Chiral-at-Ruthenium Catalyst Does the Job: Access to Enantioenriched 2-Imidazolidinones

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DOI
10.1016/J.CHEMPR.2020.07.005

Publication date
2020

Document Version
Final published version

Published in
Chemical Science

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Article 25fa Dutch Copyright Act

Citation for published version (APA):
Chiral-at-Ruthenium Catalyst Does the Job: Access to Enantioenriched 2-Imidazolidinones

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Catalytic and enantioselective ring-closing C(sp³)–H amidation of urea derivatives has been unexplored. In this issue of Chem, Meggers and co-workers address this challenge by using a chiral-at-ruthenium catalyst to obtain cyclic 2-imidazolidinones in a highly enantioselective manner. The latter can be converted to chiral vicinal diamines without appreciable loss of enantiopurity.

Catalytic asymmetric nitrene insertion into prochiral C(sp³)–H bonds has been recognized as a powerful tool for the enantioselective construction of N-heterocycles.¹ Among the known cyclized products resulting from these intramolecular reactions are sulfamidates, sulfa-

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https://doi.org/10.1016/j.chempr.2020.07.005
Dioxazolones were reported to afford the desired cyclic products with high turnover numbers in a highly enantioselective manner.

In this issue of Chem, Meggers and co-workers further expand the applicability of chiral-at-ruthenium catalysts for enantioselective C(sp<sup>3</sup>)–H formation by adding urea derivatives to the library of nitrene precursors. Using N-benzoyloxyureas, 0.05–1.0 mol% of the bis-trimethylsilyl functionalized catalyst, and 3 equiv of K<sub>2</sub>CO<sub>3</sub> (Scheme 1), the authors obtained various 2-imidazolidinones in high yields with excellent enantioselectivities (up to 99% ee) under mild reaction conditions.

Specifically, they successfully demonstrated C(sp<sup>3</sup>)–H amidation of benzylic positions (R<sup>1</sup> = aromatic or thiophene, R<sup>2</sup> = Me) and a propargylic position (R<sup>1</sup> = phenylethynyl). Desymmetrization of an indane-based substrate, to afford a 2-imidazolidinone with two stereocenters at the 4- and 5-positions, yielded 29% of the desired product with 89% ee. Similar desymmetrization of 1-benzoyloxy-1,3-diphenyl-2-propynylurea afforded a single diastereoisomer of the desired product in 93% yield with 94% ee. The authors note that the reaction is limited to activated methylene C(sp<sup>3</sup>)–H positions.

N-alkyl substituents at the urea precursor substrates are tolerated and afford 2-imidazolidinones in high yield and enantioselectivity for R<sup>2</sup> = ethyl, n-butyl, isobutyl, and ethylphenyl (R<sup>1</sup> = Ph), as was also observed for R<sup>2</sup> = H. A benzyl substituent at the R<sup>2</sup> position leads to a lower yield, but the enantioselectivity is high. Notably, employing an N-phenyl-substituted substrate obtained the corresponding C(sp<sup>3</sup>)–H amidated product.

The authors demonstrated the synthetic utility of the developed protocol by facile synthesis of (S)-4-phenyl-2-imidazolidinone (74% yield, 99.6% ee) and (R)-4-phenyl-2-imidazolidinone (72% yield, 99.9% ee), which are intermediates in the synthesis of the drug enantiomers levamisole and dexamisole, respectively (Scheme 1). Moreover, acid- and microwave-assisted hydrolysis of several of the thus obtained 2-imidazolidinones resulted in the formation of the corresponding bis-protonated chiral vicinal diamines without appreciable loss of enantiopurity (95% ee). These chiral 1,2-diamines are intermediates in the

**Scheme 1. Conversion of N-Benzoyloxyurea Derivatives to 2-Imidazolidinones with a Chiral-at-Ruthenium Catalyst via a Putative Ru-Nitrenoid Intermediate**

The cyclic ureas can be converted to vicinal diamines that serve as intermediates in the synthesis of high-valued products.
synthesis of topsentine D and sponge-tine A and are precursors to chiral organocatalysts.

A nitrene intermediate undergoing radical-type hydrogen atom transfer (HAT) reactivity was inferred by measurement of a large kinetic isotope effect ($k_d/k_0 = 4.35$) via intramolecular competition between C(sp$^3$)–H and C(sp$^3$)–D amidation. Further indications of the formation of a carbon-centered radical were obtained by olefin isomerization studies: N-benzyloxoyurea with Z- or E-vinylbenzene as R$^1$ ($R^2 = Me$) afforded an eroded $Z/E = 4.4:1$ ratio of the former, whereas the >20:1 E/Z ratio from the starting material was retained with the more stable E-isomer.

In reactions with (S)-1-(benzoyl-oxy)-3-(2-phenylpropyl)urea as the substrate, stereochemistry was retained with the (2-phenylpropyl)urea as the substrate, consistent with the initial formation of a putative Ru-nitrenoid (Scheme 1), formed upon base-assisted activation and deprotection of the (metal-bound) N-benzyloxoyurea substrate. Subsequent HAT from the weakest C–H bond generates a carbon-centered radical, followed by an enantioselective radical-rebound step to generate the product.

In conclusion, Meggers and coworkers have reported the first example of an enantioselective urea cyclization reaction via a nitrene-type C(sp$^3$)–H amidation strategy with a chiral-at-ruthenium complex. The obtained cyclic compounds are valuable products in themselves and can readily be converted to desirable chiral 1,2-diamines.

Bioorthogonal Catalysis Goes Chiral

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Bioorthogonal nanofactories have emerged in the last decade to provide xenobiotic pathways that generate nonbiological substances in living environments. In this issue of Chem, Qu and co-workers incorporate asymmetric catalytic properties and chemotactic capabilities into novel nanodevices to achieve the stereo- and site-selective synthesis of the active enantiomer of ibuprofen at inflammation sites.

Achieving precisely localized delivery of a drug—i.e., supplying a therapeutically active agent only where needed—has challenged chemists, pharmacologists, and clinicians for over a century since Paul Ehrlich coined the “magic bullet” concept. In response, a myriad of nanovehicles have been developed over the years as selective drug-