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Kinetic Resolution of β-Lactams via Enantioselective N-Acylation

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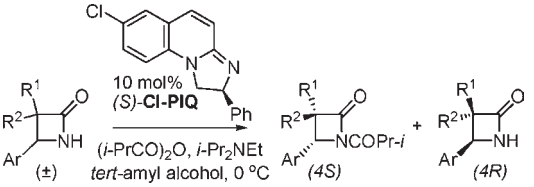
ABSTRACT



Enantioselective N-acylation of 4-aryl-β-lactams in the presence of acyl transfer catalyst Cl-PIQ provides an effective method for their non-enzymatic kinetic resolution.

β-Lactams (azetidin-2-ones) are widely known both as pharmaceuticals (e.g., antibiotics[1] and cholesterol-lowering drugs[2]) and as versatile intermediates in the preparation of other classes of organic compounds.[3] Enantioselective approaches to their synthesis, despite the many advances achieved in this field,[4] remain limited in their scope. Therefore, enzymatic kinetic resolution[5] (KR) of their racemates, mostly via β-lactam ring opening[6] or O-acylation of *N*-hydroxymethyl derivatives,[7] continues to be widely used (Figure 1).[8,9] Enantioselective N-acylation, which would provide an alternative direct method for the KR of N-unsubstituted β-lactams, has not been previously reported.

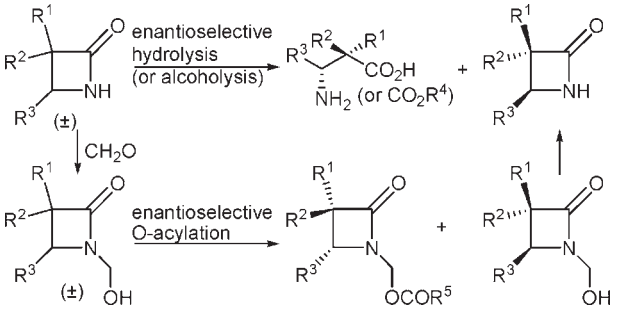


Figure 1. Enzymatic approaches to KR of β-lactams.

Several years ago, we disclosed the first examples of KR of racemic oxazolidin-2-ones via catalytic, enantioselective N-acylation.[10] As part of a broader study aimed at

(1) (a) Testero, S. A.; Fisher, J. F.; Mobashery, S. β-Lactam Antibiotics. In *Burger's Medicinal Chemistry, Drug Discovery and Development*, 7th ed.; Abraham, D. J., Rotella, D. P., Eds.; Wiley: Hoboken, NJ, 2010; Vol. 7 (Antiinfectives), pp 259–404. (b) Troisi, L.; Granito, C.; Pindinelli, E. Novel and Recent Synthesis and Applications of β-Lactams. In *Heterocyclic Scaffolds I*; Banik, B. K., Ed.; Springer: Berlin/Heidelberg, 2010; Vol. 22, pp 101–209.

(2) Discovery of Zetia (Ezetimibe): Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973.

(3) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.

(4) For select examples, see: (a) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592. (c) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. For reviews, see: (d) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988. (e) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. *Curr. Org. Chem.* **2009**, *6*, 325.

(5) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(6) (a) Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G.; Wisdom, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2276. (b) Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068. (c) Forró, E.; Paál, T.; Tasnádi, G.; Fülöp, F. *Adv. Synth. Catal.* **2006**, *348*, 917.

(7) (a) Jouglet, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 2307. (b) Csomós, P.; Kanerva, L. T.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1789.

(8) For a review of available enzymatic methods, see: Forró, E.; Fülöp, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 93.

(9) A non-enzymatic KR method based on enantioselective ring opening of β-lactams has been developed recently: Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* 2011, DOI: 10.1021/ja2058633.

(10) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536.

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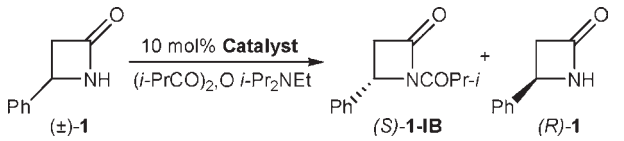
extending this methodology to other classes of secondary amides,[11−13] we decided to explore the KR of β-lactams.

Table 1. Optimization Studies



entry	catalyst	solvent	temp, °C	time, h	% convn	s
1	**2**	$CDCl_3$	23	24	0[a]	ND
2	**3**	$CDCl_3$	23	48	~10[a]	ND
3	**4**	$CDCl_3$	23	24	33	10
4[b]	**4**	$CDCl_3$	23	4.0	35[a]	1.0
5[c]	**4**	$CDCl_3$	23	10	35	1.8
6	**4**	CH_2Cl_2	23	24	21	5.5
7	**4**	THF	23	24	22	6.6
8[d]	**4**	$EtMe_2COH$	23	10	45	16
9[d]	**4**	$EtMe_2COH$	0	24	47	20
10[e]	**4**	$EtMe_2COH$	0	48	33	19
11[f]	**4**	$EtMe_2COH$	0	24	35	21
12[d]	**4**	$HC{\equiv}CMe_2COH$	23	10	41	16

General conditions: 0.1 M (±)-**1**, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2NEt$, 0.01 M (10 mol %) catalyst, unless specified otherwise. The data reported are for single runs. [a] Conversion was determined by ^1H NMR. [b] $(MeCO)_2O$ was used instead of $(i\text{-PrCO})_2O$. [c] $(EtCO)_2O$ was used instead of $(i\text{-PrCO})_2O$. [d] 0.05 M (±)-**1** and 0.005 M (10 mol %) **4** were used. [e] 0.05 M (±)-**1** and 0.0025 M (5 mol %) **4** were used. [f] 0.05 M (±)-**1**, 0.05 M $(i\text{-PrCO})_2O$, 0.05 M $i\text{-Pr}_2NEt$, and 0.005 M (10 mol %) **4** were used.

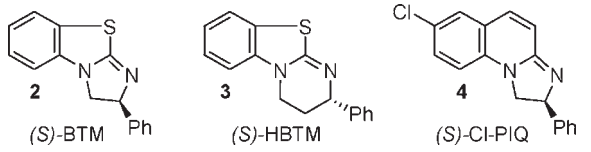
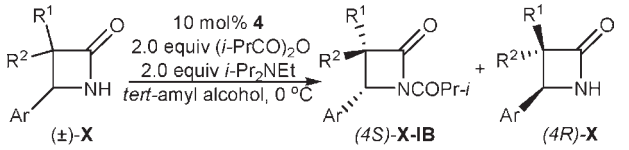
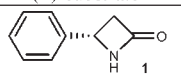
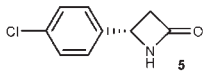
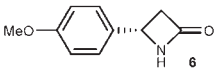
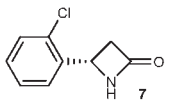
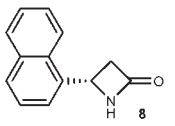
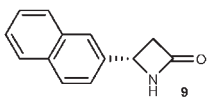
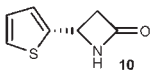
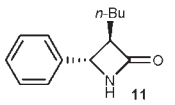
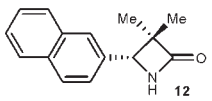
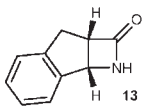
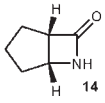


Figure 2. Amidine-based catalysts used in this study.

Table 2. Substrate Scope



entry	(±)-substrate[a]	time, h	% convn	s
1		24	43	22
2		30	54	30
3		30	42	38
4		30	14	3.1
5[b]		72	41	19
6		30	53	54
7		30	59	17
8[b]		72	38	16
9[b,d]		72	26	13
10		30	42	14
11[e]		24	0	ND

General conditions: 0.05 M racemic substrate, 0.1 M $(i\text{-PrCO})_2O$, 0.1 M $i\text{-Pr}_2NEt$, 0.01 M (10 mol %) **4**, *tert*-amyl alcohol, 0 °C, unless specified otherwise. The data reported are averages of duplicate runs. [a] Absolute configuration of the fast-reacting enantiomer is shown. [b] 0.2 M (4 equiv) of $(i\text{-PrCO})_2O$ and $i\text{-Pr}_2NEt$ were used. [c] Reaction performed in $CDCl_3$ at rt. [d] Absolute stereochemistry notation is inverted in this case according to CIP nomenclature rules.

As the starting point, we subjected (±)-4-phenyl-β-lactam **1** to the set of conditions that proved to be most successful in the KR of oxazolidinones. Disappointingly, no reaction took place within 24 h in the presence of 10 mol % of BTM[14c] **2** (Table 1, entry 1, and Figure 2). Furthermore, HBTM **3**,[14e] which typically displays higher catalytic activity than the previously developed catalysts **2**, reached

(11) The only other reported example of catalytic, enantioselective N-acylation of secondary amides: Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870.

(12) Enantioselective N-acylation of amines using non-enzymatic catalysts has also been reported: (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (c) Anstiss, M.; Nelson, A. *Org. Biomol. Chem.* **2006**, *4*, 4135. (d) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673. (e) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (f) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624. (g) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464.

(13) For recent reviews of non-enzymatic kinetic resolution and enantioselective acylation catalysts, see: (a) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (b) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (c) Spivey, A. C.; Arseniyadis, S. *Top. Curr. Chem.* **2010**, *291*, 233. (d) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (e) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

only low conversion after 2 days (entry 2). To our relief, however, Cl-PIQ **4**[14b] produced a more promising result (entry 3), which encouraged us to continue our investigation. The use of isobutyric anhydride proved critical for the success of the KR, as its less hindered analogues, acetic and propionic anhydrides, produced little to no enantioselectivity[15] (entries 4 and 5).

Survey of solvents revealed that *tert*-amyl alcohol significantly increased both the enantioselectivity and the reaction rate, although the substrate concentration had to be lowered due to its limited solubility (entry 8). This result was not particularly surprising, as the same solvent proved to be optimal for the Cl-PIQ-catalyzed KR of oxazolidinones.[16] Lowering the temperature to 0 °C increased the selectivity factor to a respectable level (entry 9). Lowering the catalyst loading or the concentration of the base and the acylating agent was deemed impractical due to the increase in reaction times (entries 10 and 11). Comparable results were also obtained at room temperature using the tertiary propargylic alcohol, 2-methyl-3-butyn-2-ol (entry 12). However, due to its higher freezing point compared to *tert*-amyl alcohol (+3 vs −12 °C, respectively), the latter was given preference in our exploration of the substrate scope (Table 2).

Somewhat unexpectedly, both *p*-chloro- and *p*-methoxy-substituted analogues of substrate **1** (**5** and **6**) were resolved with considerably higher selectivity factors (Table 2, entries 2 and 3 vs 1). On the other hand, *o*-chloro-substituted derivative **7** displayed rather disappointing enantioselectivity and very low reaction rate (entry 4). 4-(2-Naphthyl)-β-lactam **9** reacted with much higher rate and enantioselectivity than its 1-naphthyl isomer **8** (entries 5 and 6). Average results were obtained with 2-thienyl derivative **10** chosen as a representative of heteroaryl-substituted substrates (entry 7). Substitution at the C3 position of the β-lactam ring (**11** and **12**) led to significantly decreased reaction rates and enantioselectivities (cf. entries 8 vs 1 and 9 vs 6). Indene-derived substrate **13**, which may be regarded as a conformationally constrained analogue of **1**, reacted at a similar rate and with a somewhat lower selectivity factor (entry 10). This result was especially surprising given the complete lack of enantioselectivity in the acylation of 1-indanol under similar conditions.[14a] The analogous bicyclic substrate **14** lacking the benzene ring, however, proved to be completely unreactive (entry 11), which suggests the importance of π-interactions for substrate recogntion.[14a,f,17] The absolute sense of enantioselection observed with substrate **13** was confirmed to be the same as with **1**, as well as all oxazolidinones[10] and several classes of alcohols[14] investigated in our earlier studies. Although the latter two observations suggest at least qualitative similarity between the transition state operating in the KR of β-lactams and those proposed in previous cases,[14] the validity of this analogy remains to be probed by computational studies.

In conclusion, we have achieved the first enantioselective N-acylation of β-lactams leading to their effective nonenzymatic resolution. Extension of this methodology to related classes of substrates will be reported in due course.

Acknowledgment. We thank National Science Foundation for the financial support of our studies (CHE-1012979).

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

(14) Development of amidine-based catalysts: (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.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (e) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. (f) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836.

(15) Enantioselectivity in KR is expressed in terms of a selectivity factor (s) defined as the ratio of reaction rates of the fast- and the slow-reacting enantiomers of the starting material: $s = k_{fast}/k_{slow}$. In the KR of racemic mixtures, it is usually calculated from the ee values of the product and the unreacted starting material according to Kagan's equations (ref 5): (1) conversion $C = ee_{SM}/(ee_{SM} + ee_{PR})$; (2) selectivity factor $s = \ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$.

(16) Superior performance of this solvent had been noted earlier in the KR of alcohols with a planar chiral DMAP catalyst: Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

(17) To demonstrate the scalability of the new KR protocol, (±)-4-(*p*-chlorophenyl)-azetidin-2-one **5** was resolved on a 3 mmol scale. The starting material was recovered in 42% yield with 98% ee, in addition to the acylated product (57% yield, 74% ee) and 65% of the recovered catalyst. The calculated conversion (57%) and selectivity factor (s = 30) were in perfect agreement with the small scale experiment (Table 2, entry 2). See Supporting Information for further details.