

Regiodivergent Ring Opening of Chiral Aziridines

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There are two common classes of asymmetric catalysis. In one class, the catalyst preferentially accelerates formation of one enantiomeric product over the other in the reaction of a prochiral reagent. In the second class, the catalyst preferentially accelerates reaction of one enantiomeric reagent over the other, a process termed kinetic resolution (1, 2). Both of these scenarios derive selectivity purely from rate differences associated with a single conserved reaction pathway. In a third, much rarer class, the catalyst accelerates the reaction of both members of a racemic mixture but does so along divergent pathways, inducing opposing chemoselectivity or regioselectivity in its respective encounters with each enantiomeric reagent (3). An advantage of this approach is that a full racemic mixture can be transformed into a set of desirable chirally resolved products.

Traditional enantioselective desymmetrizations of meso-epoxides (4) and aziridines (5), as well as kinetic resolutions of racemic epoxides (6), have been established as highly useful processes for the synthesis of enantiopure intermediates. The family of Cr(III)-salen catalysts shows impressive regioselectivities in ring openings, although it does not appear to be at the level of fully discriminating between enantiomers (7). The report that comes closest to a regiodivergent reaction scheme for this substrate class is an enzyme-catalyzed ring opening of epoxides (8). Even this case, however, relied on the use of two

different enzymes in the same reaction mixture, each of which independently catalyzed the reaction of its favored enantiomer. Here, we report that a single chiral small-molecule catalyst (2) induces divergent regioselectivities in the ring-opening reactions of racemic aziridine mixtures. High yields of 1,2-diamine derivatives can be obtained in nearly enantiomerically pure form [$>97\%$ enantiomeric excess (ee)] from racemic aziridines by this process (Fig. 1A table). The stereospecific nature of the azide attack inverts the configuration of one of the enantiomers. Thus, the configurations of the chiral centers in both β -azidoamides are identical, and it should in principle be possible to convert both compounds into a single 1,2-diamine derivative by subsequent transformations.

In initial experiments, we found that in the presence of trimethylsilylazide (TMSN₃) the dimeric yttrium-salen complex 2 (5) (Fig. 1B) catalyzed the ring-opening reactions of the two enantiomers of **1a** with exceptionally high, complementary regioselectivities (9). Accordingly, the nucleophilic attack occurs at the primary position in (*R*)-**1a**, leading to the azidoamide **3a** as the exclusive product, whereas (*S*)-**1a** gives the product **4a**, resulting from exclusive S_N2-inversion at the secondary center. The ee (54%, *R* major) of the small amount of recovered starting material **1a** suggests that the more-reactive (*S*)-enantiomer is consumed about 3.35 times faster than the slow-reacting (*R*)-isomer. A number of structurally different aziridines were subjected to the ring-opening reactions, and the results are

listed in the table. For most substrates (entries 1 through 5, 7, and 9), the reaction proceeds with $>99\%$ enantioselectivity in the formation of the primary azide **3**. For the *t*-butyl derivative (entry 6), the selectivity is slightly lower (95% ee). Selectivities in the formation of **4** [mostly from the fast-reacting (*S*)-aziridine] are also impressive, with slightly lower values observed for **1d** (90% ee) and **1e** (93% ee). Curiously, in the case of the *t*-butylaziridine (**1f**), the normally fast-reacting (*S*)-isomer was recovered along with some of the unreacted (*R*)-isomer (entry 6). Apparently, the superior kinetic selection by the catalyst cannot completely overcome the inherent reactivity of this substrate.

The high specificity of the reactions and identity of the products were further confirmed by reactions of enantiopure aziridines with TMSN₃ (entries 7 to 10). Even in the exceptionally challenging situation where the enantiomers differ solely by placement of a methyl group (entries 9 and 10), the (*R*)-enantiomer of the aziridine gives exclusively the primary azide (*R*)-**3 g** ($>99\%$ ee) and the (*S*)-enantiomer, the secondary azide (*R*)-**4 g** (96% ee), with no trace of contamination by the regioisomeric product in either case.

The exact origin of the selectivity of this catalyst remains to be established. Control experiments [see (9)] suggest that both the rate acceleration and selectivity are quite sensitive to the catalyst structure. It is conceivable that the capsular nature of the chiral bimetallic catalyst, as revealed by its solid-state structure, helps to bind the two enantiomers of the aziridine in distinct orientations during the activation process, and each of the diastereomeric complexes has a different electrophilic carbon favorably juxtaposed for attack by the nucleophile, possibly activated by the second yttrium.

References and Notes

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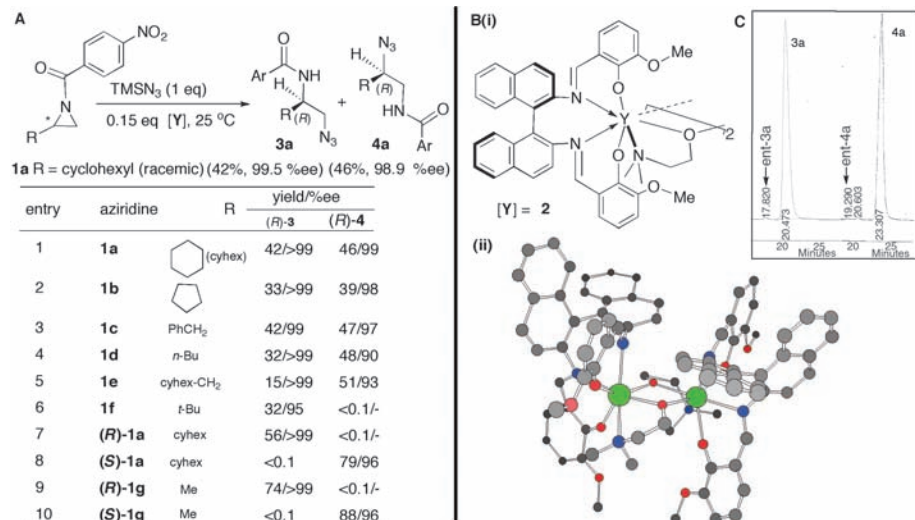


Fig. 1. (A) Regiodivergent kinetic resolution of racemic aziridines. (B) (i) Chemical and (ii) solid state [from (5)] structure of the dimeric Y catalyst; H atoms omitted for clarity. (C) Chiral stationary phase high performance liquid chromatography (HPLC) analysis of reaction products of **1a**.