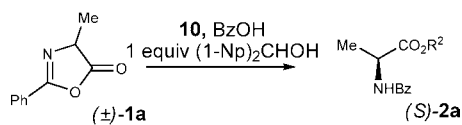
Table 1. Catalyst and Alcohol Screening

entry	catalyst (mol %)	time, d	R^2	% convn[a]	% ee
1	**11** (5)	1	Me	54	<3
2	**11** (5)	1	$PhCH_2$	47	−25
3	**11** (5)	1	Ph_2CH	5	ND
4	**11** (10)	1	1-Np_2CH	<5	ND
5	**10** (5)	2	Me	91[b]	34[b]
6	**10** (5)	2	$PhCH_2$	94[b]	48[b]
7	**10** (5)	2	1-$NpCH_2$	97[b]	51[b]
8	**10** (5)	2	2-$NpCH_2$	96[b]	47[b]
9	**10** (5)	2	Me_2CH	<5	ND
10	**10** (5)	2	Ph_2CH	91[b]	75[b]
11	**10** (5)	2	1-Np_2CH	96[b]	85[b]
12	**10** (10)	0.4	1-Np_2CH	92[b]	80[b]
13	**8** (10)	2	1-Np_2CH	47	59
14	**9** (10)	2	1-Np_2CH	47	−52

[a] Conversion was determined by ^{1}H NMR, unless indicated otherwise. [b] Reported % isolated yields and % ee's are averages of two runs.

Changing the amount of benzoic acid relative to the catalyst did not have a significant effect on the reaction rate or the enantioselectivity, although in the absence of the acid promoter the reaction did not proceed at all, consistent with Fu's original report[5] (entries 1–4, Table 2). Lower catalyst loadings, down to 2 mol %, were still effective, although required prolonged reaction times (entries 5 and 6). Decreased temperatures proved to be detrimental to the enantioselectivity, while higher temperatures resulted in a higher rates, but the same *ee* (entries 7–9). Solvents other than chloroform were less effective, in line with our earlier experience with the KR of alcohols[9c] (entries 10–13).

DKR of other azlactones bearing primary alkyl substituents **1b–e** produced uniformly good yields and ee's in the 80–90% range (Table 3, entries 1–5). Isopropyl-substituted substrate **1f** proved resistant to alcoholysis under the same conditions (entry 6). On the other hand, excellent enantioselectivity (94% ee) was obtained in the case of 2,4-diphenylazlactone **1g** (entry 7). This result was all the more remarkable given the fact that the highest ee previously reported for either enzymatic[3a] or nonenzymatic[7a] DKR of this substrate (or any other 4-aryl-substituted azlactones) has been 75%. Variation of electronic properties of the C4-aryl

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(9) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (f) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. Zhang, Y.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2525.
(10) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887.
(11) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301.

Table 2. Variation of Reaction Conditions[a]

entry	mol % 10/ mol % BzOH	time d	temp °C	solvent	% convn	% ee
1	10/0	1	23	CDCl₃	<5	ND
2	10/5	0.4	23	CDCl₃	90	83
3	10/10	0.4	23	CDCl₃	92	80
4	10/20	0.4	23	CDCl₃	93	82
5	5/5	2	23	CDCl₃	96	85
6	2/2	4	23	CDCl₃	94	84
7	5/5	2	0	CDCl₃	95	72
8	10/5	2	−20	CDCl₃	94	55
9	5/5	1	45	CDCl₃	91	84
10	5/5	2	23	C₆D₆	98	80
11	5/5	2	23	CH₂Cl₂	95	74
12	5/5	2	23	CH₃CN	85	66
13	5/5	2	23	THF	<5	ND

[a] Conversion in all cases was determined by ¹H NMR.

substituent had only a slight effect on the enantioselectivity or reaction rate (entries 8−11). DKR of the 1-naphthyl-substituted substrate **1l**, however, proceeded rather slowly and with lower enantioselectivity (entry 12). Substrate **1m** was completely unreactive, presumably due to the presence of an *ortho*-substitutuent (entry 13).

## Table 3. Structural Variation of Azlactone Substrates[a]
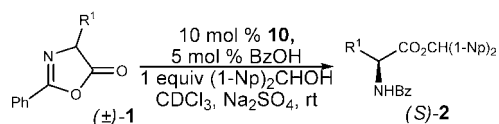
entry	substrate	time d	R¹	% yield[b]	% ee[b]
1	**1a**	0.4	Me	90	83
2	**1b**	7	Me₂CHCH₂	97	80
3	**1c**	3	MeSCH₂CH₂	92	90
4	**1d**	4	PhCH₂	94	83
5	**1e**	4	CH₂=CHCH₂	88	83
6	**1f**	4	Me₂CH	<5	ND
7	**1g**	2	Ph	89	94
8	**1h**	2	p-MeOC₆H₄	87	91
9	**1i**	2	p-ClC₆H₄	88	96
10	**1j**	2	p-BrC₆H₄	90	95
11	**1k**	2	2-naphthyl	88	91
12	**1l**	7	1-naphthyl	46	76
13	**1m**	2	2,4-(MeO)₂C₆H₃	0	ND
14[c]	**1h**	2	p-MeOC₆H₄	86	92
15[c]	**1i**	2	p-ClC₆H₄	86	97
16[c]	**1n**	2	p-FC₆H₄	90	95

[a] Na₂SO₄ was added to prevent loss of catalytic activity of BTM during prolonged reactions (see ref 9c). [b] Reported % isolated yields and % ee's are averages of two runs. [c] Azlactone was generated *in situ*. The yield is based on the N-benzoyl-α-arylglycine starting material (see Scheme 1).

Initially, azlactones **1a−m** used in this study were synthesized in a separate step and purified by recrystallization before subjecting them to the DKR conditions. Later, however, we found that *in situ* cyclization of *N*-benzoyl-α-amino acids with DCC followed by addition of di-(1-naphthyl)methanol and the catalyst works just as well as the earlier, more time-consuming protocol (cf. entries 14−16 vs 8 and 9, Table 3). Coupled with the one-step synthesis of starting materials via the Ben-Ishai amidoalkylation[12] of simple arenes, this procedure provides an attractive route to enantioenriched arylglycine derivatives[13] illustrated in Scheme 1. Hydrogenolysis of dinaphthylmethyl ester **2i** proceeded without appreciable erosion of enantiomeric purity.

Scheme 1. Asymmetric Synthesis of Arylglycines
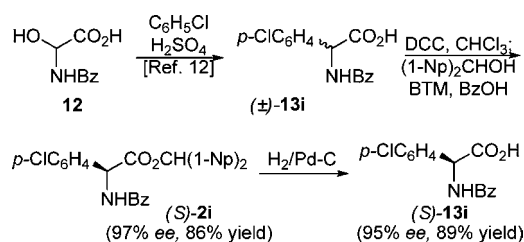
It is of interest to analyze the mechanism of enantiodifferentiation in the DKR of azlactones. Berkessel et al.[7a] proposed that the thiourea-catalyzed version of this process occurs via irreversible, hydrogen bonding-assisted attack of the alcohol on the less hindered face of the substrate, which results in the highest enantioselectivity being observed in the case of the bulkiest C4-substituents (cf. general structure **1**, R¹ = isobutyl (**1b**), isopropyl (**1f**), or *tert*-butyl). The situation is clearly different in our case. The strong dependence of the enantioselectivity on the alcohol nucleophile indicates that enantiodifferentiation occurs in the second step of the catalytic cycle (Figure 4). The absolute sense of asymmetric induction and structure-selectivity trends can be explained by transition state model **15**, which invokes hydrogen bonding between the benzamide group and the reacting carbonyl. The involvement of π−π interactions with the C2-phenyl group on the catalyst and/or lower steric repulsion may explain the higher enantioselectivity generally
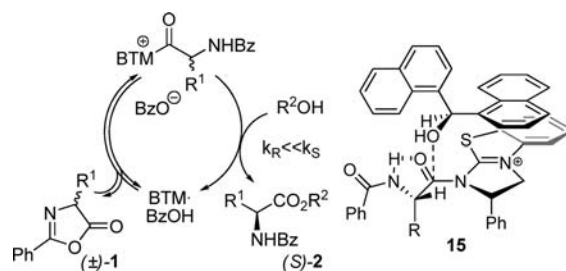
Figure 4. Proposed catalytic cycle and transition state (benzoate anion omitted for clarity).

observed in the DKR of the aryl-substituted azlactones **1g**−**k** compared to the alkyl-substituted ones **1a**−**e**. The low reactivity of substrate bearing bulky C4 substituents (cf. **1f**, **1l**, and **1m**) is also consistent with this proposal.

In conclusion, we have developed a new, highly enantioselective method for the DKR of azlactones. It is especially suited for the C4-aryl-substituted substrates, thus complementing the previously available enzymatic and nonenzymatic protocols. Further exploration of its substrate scope is under active investigation in our laboratory.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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