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Kinetic Resolution of *N*-Acyl-β-Lactams via Benzotetramisole-Catalyzed Enantioselective Alcoholysis

Valentina D. Bumbu and Vladimir B. Birman*

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

Supporting Information

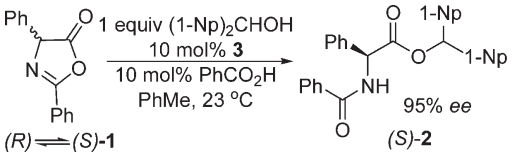
ABSTRACT: The first nonenzymatic kinetic resolution of β-lactams has been achieved. Alcoholysis of their *N*-aroyl derivatives in the presence of a simple chiral acyl transfer catalyst, benzotetramisole, produces β-amino acid derivatives with excellent enantioselectivity.

β-Amino acids and their derivatives have attracted a great deal of attention, mainly due to the uniqueness of their biological properties.[1] One important approach to their synthesis in enantiopure form is based on the ring-opening of β-lactams.[2] Despite considerable progress achieved in the asymmetric synthesis of the latter,[3] kinetic resolution[4] of the readily available racemic β-lactams[5] via enzymatic hydrolysis still remains prevalent.[6] To the best of our knowledge, the catalytic, nonenzymatic kinetic resolution of β-lactam derivatives has not been reported until now.[7,8] In this communication, we describe the first examples of this process achieving excellent levels of enantioselectivity.

In the course of our recent studies,[9] we achieved dynamic kinetic resolution (DKR)[10] of azlactones (e.g., **1**, Scheme 1) in the presence of amidine-based catalyst benzotetramisole[11a] (BTM, **3**, Figure 1) and benzoic acid.[12] Success of this enantioselective transformation prompted us to explore other classes of substrates that might be similarly activated by a combination of a chiral nucleophilic catalyst and a Brønsted acid. Initially, we turned our attention to oxazinones, the ring-expanded homologues of azlactones.[13] Although substrate (±)-**6** did react with di-(1-naphthyl)methanol in the presence of our catalytic system, the level of enantioselectivity was disappointing (Table 1, entry 1).[14] Interestingly, however, less bulky alcohols produced similar selectivity factors (entries 2 and 3), which was in contrast to the DKR of azlactones, wherein the enantioselectivity depended critically on the alcohol used. This observation suggested to us that, despite the structural similarity of oxazinones and azlactones, the mechanism of enantioselection in these two cases might be completely different, and that the modest enantioselectivity observed might originate in the first step of the catalytic cycle. With this in mind, we decided to test *N*-benzoyl-4-phenyl-β-lactam (±)-**7a**, which is isomeric with oxazinone (±)-**6** and would produce the same reactive intermediate upon ring-opening (Scheme 2).

Gratifyingly, the kinetic resolution (KR) of **7a** proved to be considerably more enantioselective than that of oxazinone **6** (Table 1, entries 4−6). Again, different alcohols produced essentially the same selectivity factors in the case of this substrate. Encouraged by these findings, we proceeded to optimize the new process (Table 2). In addition to BTM **3** (entry 1), other amidine-based catalysts, **4**[11b] and **5**[11c] (Figure 1) were found to be competent in promoting this reaction, although the enantioselectivity was diminished (entries 2 and 3). Variation of the acyl group on the β-lactam nitrogen was explored next. Both *N*-Boc (**7b**) and *N*-isobutyryl (**7c**) derivatives proved to be completely unreactive (entries 4 and 5). Introduction of a 4-chlorobenzoyl group resulted in appreciable enhancement of enantioselectivity (entry 6). 4-Nitrobenzoyl derivative **7e**, as expected, underwent the ring-opening at a faster rate, but, unfortunately, produced a lower selectivity factor (entry 7), which did not improve when the reaction temperature was

Scheme 1. BTM-Catalyzed DKR of Azlactones



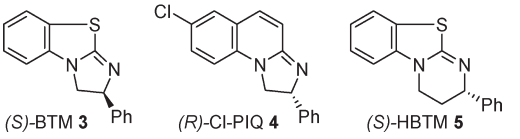
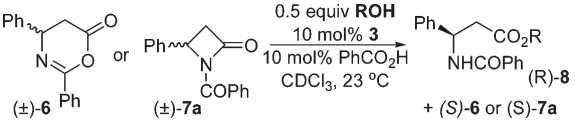


Figure 1. Amidine-based catalysts (ABCs) used in this study.

Table 1. KR of Oxazinone 6 and β-Lactam 7a[a]



entry	substrate	ROH	time (h)	% conv	*s*
1	**6**	$(1\text{-Np})_2$CHOH	28	51	2.9
2	**6**	$PhCH_2OH$	28	56	3.9
3	**6**	MeOH	28	48	3.3
4	**7a**	$(1\text{-Np})_2$CHOH	68	51	21
5	**7a**	$PhCH_2OH$	68	52	19
6	**7a**	MeOH	24	60	18

[a] Conditions: 0.1 mmol substrate, 0.05 mmol alcohol, 0.01 mmol (*S*)-BTM **3**, 0.01 mmol $PhCO_2H$, 1 mL $CDCl_3$, 23 °C.

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Scheme 2. Two Enantioselective Alcoholysis Mechanisms

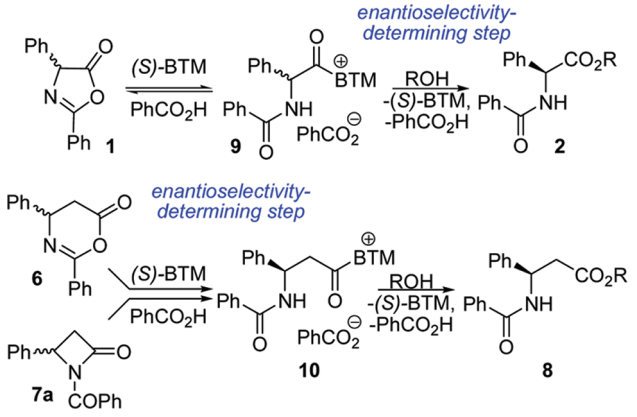
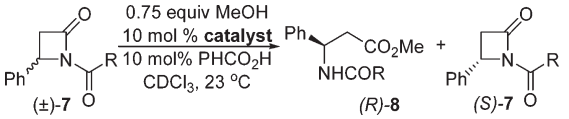


Table 2. Optimization Study[a]



entry	cat	R	time	% conv	*s*
1	**3**	Ph (**7a**)	24 h	60	18
2[b]	**4**	Ph (**7a**)	7 d	42	2.5[−1]
3	**5**	Ph (**7a**)	3 d	62	12[−1]
4	**3**	OBu-*t* (**7b**)	7 d	NR[d]	ND[e]
5	**3**	Me_2CH (**7c**)	7 d	NR	ND
6	**3**	*p*-ClC_6H_4 (**7d**)	20 h	53	26
7	**3**	*p*-$NO_2C_6H_4$ (**7e**)	5 h	53	20
8[c]	**3**	*p*-$NO_2C_6H_4$ (**7e**)	36 h	50	20
9	**3**	3,5-$(NO_2)C_6H_3$ (**7f**)	1 h	72	2.6

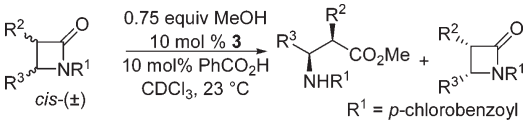
[a] Conditions: 0.1 mmol substrate, 0.05 mmol MeOH, 0.01 mmol catalyst **3**−**5**, 0.01 mmol $PhCO_2H$, 0.75 mL $CDCl_3$, 23 °C, unless specified otherwise. [b] Benzyl alcohol was used instead of methanol. [c] Conducted at 0 °C. [d] NR = no reaction. [e] ND = not determined.

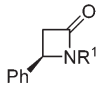
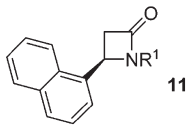
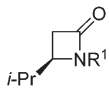
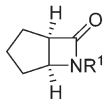
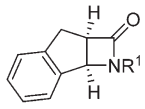
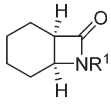
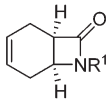
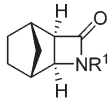
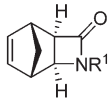
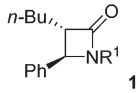
lowered (entry 8). 3,5-Dinitrobenzoyl derivative **7f** reacted even faster and with much lower enantioselectivity (entry 9).

Upon completion of the optimization studies, we undertook exploration of the substrate scope (Table 3). Replacement of the C4 phenyl group in **7d** with a 1-naphthyl resulted in a slight increase in enantioselectivity (entry 2 vs 1). 4-Isopropyl analogue **12** was resolved with an impressive selectivity factor of 78 (entry 3). Even higher enantioselectivities were recorded in the case of ring-fused β-lactams **13**−**18** (entries 4−9). On the other hand, the trans-disubstituted monocyclic substrate **19** did not react at all over the course of 1 week (entry 10). The practical utility of the new process is illustrated by the 1-g scale resolution of substrate **17** easily available via [2 + 2]-cycloaddition of norbornene and chlorosulfonyl isocyanate[5] (Scheme 3).

All available evidence indicates that in the reaction described above the enantioselectivity is determined during the irreversible nucleophilic attack of the catalyst on the acyl donor. This is in sharp contrast to all previously examined asymmetric transformations promoted by amidine-based catalysts, which rely upon enantiodifferentiation of their *N*-acylated derivatives[15−18] or the corresponding enolate zwitterions.[19] To rationalize our experimental observations, we propose the model presented in Figure 2.

Table 3. Substrate Scope[c]



entry	(±)-substrate[a]	time	% ee_{PR}[b]	% ee_{SM}[b]	% conv	*s*
1	 **7d**	20 h	79	90	53	26
2	 **11**	22 h	78	95	55	30
3	 **12**	3 d	93	84	47	78
4	 **13**	56 h	96	92	49	166
5	 **14**	24 h	89	99.8	53	111
6	 **15**	4 d	97	81	45	196
7	 **16**	7 d	98	59	38	211
8	 **17**	66	95	95	50	156
9	 **18**	32	96	82	46	124
10	 **19**	7 d	ND	ND	NR	ND

[a] Absolute configuration of the fast-reacting enantiomer is shown. [b] Averaged ee values of two or more experiments are shown. [c] Conditions: See Table 2.

We hypothesize that the catalyst approaches the β-lactam carbonyl preferentially from the unsubstituted face with the C2 phenyl group pointing outward so as to minimize steric interactions with the ring hydrogens. In this orientation, the phenyl group will be repelled by the *N*-acyl group on the slow-reacting substrate, but not on the fast-reacting one. The orientation of the proton source (benzoic acid and/or the protonated form of BTM) in the transition state is unclear at this point. It is logical to assume that it activates the substrate via hydrogen bonding to the carbonyl groups (no reaction occurs in the absence of added Brønsted acid, analogously with the DKR of azlactones[9,12]). On the basis of this model, one would predict that increasing the steric bulk of the R^3 and R^2 groups on the same face of the

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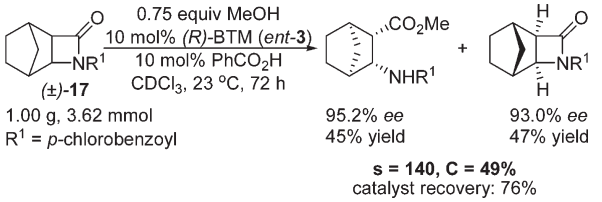
Scheme 3. Preparative-Scale KR of Substrate 17



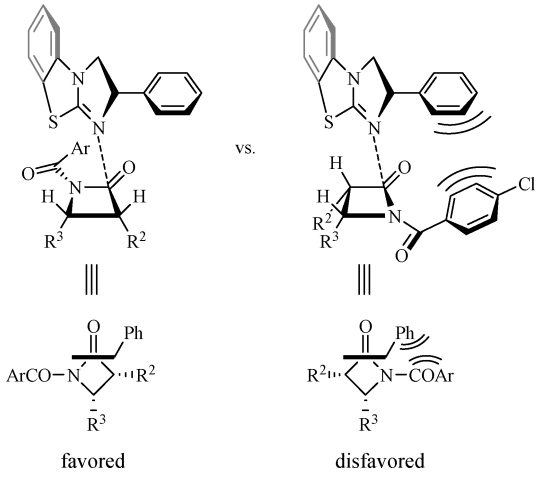


Figure 2. Proposed mode of enantiodiscrimination. The Brønsted acid is omitted for the sake of simplicity.

substrate should lead to higher enantioselectivity by suppressing the attack from that face, whereas substitution on both faces should prevent the reaction altogether. The data in Table 3 are fully consistent with this prediction.

In conclusion, we have developed the first nonenzymatic method for the asymmetric opening of the β-lactam ring, affording good to excellent enantioselectivities. In addition to providing a new route to enantioenriched β-amino acid derivatives, this study highlights a new facet in the chemistry of amidine-based catalysts. Further elucidation of the origin of enantioselectivity in this transformation and its application to new classes of substrates will be the subject of our future studies.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
birman@wustl.edu

■ ACKNOWLEDGMENT

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