JOC The Journal of Organic Chemistry

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Organocatalytic Enantioselective [1,2]-Stevens Rearrangement of Azetidinium Salts

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Cite This: https://doi.org/10.1021/acs.joc.4c00534 Read Online

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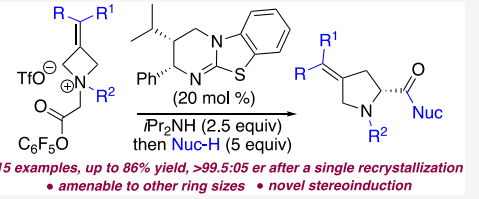
ABSTRACT: The first organocatalyzed enantioselective [1,2]-Stevens rearrangement is reported. 4-Alkylideneproline derivatives are produced in up to 86% yield and in up to 90:10 er, with recrystallization enhancing er up to >99.5:0.5. Product configuration was opposite that predicted by existing stereochemical models for this organocatalyst class, and DFT calculations revealed a novel mode of asymmetric induction. The adaptability of this catalytic strategy for asymmetric [1,2]-Stevens rearrangements of other heterocyclic amines was demonstrated.



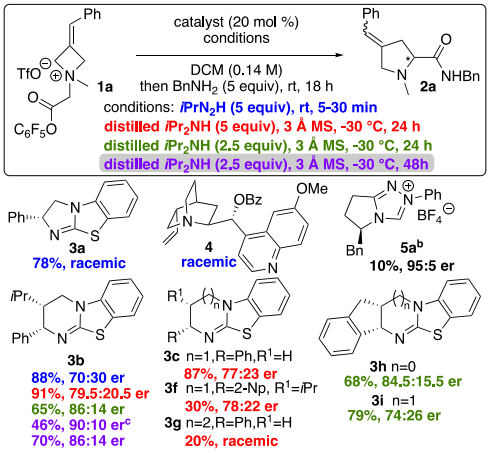
[1,2]-Stevens rearrangements of cyclic ammonium ylides produce ring-expanded heterocycles.[1,2] Application of this transformation in alkaloid synthesis,[3] however, is limited by the near total void of catalytic asymmetric methods.[4] Syntheses employing this rearrangement provide racemic natural products,[5] or require enantiopure quaternary ammonium salt substrates to access alkaloids as single enantiomers.[6] Catalytic asymmetric [1,2]-Stevens rearrangements of ammonium ylides have been hampered by several considerations. First, its reaction mechanism has been debated in the literature as recently as 2020.[7] Further, a competing [2,3]-sigmatropic rearrangement is possible, and is proposed to proceed via the same transition state, complicating differentiation between these two reaction pathways.[8] Consequently, the first catalytic asymmetric [2,3]-sigmatropic rearrangement of ammonium ylides was reported only within the past decade, and utilized an isothiourea organocatalyst.[9]

The first catalytic enantioselective [1,2]-Stevens rearrangements of ammonium ylides were reported very recently.[4] The corresponding rearrangements of oxonium and sulfonium ylides have been known for longer, with the former first reported over half a century ago.[10,11] Notably, to date, all catalytic enantioselective [1,2]-Stevens rearrangements effectively employ the same catalytic strategy. All proceed via chiral metal-bound or metal-associated ylides, generated, with few exceptions,[4a,10e] by insertion of a chiral metal catalyst into a diazo substrate and subsequent heteroatom trapping.

Since Lewis base organocatalysis was effective for enantioselective [2,3]-sigmatropic rearrangements,[9] which share a transition state with the [1,2]-Stevens rearrangement,[8] we wondered whether this class of organocatalysts would be amenable to the latter transformation. Gratifyingly, we report herein the first metal-free catalyzed asymmetric [1,2]-Stevens rearrangement.[4e]

Azetidinium **1a** (Scheme 1) was selected for development of this transformation, as it is primed for ring expansion, and its geometric constraints suppress a concerted [2,3]-sigmatropic rearrangement. A TfO− counterion prevented in situ ring-opening observed with a more nucleophilic, Br− counterion.[12]

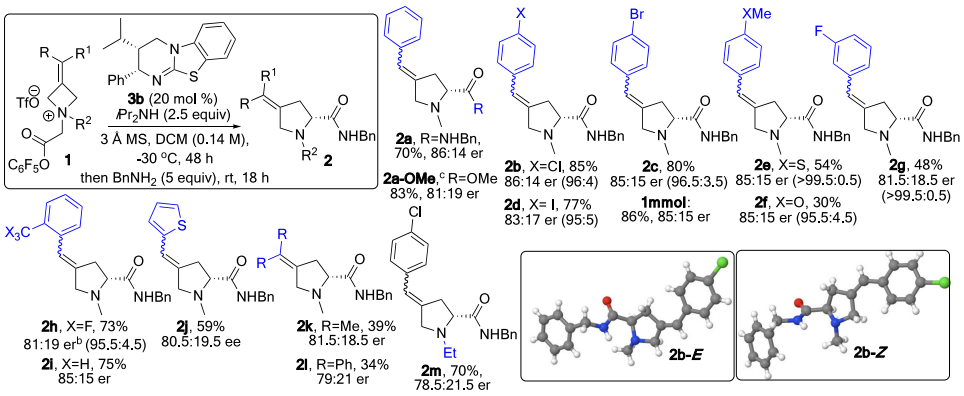
Scheme 1. Key Observations[a]



[a]Combined isolated yields of *E*/*Z* isomers; er of *E* isomer as determined by chiral HPLC. [b]Using **5a** (1 equiv), iPr_2NEt, **1ac**, in MeCN.[12] [c]DABCO as base.

Received: February 28, 2024
Revised: May 22, 2024
Accepted: May 24, 2024
Published: June 7, 2024

Scheme 2. Azetidinium Scope[a]



[a]Combined isolated yields of *E*/*Z* isomers; er is of *E* isomer as determined by chiral HPLC; er of *Z* isomer, where quantified (i.e., **2a-OMe-*Z***, **2c-OH-*Z***, **2j-*Z***),[12] was identical; er in parentheses is after recrystallization. [b]Temp = −40 °C. [c]Quenched with MeOH.

Several classes of Lewis base organocatalysts were examined extensively.[12] The optimal catalyst for enantioselective [2,3]-sigmatropic rearrangements of ammonium ylides, **3a**,[9] generated product without any enantioselectivity. Cinchona alkaloid-derived **4** also provided racemic product. Chiral NHC catalysts afforded some stereoinduction, but product yields exceeding catalyst loadings could not be realized.[12] Stoichiometric **5a** generated **2a** in excellent er but in 10% yield. Remarkably, while **3a** provided racemic product, the corresponding ring-expanded catalysts produced **2a** in moderate er. Lower temperatures (red entries) led to product formation in high yield and considerably improved er. The use of distilled base and activated 3 Å MS was adopted to avoid ester hydrolysis by adventitious water.[12] Catalyst **3c**, which lacks a vicinal stereocenter, had minimal impact on product yield or er. Bulkier 2-naphthyl catalyst **3f**, had no effect on er, but eroded product yield. Seven-membered catalyst **3g**, reported here for the first time, provided racemic products. Product er significantly improved with less base (green entries), albeit at the expense of reaction yield. Neither recently reported catalyst **3h**,[13] nor corresponding ring-expanded catalyst **3i** provided results superior to **3b**. At or below −50 °C, only the *Z* isomer of product formed, indicating a possible kinetic resolution (Table S5).[12] A base screen revealed that DABCO provided product in 90:10 er, but in moderate yield that could not be increased despite aggressive reoptimization.[12] Increasing reaction time (purple entries) improved product yield while maintaining er, and these reaction conditions were considered optimal for this transformation.

Next, substrates, **1**, were evaluated (Scheme 2). Substrates in which $R \neq R^1$ are racemic mixtures, as they have axial chirality; products arising from these substrates were generated as 1:1 mixtures of *E*:*Z* alkene isomers. In all cases except **2g** and **2m**, alkene isomers were separable via silica gel chromatography. Substrates containing phenyl groups without substituents or with *para*-halogens underwent rearrangement in high yields and er values (**2a-d**). The reaction was scalable (**2c**). Substrates with strongly electron-donating *para*-substituted phenyl groups formed products (**2e-f**) in high er, but in reduced yield due to byproduct formation. Electron-withdrawing substituents at the *meta*- or *ortho*-positions afforded products in slightly reduced er (**2g-2h**). A *p*-NO_2 substrate (**1n**) afforded a low yield of product that was prone to decomposition.[12] *Ortho*-substitution did not hamper product (**2i**) formation or enantioinduction, presumably because this position is sufficiently removed from the reactive centers. This transformation tolerated heteroaromatic and disubstituted olefins (**2j-2l**). Importantly, an aromatic substituent on the alkene is not required for rearrangement (**2k**). Substitution on the azetidinium *N*, being one of the reactive centers, had a pronounced impact on product er (**2m**). An alternate, MeOH, quench provided the corresponding ester product, **2a-OMe**.

Most products were solids, and er improved substantially up to >99.5:0.5 after a single recrystallization; representative examples appear in Scheme 2. The ease of separating alkene isomers and of crystalline product formation facilitated the assignment of product configuration by X-ray crystallography. The configuration of both isomers of **2b** was thusly established as *R*.[14] Alkene geometry and configuration of all other products were assumed analogous.

Curiously, the *R* configuration of products was opposite that predicted by existing models for stereoinduction by catalyst **3b**.[15] Density Functional Theory (DFT) was used to investigate this observed stereoselectivity. We used the PBE level of theory with Grimme's empirical dispersion forces with Becke Johnson dampening parameter (D3BJ) and the 6-31G(d) basis set. All computations were performed under SMD solvation with dichloromethane solvent at 243.15 K.[16−19] The system was investigated with and without TfO−.

Using azetidinium **1k**, which features a symmetric alkene, the catalytic cycle (Figure 1) begins with acylation of **LB**, followed by deprotonation of the α-carbon to give the ammonium ylide. Initial C−N bond cleavage of the azetidinium ring leads to the ring-opened allyl-anion iminium intermediate. Subsequent ring-closure and $C_6F_5O^-$ exchange releases the catalyst, and final product pyrrolidine **2k** is ultimately generated after the reaction quench with benzylamine. In support of this proposed mechanism (i.e., vs a radical mechanism), identical yields of **2a** (64% and 61%) were obtained with and without 1 equiv of TEMPO, respectively, under our conditions for racemic [1,2]-Stevens rearrangement product formation.[12]

The investigation focused on the ring-opening and -closing steps, as those determine the stereochemical outcome of the reaction. The ring-closing process was found to be barrierless, likely due to the ionic nature of the transient **allyl-anion**

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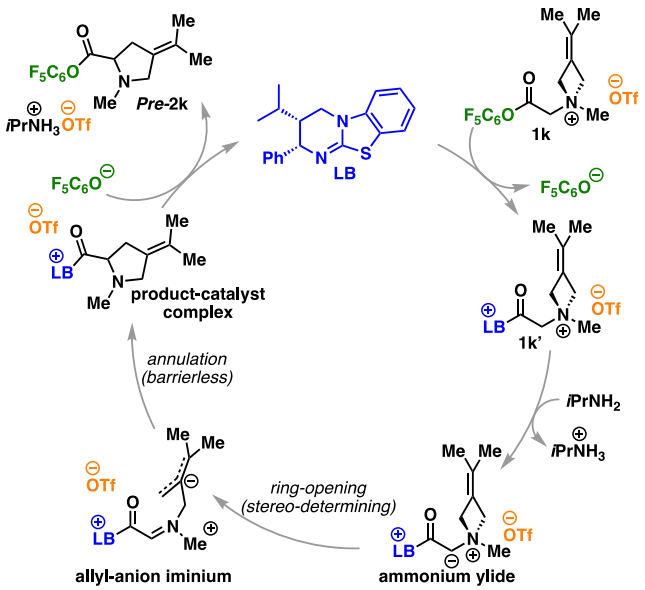


Figure 1. Catalytic cycle of the [1,2]-Stevens rearrangement catalyzed by benzotetramisole (LB).

iminium, strongly suggesting that it occurs from the same face as the preceding ring-opening C−N bond cleavage.

The DFT transition structures for the ring-opening are shown in Figure 2.[12] The computed selectivity ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol) is in reasonable agreement with experimental observation (81.5:18.5 er; i.e. $\Delta\Delta G^{\ddagger}$ = 0.72 kcal/mol).

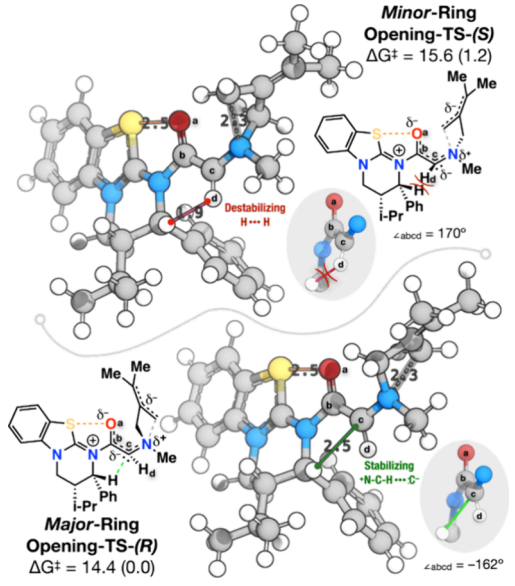


Figure 2. Transition structures for C−N bond-cleavage of **1k**.

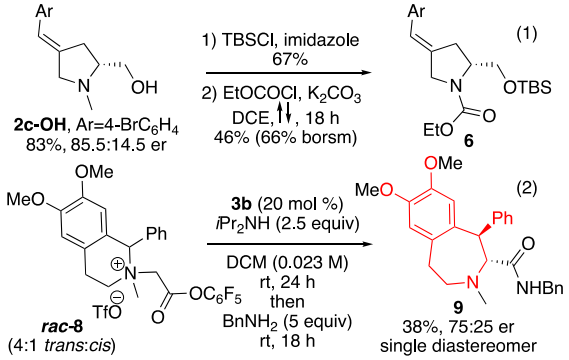
The transition structures are nearly identical, except for the environment around the benzylic hydrogen of the catalyst. In **Major-TS-(*R*)**, the enolate α-carbon is in close proximity (2.5 Å) to the catalyst benzylic hydrogen. In **Minor-TS-(*S*)**, the enolate α-hydrogen is in closer proximity (1.9 Å) to the catalyst benzylic hydrogen. Computation of the ChelpG charges of the ammonium ylide indicated a substantial negative charge (−0.65) on the α-carbon, consistent with an enolate carbanion.[12,20] The enolate α-hydrogen and the catalyst benzylic hydrogen exhibit positive charge character (0.09 and 0.16, respectively). These data imply that, in **Major-TS-(*R*)**, the enolate α-carbon is pyramidalized such that the lone pair is directed toward, and stabilized by electrostatic interaction with, the catalyst benzylic hydrogen ($^{+}$N−C−H ●●● :C^{-}). In **Minor-TS-(*S*)**, the pyramidalization is opposite, forcing the enolate α-hydrogen toward the catalyst benzylic hydrogen, and a destabilizing hydrogen−hydrogen interaction occurs (H ●●● H).

Thus, stereocontrol is governed by the direction of pyramidalization of the enolate α-carbon in the ring-opening transition state. This sterocontrolling pyramidalization phenomenon was first observed by Houk.[21] In our system, pyramidalization arising from C−N bond cleavage *syn* to the stereodirecting catalyst phenyl is favored for reasons described above. Subsequent barrierless bond formation (ring-closing) thus occurs *syn* to the stereodirecting catalyst phenyl, counter to typical asymmetric induction by **3b**.

As with **1k**, for azetidiniums featuring nonsymmetric alkenes, the catalyst dictates the facial selectivity of C−C bond cleavage and formation. This is evidenced by the identical configuration of the chiral center in both product alkene isomers. As mentioned earlier, substrates **1** in which R ≠ R^{1} are racemic mixtures, as they have axial chirality. The observed 1:1 *E*:*Z* product ratio could arise from the generation of one alkene isomer from one reactant enantiomer, and the opposite alkene isomer from the other reactant enantiomer. We cannot, however, exclude the possibility that *E*:*Z* isomerization of the corresponding **allyl-anion iminium** via resonance is competitive with annulation.

Finally, to showcase the utility of this process, reductive reaction quench provided **2c−OH** (Scheme 3, eq 1) in identical yield and er to **2c**. Protection of the free alcohol, then *N*-demethylation, provided versatile carbamate **6**. Additionally, when release of ring strain was eliminated as a driving force,[12] rearrangement was facilitated by double activation of the reactive center. Under conditions unoptimized for this substrate class, *rac*-**8**[22] afforded a single diastereomer of product in modest er (eq 2). The bicyclic core highlighted in **9** is characteristic of benzazepine drugs, including Fenoldopam, a D1 receptor agonist. This result demonstrates the amenability of this catalytic strategy for enantioselective [1,2]-Stevens rearrangements of other synthetically relevant amine scaffolds.

Scheme 3. *N*-Demethylation and beyond Azetidiniums



In conclusion, the first organocatalyzed enantioselective [1,2]-Stevens rearrangement has been developed.[4e] 4-Alkylideneprolinamides, -esters, and -alcohols were generated in up to 86% yield and in up to 90:10 er, with recrystallization enhancing er up to >99.5:0.5. DFT calculations revealed the

https://doi.org/10.1021/acs.joc.4c00534
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most influential enantiodetermining factors were pyramidalization of the enolate α-carbon, and the catalyst benzylic hydrogen, not the so-called stereodirecting catalyst phenyl. Product *N*-demethylation provided an orthogonally protected 4-alkylideneprolinol amenable to further synthetic elaboration. Rearrangement of a tetrahydroisoquinolinium substrate illustrated the potential for adaptation of this catalytic strategy to other heterocyclic amines.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00534.

Full details of reaction optimization and scope, preparation of substrates and catalysts, characterization data, and copies of ^{1}H, $^{13}C\{^{1}H\}$, and HPLC chromatograms (PDF)

Further discussion of stereocontrolling anion pyramidalization and full computational details (DOCX)

Accession Codes

CCDC 2300729−2300730 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

[§]Ana De Oliveira Silva and Shruti A. Masand contributed equally. Project conception: S.E.B.-M. Experimental work: A.D.O.S., S.A.M., K.U., M.R.-A. X-ray crystallography: R.A.L. Computational analysis: A.O.F., J.L., P.H.-Y.C. All authors contributed to writing the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the National Science Foundation (S.E.B.-M., CHE-1955044). PHYC is the Bert and Emelyn Christensen professor of OSU, and gratefully acknowledges financial support from the Vicki & Patrick F. Stone family and the National Science Foundation (NSF, CHE-1352663). AOF also acknowledges financial support from The Larry W. Martin & Joyce B. O'Neill Endowed Fellowship.

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(14) Deposition numbers 2300729 (for **2b**-*Z*) and 2300730 (for **2b**-*E*) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on June 7, 2024. An additional SI file was added to the paper, and the corrected version was reposted on June 10, 2024.

https://doi.org/10.1021/acs.joc.4c00534
J. Org. Chem. XXXX, XXX, XXX−XXX