Enantioselective Synthesis

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Enantioselective Synthesis and Stereoselective Ring Opening of *N*-Acylaziridines**

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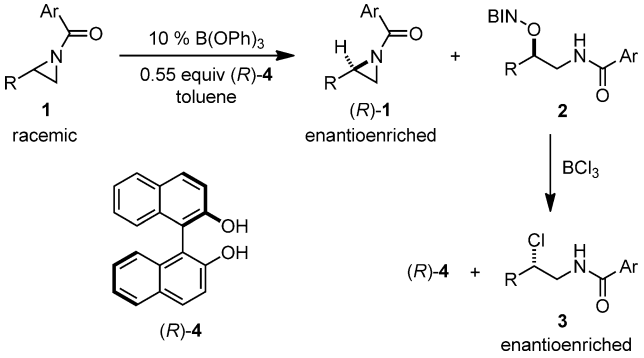
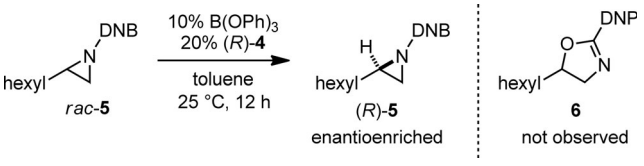
Enantiomerically pure aziridines are important synthetic intermediates for the synthesis of biologically active molecules.[1] The inherent ring strain and presence of stereogenic carbons attached to nitrogen make the aziridine a linchpin structure for the formation of enantioenriched 1,2-amino alcohols, 1,2-diamines, 1,2-amino thiols, and remote secondary amines.[2] Catalytic asymmetric aziridination has been reported for *N*-sulfonyl,[3] *N*-acyloxy,[4] *N*-alkyl,[5] and *N*-phosphoryl[6] aziridines with varying substrate scope; however, stereodefined *N*-acylaziridines cannot be directly produced in this manner. Enantioenriched *N*-acylaziridines can be generated from existing functionalized chiral synthons.[7] An alternative process for single enantiomer synthesis is kinetic resolution[8] which is known for reproducible production of enantiopure material, even on large scale. Despite the synthetic utility of single enantiomer aziridines, their production by kinetic resolution remains underdeveloped.[9] Moretti et al. disclosed an enzyme-catalyzed resolution of *N*-acylaziridines with limited substrate scope.[9c] The successful development of a versatile kinetic resolution for terminal epoxides,[10] the oxygen-analogue of aziridines, revolutionized their production as single enantiomers. Herein we report an operationally simple kinetic resolution of *N*-acylaziridines with a broad substrate scope using non-racemic 1,1′-bi-2-naphthol (BINOL, **4**) as the resolution reagent. The BINOL-derived byproduct (**2**) is further processed to recover BINOL and produce an enantiomerically pure 1,2-chloroamide (**3**, Scheme 1). The high synthetic utility of enantioenriched *N*-acylaziridines is also demonstrated.



Scheme 1. Boron-catalyzed kinetic resolution of *N*-acylaziridines. BIN = BINOL

N-Acylaziridines have a significant place in the development of aziridine ring opening reactions. The twisted amides are highly activated for nucleophilic addition at both the carbonyl carbon and the aziridine carbon backbone.[2c] Lewis acids[11] and Lewis bases[12] can promote the rearrangement of *N*-acylaziridines to oxazolines; however, with the correct choice of Lewis acid, desymmetrization[13] of *meso*-aziridines by nucleophiles can be achieved.[14] Early examples by Oguni et al.[15] employed zinc-tartrate reagents for the asymmetric thiolysis of aziridines. More recently, Shibasaki et al. have exploited the propensity for ring opening of *N*-acylaziridines to develop desymmetrization reactions with carbon[16] and nitrogen[17] nucleophiles. Antilla et al.[18] and Della Sala et al.[19] have demonstrated that chiral phosphoric acids also catalyze efficient desymmetrization reactions of *meso*-*N*-acylaziridines. Hydrogen bonding catalysts have also been developed for asymmetric chlorination[20] and thiolation[21] by aziridine desymmetrization. RajanBabu et al. recently reported the desymmetrization[22] and regiodivergent ring opening[23] of *N*-acylaziridines with azide. Despite the wide interest in asymmetric reactions of *N*-acylaziridines, their production as single stereoisomers by non-enzymatic kinetic resolution has not been disclosed.

N-Acylaziridines similar to **5** are known to undergo rearrangement under Lewis acid conditions[11] to the corresponding oxazoline (**6**), a process that could be engineered to produce enantioenriched **5** and **6** by kinetic resolution (Scheme 2). We hoped to extend our recent work with *N*-acylaziridines[24] to develop an asymmetric method for their



Scheme 2. Observation of aziridine kinetic resolution. DNB = 3,5-dinitrobenzoyl; DNP = 3,5-dinitrophenyl.

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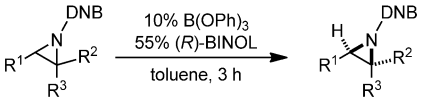
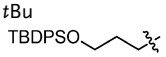
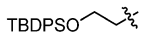
production. During a screen of enantioenriched Lewis acid complexes, a 3,5-dinitrobenzoyl(DNB)-protected aziridine (**5**) underwent kinetic resolution in the presence of triphenyl borate ($B(OPh)_3$) and (*R*)-**4**.[25] Instead of the anticipated 3,5-dinitrophenyl (DNP) oxazoline **6** or phenol addition,[26] a BINOL-derived side product was identified by ^1H NMR spectroscopy. Therefore, we concluded that BINOL had facilitated a kinetic resolution by functioning as a nucleophile.

Considering the low cost of non-racemic BINOL,[27] the process in Scheme 2 appeared to have significant synthetic importance, even if it may ultimately require 0.5 equiv of the chiral nucleophile. Following brief optimization of reaction conditions (see Supporting Information), a series of structurally diverse DNB-protected aziridines were subjected to kinetic resolution (Table 1). Reactions were generally performed in toluene at low temperature with (*R*)-**4** (0.55 equiv) for 3 h followed by column chromatography to isolate the scalemic aziridine. The selectivity factor (*s*)[28] was calculated from the determined yield and enantioselectivity data. Substrates containing an unhindered aliphatic chain underwent resolution with excellent selectivity (entry 1). A remote alkene was tolerated with no change in the *s*-factor (entry 2). Steric bulk played an important role in both reactivity and selectivity. The isobutyl substituted aziridine produced a slight increase in *s* (entry 3 versus 1). Aziridines with tertiary substituents were the most selective substrates, producing nearly enantiopure material under standard conditions (entries 4 and 5). Limitations in the method began to appear if the aziridine substituent was too small (entry 6) or too large (entry 7). In fact, the *tert*-butyl substrate required 24 h at room temperature to reach 13% conversion. Disubstituted aziridines gave markedly different results depending on substituent relationship. A *trans*-aziridine was poorly selective (entry 9), while a *cis*-aziridine was resolved with excellent selectivity (entry 10). Silyl ethers were tolerated with synthetically useful *s*-factors (entries 8 and 11); however, increased catalyst loading was required to produce efficient conversion. Attempts to generate DNB-protected aziridines containing tertiary or benzylic stereocenters were unsuccessful.[29]

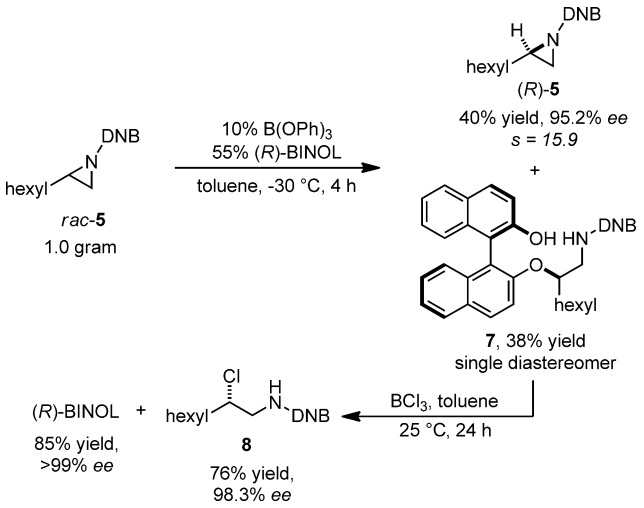
Table 1: Substrate scope for the kinetic resolution of *N*-acylaziridines with (*R*)-**4**.[a]



Entry	R^1	R^2	R^3	*T* [°C]	Yield [%][b]	*ee* [%]	*s*[c]
1	hexyl	H	H	−30	43	98.8	34
2		H	H	−30	48	92.8	44
3	*i*Bu	H	H	−40	46	98.1	51
4	*i*Pr	H	H	−40	48	99.4	131
5[d]	Cy	H	H	−40	49	99.4	255
6[e]	Me	H	H	−40	49	41.9	4
7[f]	*t*Bu	H	H	25	87	5.6	2
8[g]		H	H	−30	49	80.4	19
9	*n*Pr	*n*Pr	H	25	61	24.2	3
10	*n*Bu	H	Me	−30	48	79.6	16
11[g]		H	Et	−30	48	88.0	28

[a] Conditions: Resolutions were carried out on a 0.3 mmol scale with racemic aziridine (1.0 equiv), $B(OPh)_3$ (10 mol%), and (*R*)-**4** (0.55 equiv) in toluene (0.2 M) at the specified temperature for 3 h. Data represents a single run; however, runs were repeated a minimum of three times with the following standard deviations for entries 1–5: yield < 2% and *ee* < 2% (see Supporting Information for details). Entries 6–11 were reproducible, but had more variable standard deviations. [b] Yield of unreacted, isolated aziridine. [c] See Ref. [28]. [d] Reaction performed in 2:1 toluene/DCM. [e] Reaction performed for 30 min. [f] Reaction performed in DCM for 24 h. [g] 20 mol% $B(OPh)_3$ required.

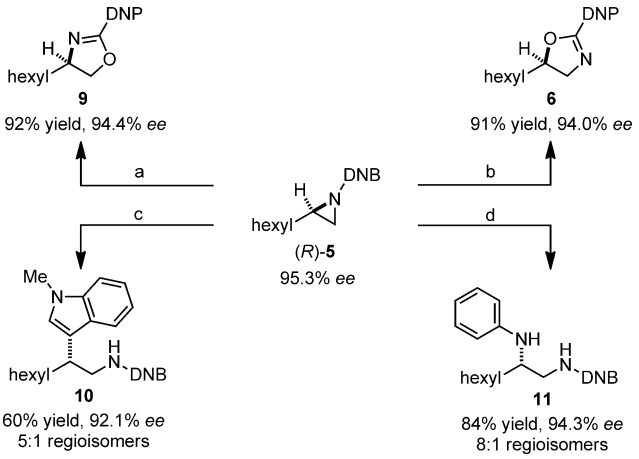
The described method is not catalytic in chiral modifier, and the recovery of BINOL on large scale would greatly improve reaction utility and lower the cost. The aziridine resolution was performed on 1 g of racemic **5** (Scheme 3). The



Scheme 3. Large-scale resolution of **5** with BINOL recovery.

s-factor decreased on this scale; however, the remaining aziridine could be isolated in 40% yield and 95% *ee*. The BINOL-derived byproduct (**7**) was isolated as a bright yellow solid in 38% yield as a single diastereomer. Elucidation of the new bond connection in **7** was completed by 2D NMR spectroscopy.[30] Treatment of **7** with 4 equiv of BCl_3 at room temperature led to quantitative conversion over 24 h, and (*R*)-**4** was recovered in 85% yield without loss of enantiopurity. BINOL cleavage had occurred by chlorination to produce the 1,2-chloroamide (**8**) in high yield. Interestingly, the reaction occurred stereospecifically, so **8** was generated with > 98% *ee*. Chlorination of (*R*)-**5** provided an independent synthesis of **8**, suggesting inversion of stereochemistry occurred during the BINOL cleavage of **7**. Hence, racemic aziridine can be processed to highly enantioenriched materials in 69% overall yield ((*R*)-**5** + **8**).

N-Acylaziridines are synthetically useful because of their propensity to undergo rearrangement and ring opening reactions to a series of functionalized molecules. Both regioisomers of oxazoline can be produced in high yield with excellent enantioselectivity depending on reaction conditions. Treatment of (*R*)-**5** with catalytic sodium iodide leads to oxazoline **9** by Heine rearrangement[12a] without loss of

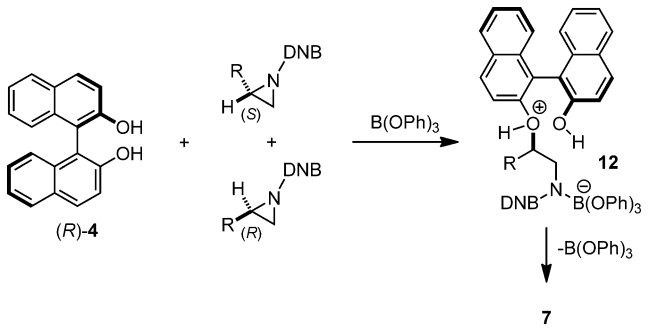


Scheme 4. Ring opening reactions of enantioenriched **5**. a) NaI (10 mol%), THF, 60°C, 12 h. b) TfOH (10 mol%), DCM, 0→25°C, 2 h. c) $Zn(OTf)_2$ (20 mol%), *N*-methylindole (4 equiv), DCM, 25°C, 18 h. d) $Zn(OTf)_2$ (20 mol%), aniline (4 equiv), DCM, 25°C, 18 h.

enantiopurity (Scheme 4). Alternatively, triflic acid (TfOH) catalyzes the regioisomeric rearrangement to oxazoline **6**.[11c,31] Only a very slight erosion of enantiopurity occurs despite bond formation at the stereogenic carbon.[11d,32] Lewis acids have been shown to catalyze the addition of nucleophiles to *N*-acylaziridines; however, nucleophilic attack must beat out rearrangement to **6**.[11e] While oxophilic Lewis acids generally prefer ring opening, the addition of excess indole to (*R*)-**5** in the presence of catalytic $Zn(OTf)_2$ results in ring opening at the more substituted aziridine carbon.[33] Tryptamine derivative **10** is isolated in 60% yield and 92% *ee*. The high regioselectivity and enantiospecificity for indole addition to the more hindered carbon of terminal *N*-acylaziridines is unprecedented.[34] Unprotected anilines are also competent nucleophiles for aziridine opening[35] with bond formation occurring on nitrogen to produce **11** in excellent yield and 94% *ee*. This data represents the first highly stereospecific example of aniline addition to the stereogenic carbon in terminal *N*-acylaziridines.[36]

A reaction mechanism for kinetic resolution is proposed in Scheme 5. The amide nitrogen in *N*-acylaziridines is pyramidalized because of ring strain, creating the opportunity for Lewis acid binding at either the amide nitrogen or oxygen.[37] Addition of $B(OPh)_3$ catalyzes the C–O bond formation with ring opening, likely by Lewis acid activation of the amide oxygen to generate intermediate **12** followed by proton transfer to regenerate the catalyst. For highly selective substrates, (*R*)-BINOL (**4**) preferentially attacks the *S*-configured aziridine enantiomer with inversion of stereochemistry at the aziridine carbon. Exchange of BINOL with phenol ligands on boron occurs at room temperature[25] and cannot be ruled out; however, we have never isolated phenol addition to aziridines suggesting $B(OPh)_3$ remains intact during the reaction.

In conclusion, a unique method for kinetic resolution of *N*-acylaziridines is disclosed. The consumed enantiomer of aziridine can be further processed to enantioenriched 1,2-chloroamides with BINOL recovery. We are actively working



Scheme 5. Proposed mechanism for borate-catalyzed kinetic resolution.

to harness the unique preference for stereospecific addition to terminal DNB-protected *N*-acylaziridines in further Lewis acid-catalyzed nucleophile additions. Mechanistic studies and expansion of the substrate scope for kinetic resolution are underway.

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[27] Non-racemic BINOL is a cheap source of chiral material when compared to the cost of achiral stoichiometric reagents used for asymmetric aziridination, such as tosyl azide ($5864/mol, Aldrich) and ethyl diazoacetate ($403/mol, Aldrich). For this study, we purchased (*R*)-BINOL from D-L Chiral Chemicals for $149/mol.

[28] Selectivity factor (*s*) is defined as $s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ where $C = (100-\text{yield of recovered aziridine})/100$ and $ee = \%\ ee/100$. A practical resolution is considered to be $s > 10$, see: a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249 – 330; b) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**; c) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040 – 4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974 – 4001.

[29] We have found that synthetically useful 2-aryl and trisubstituted DNB-protected aziridines readily rearrange to the corresponding oxazolines at the activated benzylic or tertiary C–N bond. Other terminal *N*-acyl and *N*-acyloxyaziridines undergo ring opening under our optimized conditions, but DNB-protected aziridines displayed superior selectivity factors.

[30] See Supporting Information for spectra and stereochemical rational. We propose an absolute configuration of *R* for the stereogenic carbon in **7**.

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[34] For indole additions to *N*-acylaziridines, see: a) J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59 – 68; b) L. Dubois, A. Mehta, E. Tourette, R. H. Dodd, *J. Org. Chem.* **1994**, *59*, 434 – 441; c) M. Bucciarelli, A. Forni, I. Moretti, F. Prati, G. Torre, *Tetrahedron: Asymmetry* **1995**, *6*, 2073 – 2080; for a stereospecific example with *N*-nosylaziridines, see: d) R. N. Farr, R. J. Alabaster, J. Y. L. Chung, B. Craig, J. S. Edwards, A. W. Gibson, G. J. Ho, G. R. Humphrey, S. A. Johnson, E. J. J. Grabowski, *Tetrahedron: Asymmetry* **2003**, *14*, 3503 – 3515.

[35] For examples of aniline additions to *N*-acylaziridines, see: a) K. Nakajima, T. Tanaka, K. Morita, K. Okawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 283 – 284; b) S. Peruncheralathan, M. Henze, C. Schneider, *Synlett* **2007**, 2289 – 2291; for aniline additions to aziridines catalyzed by metal triflate salts, see: c) M. Meguro, N. Asao, Y. Yamamoto, *Tetrahedron Lett.* **1994**, *35*, 7395 – 7398; d) G. Sekar, V. K. Singh, *J. Org. Chem.* **1999**, *64*, 2537 – 2539.

[36] For a stereospecific example with an *N*-tosylaziridine, see: M. K. Ghorai, A. K. Sahoo, S. Kumar, *Org. Lett.* **2011**, *13*, 5972 – 5975.

[37] a) F. A. L. Anet, J. M. Osyany, *J. Am. Chem. Soc.* **1967**, *89*, 352 – 356; b) G. R. Boggs, J. T. Gerig, *J. Org. Chem.* **1969**, *34*, 1484 – 1486; c) G. V. Shustov, G. K. Kadorkina, S. V. Varlamov, A. V. Kachanov, R. G. Kostyanovsky, A. Rauk, *J. Am. Chem. Soc.* **1992**, *114*, 1616 – 1623.

Communications

Enantioselective Synthesis

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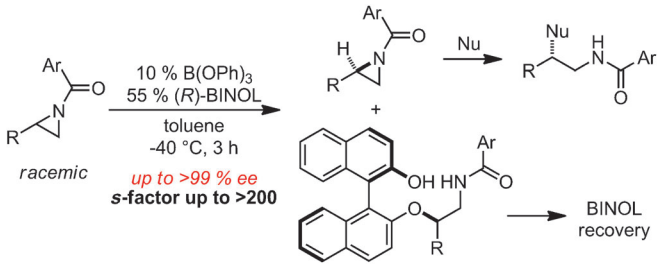
Enantioselective Synthesis and Stereoselective Ring Opening of *N*-Acylaziridines



Kinetic resolution of *N*-acylaziridines by nucleophilic ring opening was achieved with (*R*)-BINOL as the chiral modifier under boron-catalyzed conditions (see scheme; Ar = 3,5-dinitrophenyl). The consumed enantiomer of aziridine can be further converted to an enantioenriched 1,2-chloroamide with recovery of (*R*)-BINOL.