Communication

Dynamic Kinetic Resolution of Allylic Azides via Asymmetric Dihydroxylation

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Dynamic Kinetic Resolution of Allylic Azides via Asymmetric Dihydroxylation

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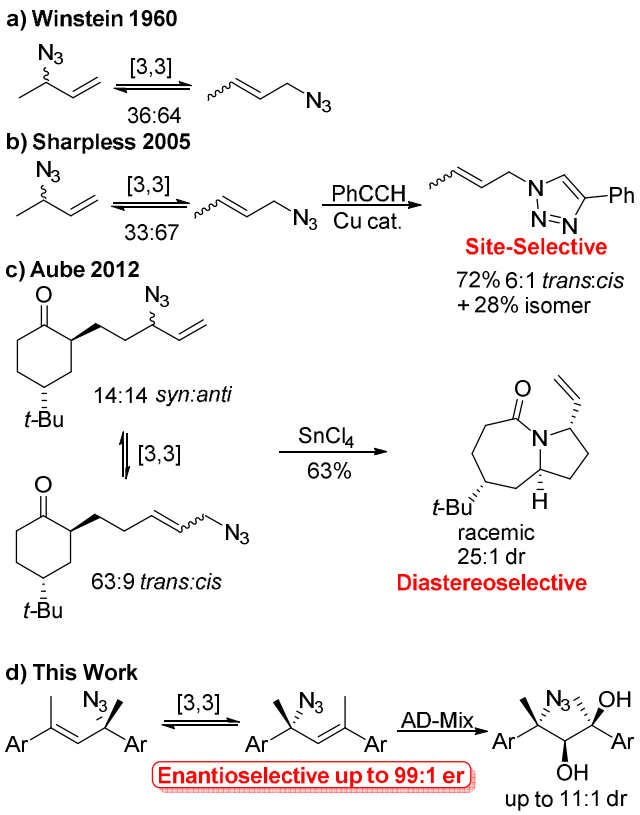
Supporting Information Placeholder

ABSTRACT: The catalytic enantioselective preparation of densely functionalized amines is a fundamental synthetic challenge. To address this challenge, we report for the first time that the Winstein rearrangement can be enlisted as the racemization pathway in a dynamic kinetic resolution of allylic azides. Alkene functionalization by Sharpless dihydroxylation affords tertiary azides in excellent enantioselectivity (up to 99:1 er). This approach establishes the chirality of the tertiary azide, obviates the need to directly forge either a congested C-N or C-C bond at the new nitrogenous stereocenter, and establishes additional functionality. Several examples demonstrate further elaboration of this functionality.

The seminal report describing the rearrangement of allylic azides was authored by Winstein in 1960.[1] The rearrangement, which is thought to occur via a sigmatropic process, typically occurs at or near room temperature (Scheme 1a). While the Winstein rearrangement has been observed in many contexts,[2] selectivity challenges inherent in the azide mixture have limited its synthetic applications. In 2005, Sharpless and co-workers reported that site-selectivity could be achieved in some instances by exploiting different alkene substitution patterns (Scheme 1b).[3] Subsequently, it was shown by Aubé and co-workers that the equilibrating mixture of azides could be differentially functionalized in an intramolecular Schmidt reaction that differentiated the azides based on the relative rates of ring closure (Scheme 1c).[4] Based on this precedent, we hypothesized that the Winstein rearrangement could be used as the racemization pathway in a dynamic kinetic resolution. Herein, we report the successful achievement of this goal.

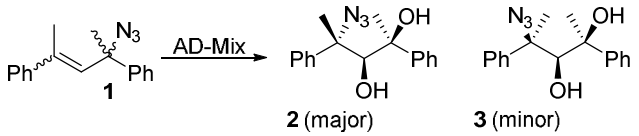
Dynamic kinetic resolution (DKR) is a premier approach for asymmetric synthesis.[5,6] The principle attribute of DKR is the obtention of enantioenriched material from a racemic mixture. A wide array of catalysts can participate in a DKR including enzymes,[7] transition metal complexes,[8] Brønsted acids/bases,[9] and organocatalysts.[10] While DKR is a powerful approach to establish absolute configuration, it commonly suffers from several limitations including the (i) requirement for a mechanistic pathway for racemization, (ii) common need for two separate catalysts, which must be mutually compatible, and (iii) delicate balance of relative rates in the synchronized catalytic cycles. In practice, this has largely limited DKR to easily epimerizable α-carbonyl stereocenters, redox active sites (i.e. secondary alcohols), or hydrolysis reactions.[5] Employing sigmatropic reactions as the racemization pathway in a DKR is appealing because these reactions do not require an exogenous catalyst. However, this has only rarely been described, presumably due to the relatively high activation energies of these processes.[11] Thus, it appeared that the relatively low activation barrier of the Winstein rearrangement would make it a particularly powerful racemization pathway in DKR if a suitable alkene functionalization reaction was identified. A Winstein rearrangement-facilitated DKR would have the further attribute of directly affording sterically congested amine equivalents present as stereodefined tertiary azides. Sterically congested chiral amines of this nature comprise a motif of considerable significance in the preparation of biologically

Scheme 1. Winstein Rearrangement and Dynamic Resolutions



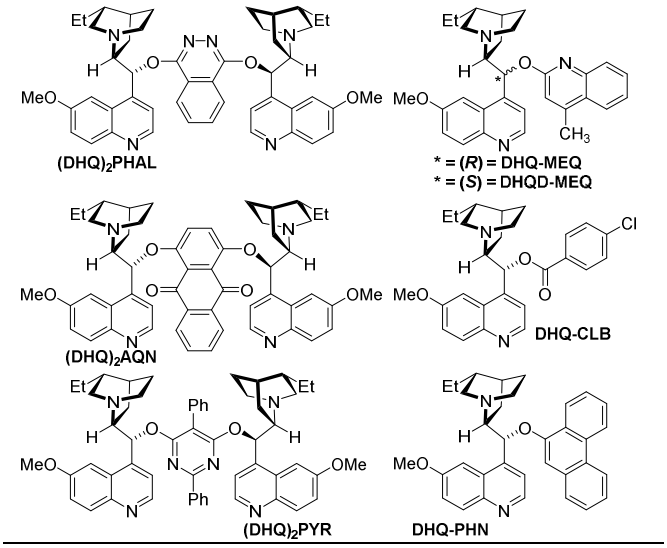
relevant compounds including recent families of BACE-1 inhibitors.[12] Herein, we disclose our initial efforts in this regard by coupling the Winstein rearrangement with one of the most venerable alkene functionalization reactions, namely the Sharpless asymmetric dihydroxylation (SAD, Scheme 1d).[13]

Table 1. Screening SAD based DKR[a]



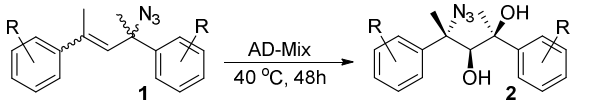
entry	ligand	temperature (°C)	yield (%)	er (of **2**)	dr
1	$(DHQ)_2PHAL$	40	82	91:9	4:1
2	$(DHQ)_2AQN$	40	79	83:17	5.5:1
3	$(DHQ)_2PYR$	40	91	89:11	4.5:1
4	DHQ-CLB	40	86	86:14	8.5:1
5	DHQ-PHN	40	81	97:3	19:1
6	DHQ-MEQ	40	82	99:1	11:1
7	DHQD-MEQ	40	83	98:2	8:1
8	DHQ-MEQ	rt	85	99:1	8:1
9	DHQ-MEQ	30	87	98:2	7:1
10	DHQ-MEQ	50	86	97:3	8:1
11	DHQ-MEQ	60	78	95:5	7:1

[a]Reaction Conditions: substrate (0.08 - 0.2 mmol), *t*-BuOH (10 mL/mmol), water (10 ml/mmol), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (3 equiv), $K_3Fe(CN)_6$ (3 equiv), OsO_4 (5 mol%), L (10 mol%), under air, 48 h. Yields and dr where determined by ^1H NMR spectroscopic analysis using triphenylmethane as an internal standard. The represented dr is the integration ratio of the respective hydroxylated methine. The enantiomeric ratio was determined by chiral HPLC analysis. All values reported are the average of duplicate trials.



Our investigation began with azide **1**, which was prepared in three steps from the dimerization of acetophenone.[14] Exposure of azide **1** to standard SAD conditions provided poor conversion and modest enantioselectivity. Gratifyingly, a brief optimization afforded satisfactory results for the formation of diol **2** (82% yield 91:9 er, Table 1, entry 1) and a minor diastereomer. A screen of known SAD ligands (entries 2-6) led to the identification of DHQ-MEQ as the ligand of choice due to its excellent performance (entry 6, 82%, 99:1 er, 11:1 dr) and relatively low cost. The pseudoenantiomer DHQD-MEQ provided nearly identical results but provided the opposite enantiomer (entry 7). Given that the rate of racemization via the background rearrangment is temperature dependent, we examined the effect that temperature had on the reaction outcome (entries 8-11). Acceptable yields and enantioselectivity were maintained across the temperature range investigated, although 40 °C appeared to be optimal. The absolute configuration of the product was assigned based on the model of Sharpless.[13,15] When at equilibrium, the starting azide **1** contains about 5% of the *Z* isomer by ^1H NMR analysis. It was not initially clear if the minor diastereomer **3** arose from dihydroxylation of the *Z* isomer or from the opposite enantiomer of the *E* isomer. The relative configuration of the major and minor diastereomer were assigned based on X-ray crystallographic analysis.[16] The minor diastereomer differs in the relative arrangement of the azide and arises from dihydroxylation of the same face of the enantiomeric *E* azide isomer. No products were observed that arise from the *Z* isomer. Diastereocontrol in this system likely arises from negative hyperconjugation.[17] The high level of control in this system is due to a combination of enantioselectivity and diastereoselectivity. It is noteworthy that this catalytic process simultaneously establishes three consecutive stereocenters, two of which are to fully substituted carbons, in a single operation. Of the 8 possible stereoisomers that could arise from this reaction, ~90% of the product is a single stereoisomer.

Table 2. Substrate Scope of SAD based DKR[a]



entry	R =	yield (%)	er (of **2**)	dr
1	H	79	99:1	11:1
2[b]	4-*t*-Bu	77	99:1	10:1
3[b]	4-*i*-Bu	81	95:5	10:1
4	4-F	75	98:2	9.5:1
5	4-Cl	80	98:2	10:1
6	4-Br	72	98:2	9:1
7	4-CF_3	73	97:3	9:1
8[b]	3-F	76	98:2	9:1
9	3-Cl	81	97:3	10:1
10[b]	3,5-diF	65	96:4	6:1

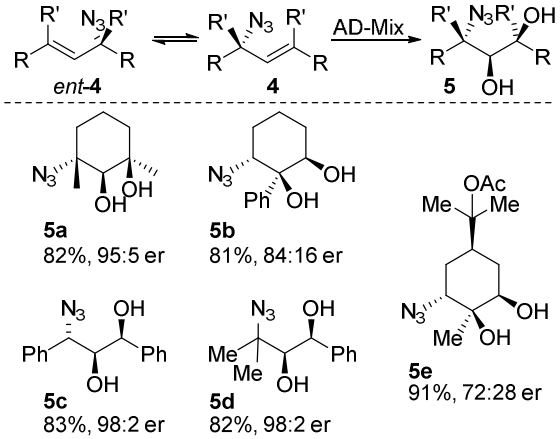
[a]Reaction Conditions: substrate (0.3 – 0.4 mmol), *t*-BuOH (10 mL/mmol), water (10 ml/mmol), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (3 equiv), $K_3Fe(CN)_6$ (3 equiv), OsO_4 (5 mol%), DHQ-MEQ (10 mol%), 40 °C, under air, 48 h. Yields reported are for isolated material. The dr was determined by ^1H NMR spectroscopic analysis. The represented dr is the integration ratio of the respective hydroxylated methine. The enantiomeric ratio was determined by chiral HPLC analysis after purification. All values reported are the average of duplicate trials. [b]Reaction was conducted at 35 °C

We investigated the scope of this Winstein rearrangement tandem SAD based DKR (Table 2). The model system was isolated in acceptable yield (entry 1). An array of other aromatic substituents were tolerated in this process including electron rich (entries 2-3), halogenated (entries 4-6), electron deficient (entry 7), and 3-substituted arenes (entries 8-10).

Across this range of substituents, the selectivity was maintained and high levels of enantioselectivity were observed.

We examined substrates other than symmetric acetophenone derivatives (Scheme 2). Highly substituted cyclohexane derivatives lacking any aryl rings provided excellent er in the diol product (compound 5a), as did less substituted cyclohexyl-rings (compound 5b). This process was capable of affording secondary azides with excellent enantioselectivity (compound 5c) and was viable on non-symmetric allylic azides (compound 5d). A derivative of *trans*-sobrerol was also dihydroxylated in satisfactory yield and selectivity.

Scheme 2. Dihydroxylation of Other Substrate Classes

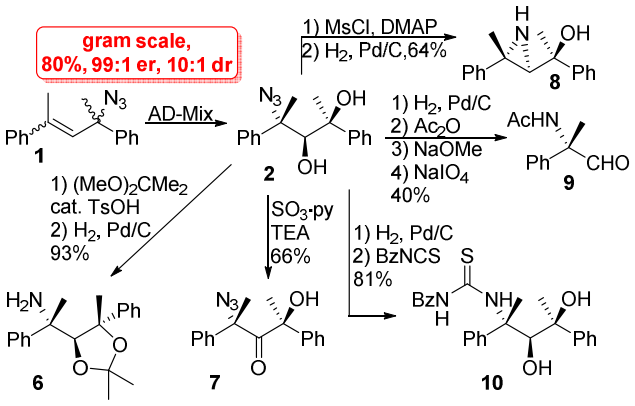


[a]Reaction Conditions: substrate (0.3 – 0.4 mmol), *t*-BuOH (10 mL/mmol), water (10 ml/mmol), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (3 equiv), $K_3Fe(CN)_6$ (3 equiv), OsO_4 (0.2 - 5 mol%), L (0.4 - 10 mol%), rt, under air, 24 h. Yields reported are for isolated material. The enantiomeric ratio was determined by chiral HPLC analysis after purification. All values reported are the average of duplicate trials.

This DKR is readily scalable and both the enantioselectivity and yield remained constant for a reaction performed using more than one gram of substrate (Scheme 3). Furthermore, the products formed from this dynamic kinetic resolution are of potential synthetic value (Scheme 3). For instance, the diol was selectively protected and the azide reduced to the amine (compound **6**). The secondary alcohol can be selectively oxidized to form ketone **7**. Alpha-azido ketones pose unique reactivity and are valuable intermediates.[18] Activation on the secondary alcohol and azide reduction affords aziridine **8**. The diol can be subjected to glycolytic cleavage to afford the corresponding α-amino aldehyde **9**. Finally, the azido diol can be converted to thiourea **10**, a direct aminothiazine precursor. Numerous aminothiazine based BACE-1 inhibitors have been reported and are currently under clinical investigation for the treatment of Alzheimer's disease.[12] The chiral amine motif in these BACE-1 inhibitors has been established almost exclusively by the use of Ellman's auxiliary.[19] Our DKR approach is a potential catalytic alternative for some of these inhibitors where the requisite hydroxyl group is also established during the DKR.

In conclusion, we have successfully accomplished the first DKR that takes advantage of the Winstein rearrangement as the racemization pathway. When this background rearrangement is coupled to a Sharpless asymmetric dihydroxylation, high levels of stereocontrol are observed in the resulting tertiary azide. This azide can be converted to products of interest or to other reactive intermediates. The Winstein rearrangement, acting as a racemization process, has the potential to be coupled with numerous other alkene functionalization reactions. Our continued efforts in this regard will be reported in due course.

Scheme 3. Elaboration of Product Diol



ASSOCIATED CONTENT

Supporting Information

Supporting information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and data (PDF)

Crystallographic data for compounds **2** and **3** (CIF)

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Notes

The authors declare no competing financial interests.

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[15] For a full discussion of the stereochemical outcome of this reaction, please see the supporting information section "Discussion of Stereochemical Outcome and Diastereoselectivity."

[16] See supporting information for ORTEP.

[17] See the supporting information for a full discussion of stereocontrol. For seminal works on negative hyperconjugation see: (a) Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P. R., Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221. (b) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371.

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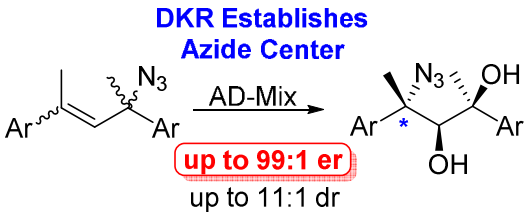
DKR Establishes
Azide Center
N3
Ar
Ar
AD-Mix
N3
OH
Ar
*
Ar
OH
up to 99:1 er
up to 11:1 dr