

Asymmetric Synthesis of β -Amino Amides by Catalytic Enantioconvergent 2-Aza-Cope Rearrangement

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S Supporting Information

ABSTRACT: Dynamic kinetic resolutions of α -stereogenic- β -formyl amides in asymmetric 2-aza-Cope rearrangements are described. Chiral phosphoric acids catalyze this rare example of a non-hydrogenative DKR of a β -oxo acid derivative. The [3,3]-rearrangement occurs with high diastereo- and enantiocontrol, forming β -imino amides that can be deprotected to the primary β -amino amide or reduced to the corresponding diamine.

The hydrogenative dynamic kinetic resolution (DKR) of β -oxo esters is an indispensable synthetic technology used to generate hectoton quantities of optically enriched β -hydroxy esters annually (Scheme 1a).¹ Since Noyori's foundational report² describing DKRs of α -alkyl and α -amino substituted β -oxo acid derivatives, a wide array of additional α -substitution patterns have been reduced with high stereoselection.³ Conversely, involvement of β -oxo esters and their congeners in non-hydrogenative DKR reactions remain surprisingly

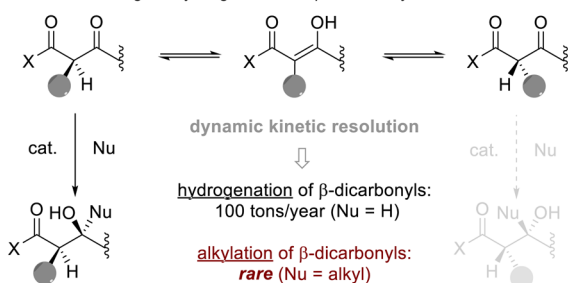
scarce.^{4,5} Toward the advancement of this latter process, this communication describes enantioconvergent and diastereoselective aza-Cope rearrangements of racemic β -formyl amides for the generation of new β -amino acid derivatives.⁶ The reaction is catalyzed by a chiral organic acid and concurrently establishes new C–N and C–C bonds and vicinal stereogenic centers (Scheme 1b).

While catalytic asymmetric sigmatropic rearrangements are well-established,⁷ examples of enantioselective 2-aza-Cope rearrangements are comparatively rare,⁸ and the 2-aza-Cope reaction as a DKR process has only been demonstrated utilizing stereochemically defined aminoallyl reagents.⁹ Chiral acid catalyzed aza-allylations of simple aldehydes have been reported from the laboratories of Rueping and Wulff, and this body of work provided the mechanistic framework for our experimental plan.⁸ Our initial investigations were guided by our recent successes using α -keto ester (\pm)-**1** in stereoconvergent reactions.¹⁰ In combination with allyl amine **2a** under chiral phosphoric acid catalysis,¹¹ productive reactivity was observed, but we were unable to achieve any promising diastereo- or enantioselectivity (Scheme 2a).¹² A racemization study of enantioenriched **1** revealed that under the buffered reaction conditions racemization via tautomerization was slower than the rate of sigmatropic rearrangement.¹³ Due to the inability of **1** to achieve kinetically useful enantiomerization, we switched to β -formyl ester **4**, which we hypothesized would favor enamine formation relative to **1**, thereby enhancing the rate of enantiomer interconversion. Unfortunately, the derived enamine **5** was impervious to [3,3]-rearrangement under any conditions that could be rendered catalytic (Scheme 2b), a circumstance we attribute to a debilitating thermodynamic preference for the unreactive enamine relative to the needed iminium ion $\mathbf{5}\cdot\mathbf{H}^+$.¹⁴ Considering our inadvertent overcorrection, we speculated that replacing the ester with a more sterically demanding dialkyl amide might provide a proper balance by destabilizing the enamine tautomer through A(1,3) strain¹⁵ while still maintaining a faster rate of enantiomerization than was observed with α -keto ester **1**.¹⁶

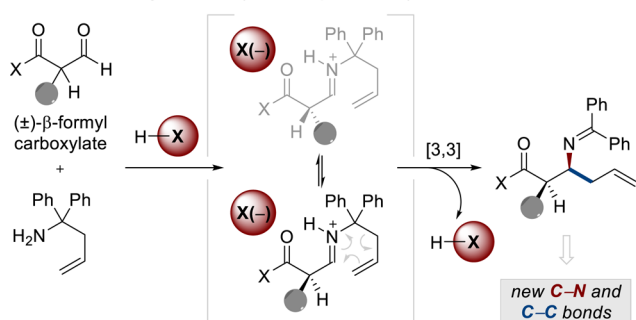
When β -formyl amide (\pm)-**6a** and allyl amine **2a** were subjected to chiral phosphoric acid **A**, β -amino amide **7a** was formed in 7:1 dr and 96:4 er (Table 1, entry 1). A screen of chiral phosphoric acids revealed **A**¹⁷ and **B**¹⁸ as the best candidates for further optimization.¹⁹ Elevating the reaction temperature increased the reaction rate with little loss of

Scheme 1. Dynamic Kinetic Resolutions with β -Oxo Acid Derivatives

a. Enantioconvergent hydrogenation of β -dicarbonyls



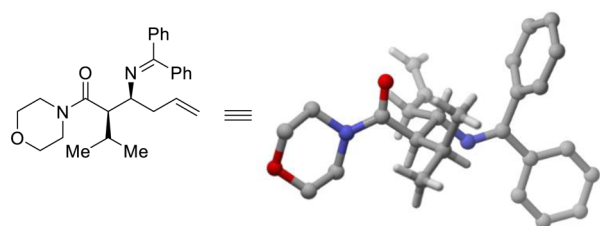
b. Enantioconvergent aza-allylation of β -dicarbonyls



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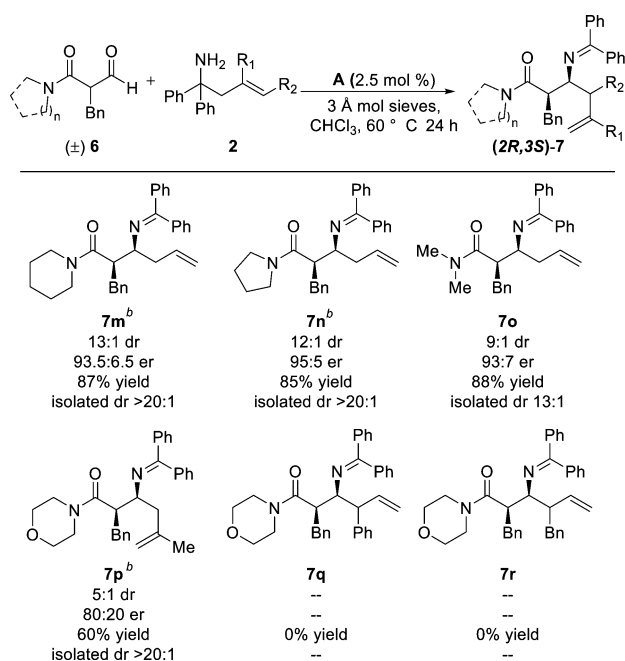
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Scheme 3. Determination of Relative and Absolute Stereochemistry of the [3,3]-Aza-Cope Rearrangement



the product stereochemistry as (2*R*,3*S*).²¹ Electronically differentiated benzyls provided **7i** and **7j** with >10:1 dr and 97:3 er. Using fur-2-yl and thien-2-yl variants instead of benzyl derivatives yielded products **7k** and **7l** with high stereocontrol.

Cognizant that modifying the amide identity would result in differentiated diamines after amide reduction, we next examined structural variation at that position (Table 3). The

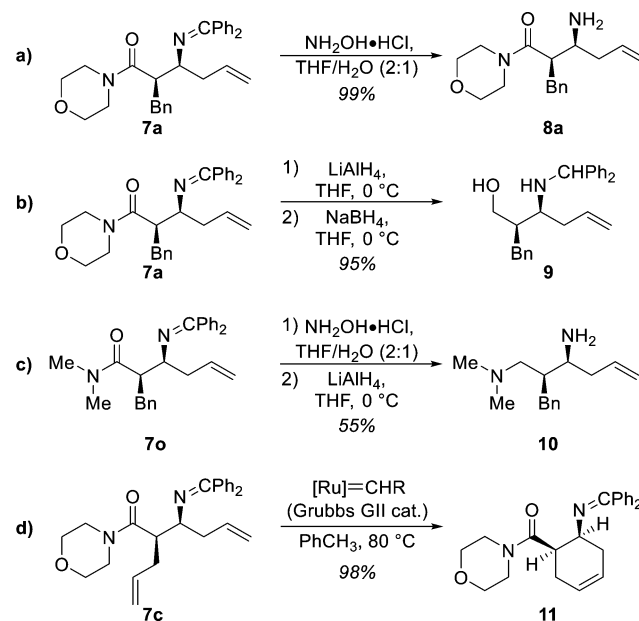
Table 3. Variation of Amide and Allyl Amine Identity in the [3,3]-Rearrangement of α -Stereogenic- β -formyl Esters^a

^aAll reactions were run on a 0.20 mmol scale at 60 °C for 24 h. Diastereomeric ratios were determined by ¹H NMR or HPLC analysis of the crude reaction mixture; enantiomeric ratios by chiral SFC or HPLC. Yields are of isolated products. ^bYield reported is of the primary amine after hydrolysis of the benzophenone imine.

β -amino amides generated from piperidine **7m**, pyrrolidine **7n**, and dimethyl amine **7o** were all formed in high yield and stereoselectivity. We also probed the allowed variance of the allyl amine donor. Internally substituted allyl amine **2b** provided the formal aza-methallylation adduct **7p** in 60% yield with 5:1 dr and 80:20 er. Terminally substituted allyl amine donors condensed with the β -formyl amide **6**, but did not undergo [3,3]-rearrangement, results we attribute to greater steric encumbrance at the reaction site.

For our final investigations we turned our attention to assessing the reactivity of the product β -imino amides. Hydrolysis of **7a** to form primary amine **8** proceeded under mild conditions and in 99% yield (Scheme 4a). Initial

Scheme 4. Chemical Transformation of Aza-Cope Products



reduction of **7a** with LiAlH₄ results in an intermediate aldehyde, which can be further reduced by sodium borohydride to form benzhydryl-protected amino alcohol **9** in 95% yield (Scheme 4b). If the benzophenone imine is cleaved prior to reduction, the diamine **10** is obtained in good yield (Scheme 4c). Finally, diene **7c** underwent facile ring-closing metathesis with Grubbs's second generation catalyst to provide cyclohexene **11** in 98% yield (Scheme 4d).

In conclusion, we have developed stereoconvergent 2-aza-Cope reactions employing stereocontrol from a chiral organic acid catalyst. This DKR between homoallylic amines and α -stereogenic- β -formyl amides constitutes a rare example of a non-hydrogenative DKR reaction of β -oxo acid derivatives and delivers new β -amino amides in high diastereo- and enantioselectivity. These products can be readily converted into an array of functional small molecule building blocks. Mechanistic studies delineating the factors that lead to the observed stereoselectivity and the use of this information in the development of other stereoconvergent reactions of racemization-prone β -oxo carboxylic acid derivatives will be reported in due course.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09593.

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Experimental procedures and spectral and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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- (12) For a full account of these trials see the [Supporting Information](#).
- (13) Under buffered conditions enantioenriched β -halo- α -keto esters fail to fully racemize after 24 h. For full details see the [Supporting Information](#).
- (14) Refer to the [Supporting Information](#) for details of tested conditions.
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- (19) For a comprehensive account of all catalyst, temperature, and solvent optimization see the [Supporting Information](#).
- (20) The β -formyl amides **6** were prepared via crossed Claisen condensation using the appropriate amide and either methyl or ethyl formate (see the [Supporting Information](#)). In practice the aldehyde **6** was brought into the rearrangement with variable quantities of impurities inseparable by chromatography. These impurities did not impinge upon the rearrangement, but to compensate, we opted for a reaction stoichiometry of 1.0:1.2 (2:6) and yields are calculated based on the amine component.
- (21) CCDC 1423130 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.