# Stereocontrolled 1,3-Nitrogen Migration To Access Chiral α-Amino Acids

There is great demand for unnatural and non-proteinogenic α-amino acids, which find a number of applications both in basic and applied research. For example, unnatural amino acid side chains modulate the chemical, physical, and pharmaceutical properties of peptides, proteins and other bioactive molecules. Chiral amino acids are also used as chiral building blocks for chiral catalysts and as chiral auxiliaries. Despite the development of many powerful synthetic methods to access optically active α-amino acids, efficient catalytic enantioselective methods are still sought after and the subject continues to attract strong interest in modern organic chemistry.[1]

The research group of Professor Eric Meggers at the University of Marburg (Germany), in collaboration with Professor Shuming Chen at Oberlin College (Ohio, USA), recently reported a new synthetic strategy to access chiral non-racemic α-amino acids (Scheme 1). "Our two-step method is surprisingly simple and straightforward," said Chen-Xi Ye, who is first author of the title article, adding: "Abundant and easily accessible carboxylic acid feedstock molecules are first ligated to a nitrene precursor followed by a stereocontrolled 1,3-nitrogen shift from the carboxylic acid oxygen to the α-carbon." According to the authors, the method displays a broad scope, providing rapid access to non-racemic α-amino acids with aryl, allyl, propargyl, and alkyl side chains, also permitting stereocontrolled late-stage amination of carboxylic acid containing drugs and natural products. The method builds on recent advances in asymmetric nitrene C(sp³)–H insertion chemistry. "While these reported examples are typically designed as intramolecular reactions to provide cyclic nitrogen-containing compounds with high regio- and stereocontrol,[2] our new method combines the advantages of an intramolecular nitrene insertion with the ability to access acyclic amine-containing molecules by using an unprecedented stereocontrolled 1,3-migratory nitrene C(sp³)–H insertion process," said Professor Meggers. Professor Chen added: "Density function theory (DFT) calculations support a triplet nitrene mechanism via a hydrogen atom transfer (HAT) followed by a C–N bond formation."

While initial experiments were performed with a chiral-at-metal ruthenium catalyst, it later turned out that a chiral iron complex serves as an equally powerful catalyst for the stereocontrolled 1,3-nitrogen migration. "There is currently great interest in the development of iron-catalyzed reactions, including asymmetric reactions,[3] due to the high abundance of iron on Earth in combination with its low toxicity profile," said Xiang Shen, the second author on this *Nat. Chem.* paper.
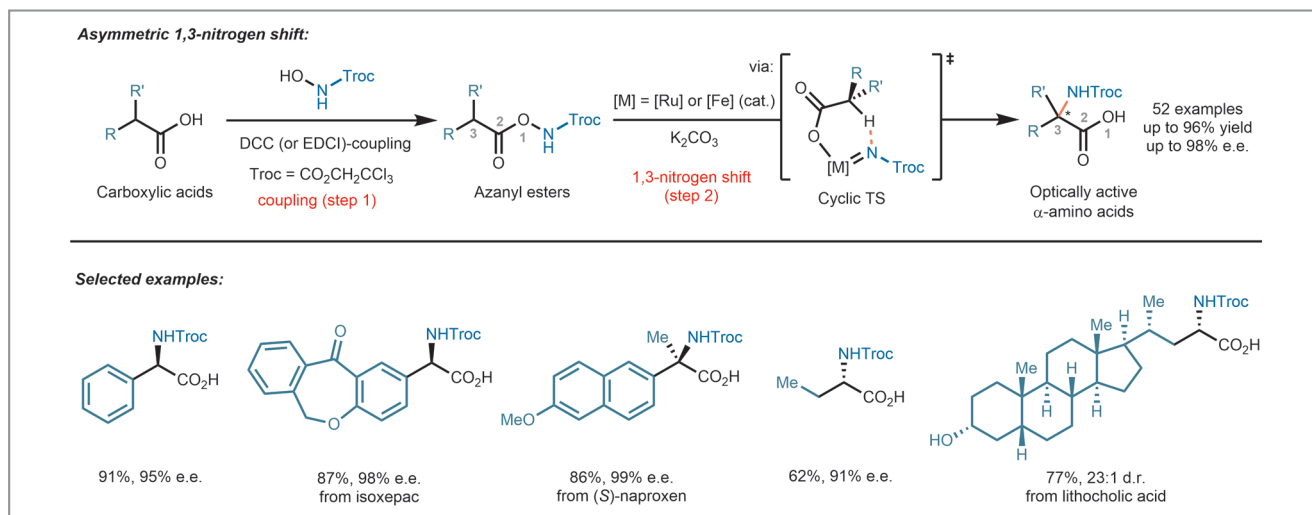


**Scheme 1** Overview of the developed α-amino acid synthesis by stereocontrolled 1,3-nitrogen migration

He added: "The robust iron catalyst is easy to synthesize and stable on the benchtop. Besides the economic and environmental benefits, the iron catalyst has the additional advantage that it allows access to non-racemic α-amino acids with aliphatic side chains."

Professor Meggers concluded: "We are convinced that this work will expedite the synthesis of unnatural α-amino acids. The developed method has several attractive features: it uses easily accessible carboxylic acid feedstock molecules; it provides chiral α-amino acids with a protecting group that can be removed under mild reaction conditions; the nitrogen shift features excellent stereocontrol, and can even be catalyzed with a robust iron catalyst; last but not least, the reaction scope is excellent, also permitting stereocontrolled late-stage aminations of carboxylic acid containing drugs and natural products."

## REFERENCES

(1) C. Nájera, J. M. Sansano *Chem. Rev.* **2007**, *107*, 4584–4671.
(2) M. Ju, J. M. Schomaker *Nat. Rev. Chem.* **2021**, *5*, 580–594.
(3) A. Casnati, M. Lanzi, G. Cera *Molecules* **2020**, *25*, 3889.

## About the authors

**Chen-Xi Ye** received his B.Sc. and M.Sc. from Xiamen University (P. R. China), where he worked in the area of (enantioselective) radical chemistry under the supervision of Prof. Xiao Zheng and Prof. Pei-Qiang Huang. Currently, he is pursuing his Ph.D. under the guidance of Prof. Eric Meggers at the University of Marburg (Germany). His current research is focused on enantioselective C(sp³)–H aminations.

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**Xiang Shen** received his M.Sc. in organic chemistry from Xiamen University (P. R. China) and recently received his Ph.D. from the University of Marburg (Germany) under the supervision of Professor Eric Meggers, where he developed stereocontrolled iron-catalyzed C(sp3)–H aminations for the synthesis of α-amino acids.

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**Shuming Chen** was born and raised in Hangzhou, P. R. China. After earning her B.A. from Grinnell College (USA), she carried out her Ph.D. studies under the direction of Professor Jonathan A. Ellman at Yale University (USA). She then became the Donald J. Cram Teacher-Scholar at the University of California, Los Angeles (USA), working with Professor Kendall N. Houk during the period of 2016–2020. Dr. Chen began her independent career as an Assistant Professor of Chemistry and Biochemistry at Oberlin College (USA) in 2020.

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**Eric Meggers** studied chemistry at the University of Bonn (Germany) and received his Ph. D. from the University of Basel (Switzerland). After postdoctoral research at the Scripps Research Institute (USA) he started his independent career as Assistant Professor at the University of Pennsylvania (USA). Since 2007, Eric Meggers is Full Professor in the Department of Chemistry at the University of Marburg (Germany). The Meggers laboratory is currently focused on the design and development of chiral-at-metal complexes for applications in asymmetric catalysis.

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