Literature Report

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

Reporter: Sheng-Mei Lu

Checker: Shan-Shan Xun

Ye, C.-X.; Shen, X.; Chen, S.; Meggers, E.* *Nat. Chem*. **2022**, *14*, 566.

2023-02-27

CV of Prof. Eric Leif Meggers

Research:

1. **Chiral-at-metal catalyst design**
2. **Sustainable catalysis with iron**
3. **Stereocontrolled organic photochemistry**
4. **Stereocontrolled electrochemistry**
5. **Enantioselective nitrene chemistry**

Background:

1991-1995 B.S., Diploma in Chemistry, University of Bonn, Germany

1995-1999 Ph.D., in Organic Chemistry, University of Basel, Switzerland

1999-2002 Postdoc., The Scripps Research Institute

2002-2007 Assistant Professor, University of Pennsylvania, USA

2007-now Professor, Department of Chemistry, University of Marburg, Germany

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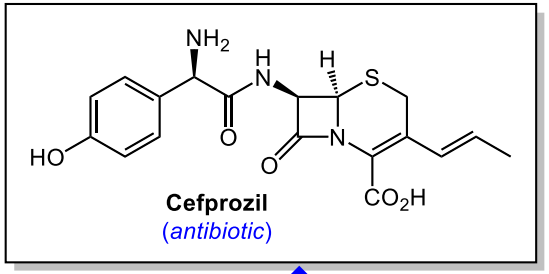
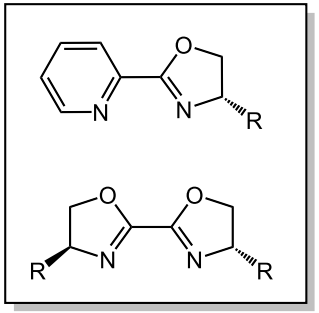
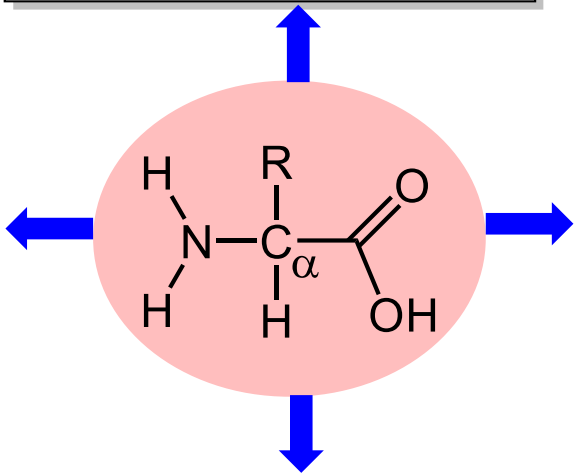
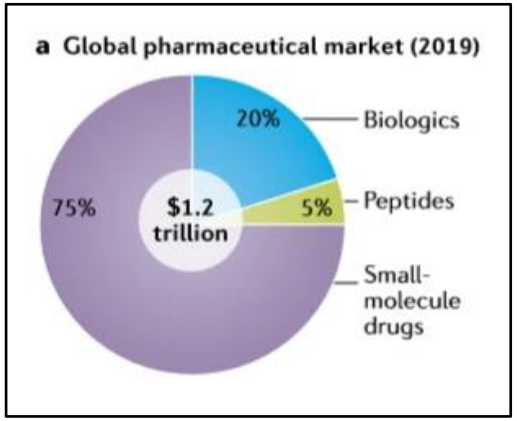
Introduction



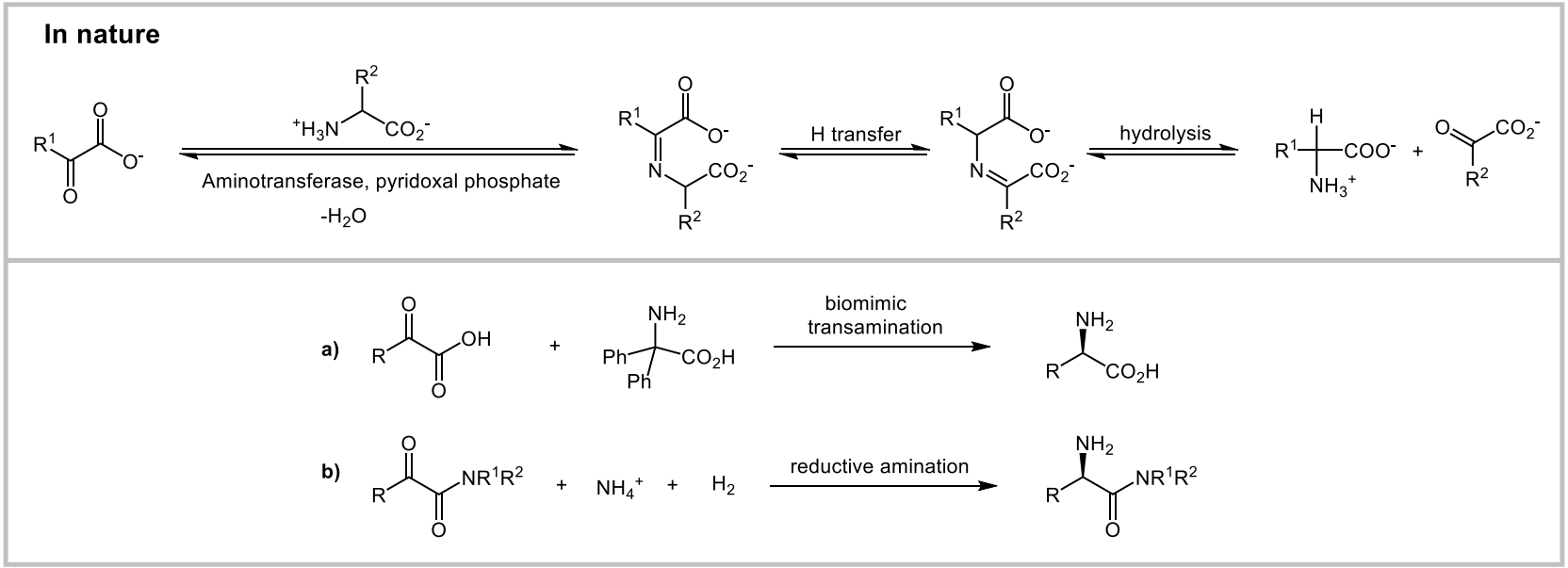






No amino acids, no life.

Synthesis of Amino Acids in Nature



Liu, Y. E.; Zhao, B. *J. Am. Chem. Soc.* **2016**, *138*, 10730.
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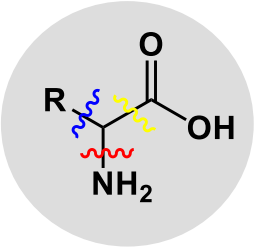
Synthetic Analysis of Amino Acids

Introducing a carbon chain

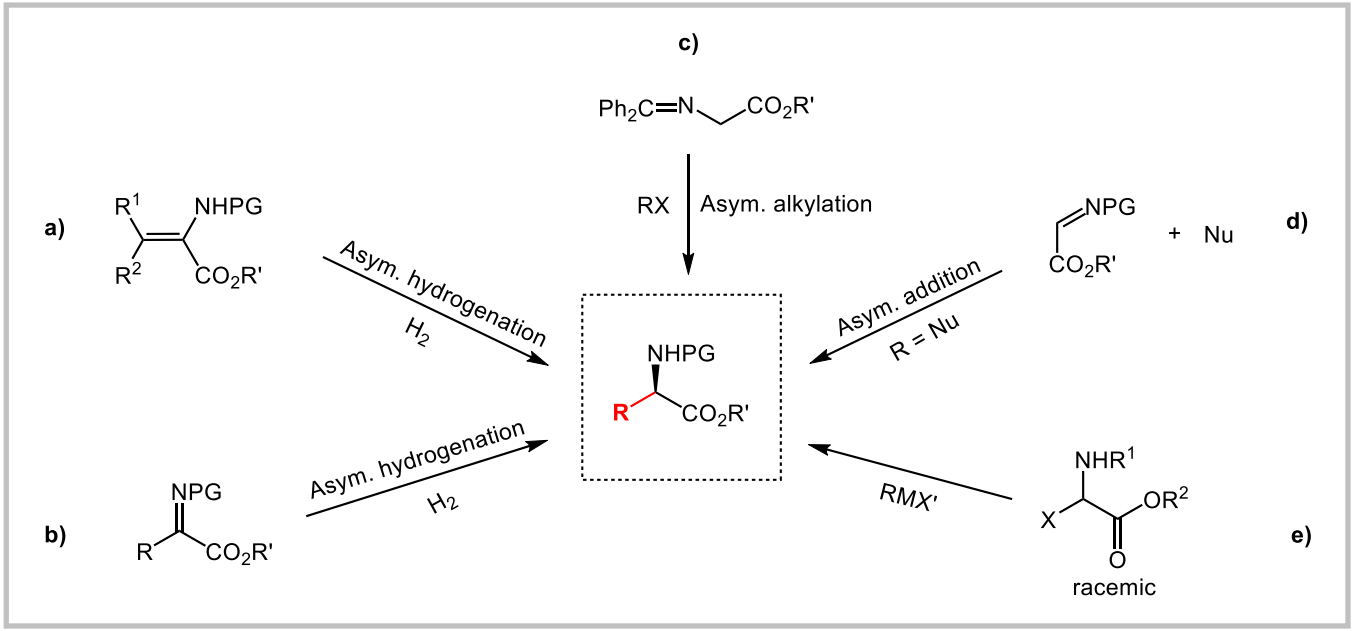
Introducing a carboxyl group



Introducing an amino group

Nájera, C.; Sansano, J. M.; *Chem. Rev*. **2007,** *107*, 4584.

Introducing a Carbon Chain



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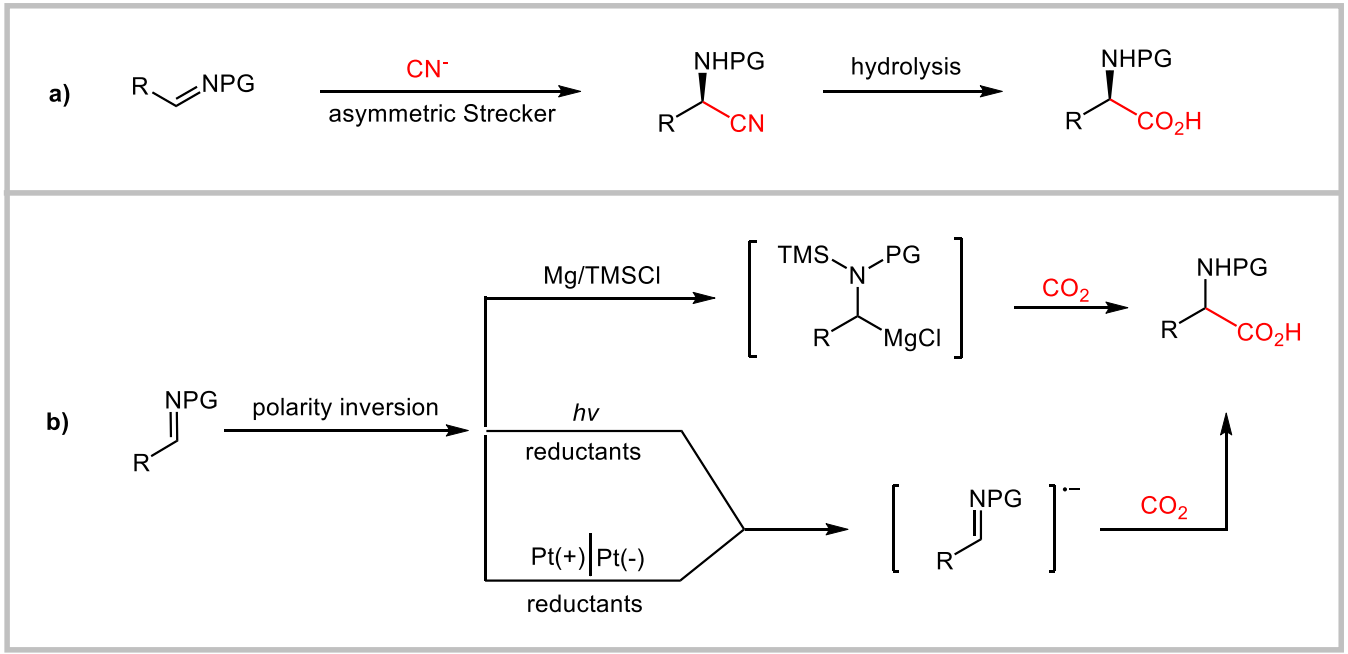
Introducing a Carboxyl Group



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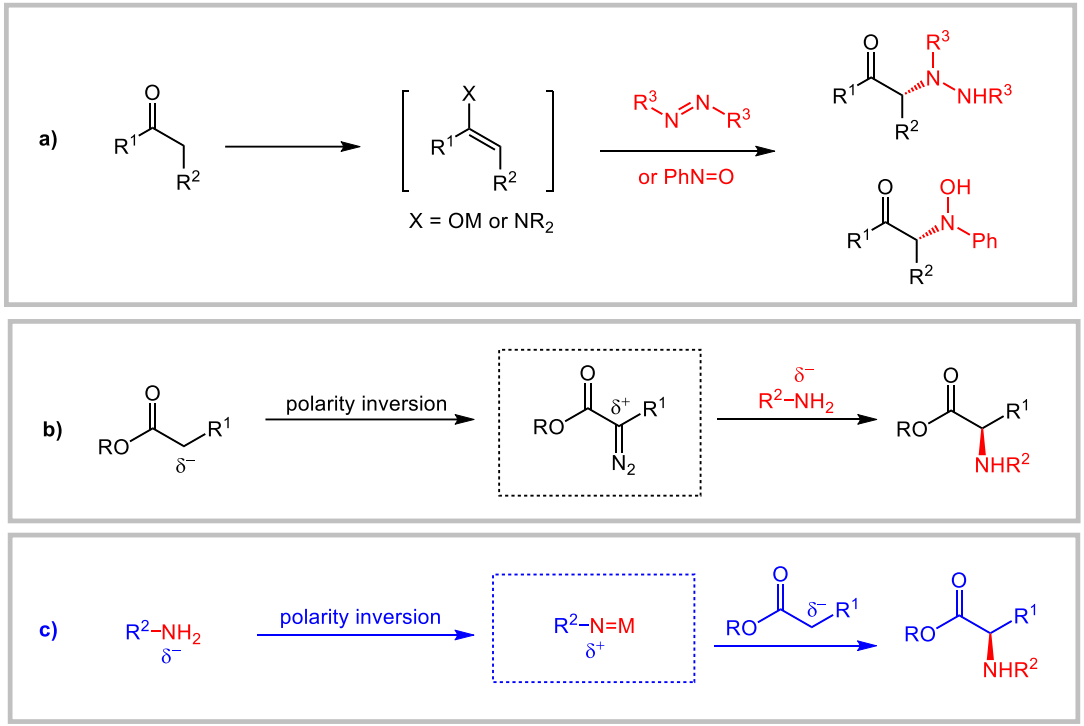
Introducing an Amino Group



Janey, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4292.
Li, M.-L.; Zhu, S.-F.; Zhou, Q.-L. *Science* **2019**, *366*, 990.
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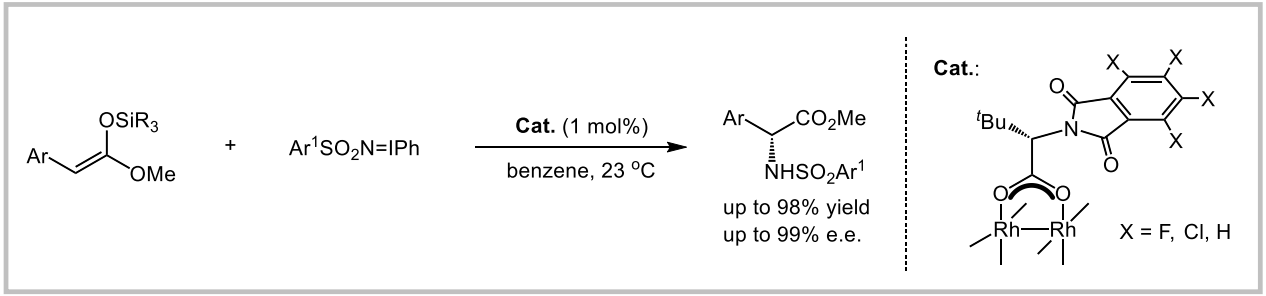
The Intermolecular Amination of *α*-Position of Esters



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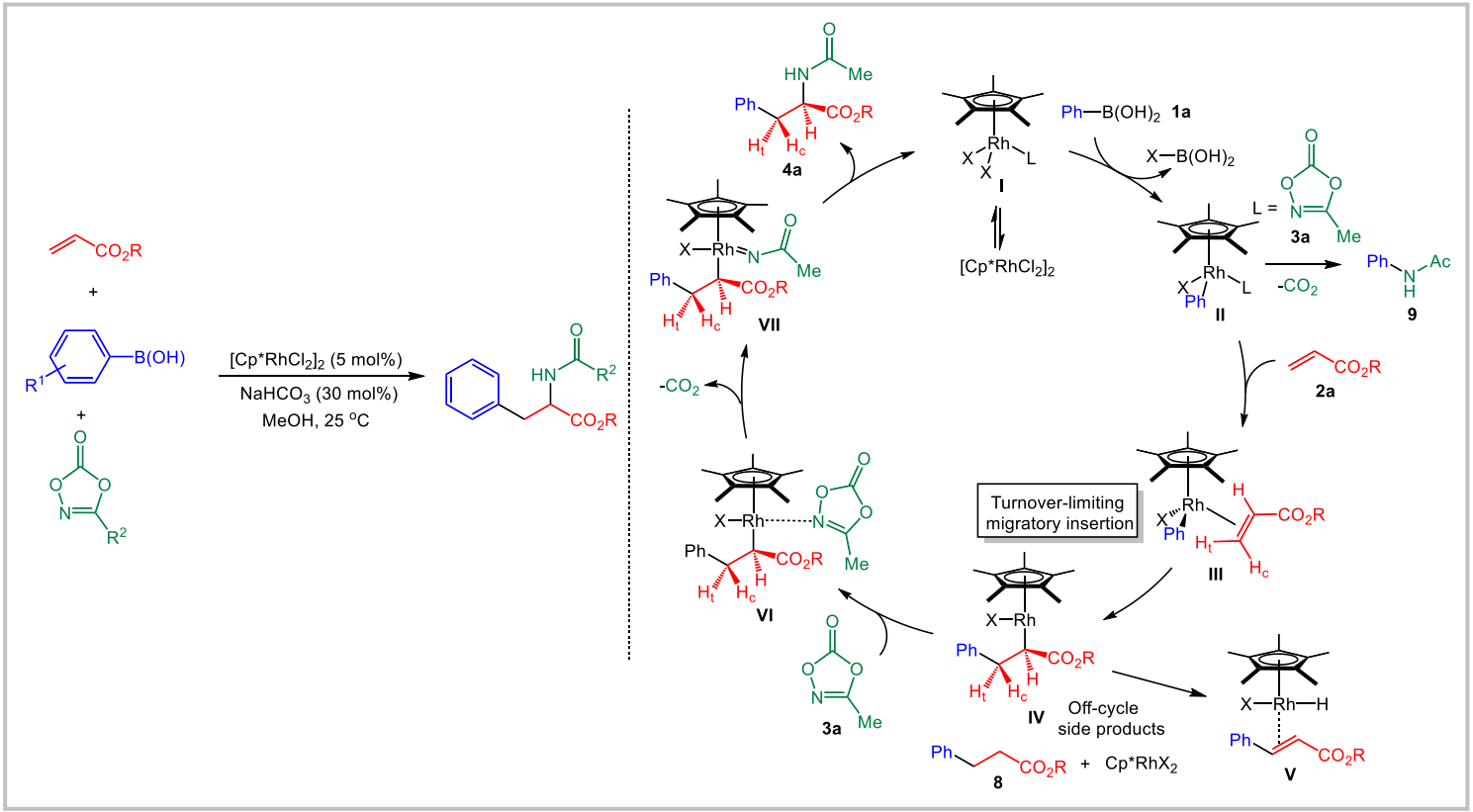
Carboamination of Alkenes to Access α-Amino Acids



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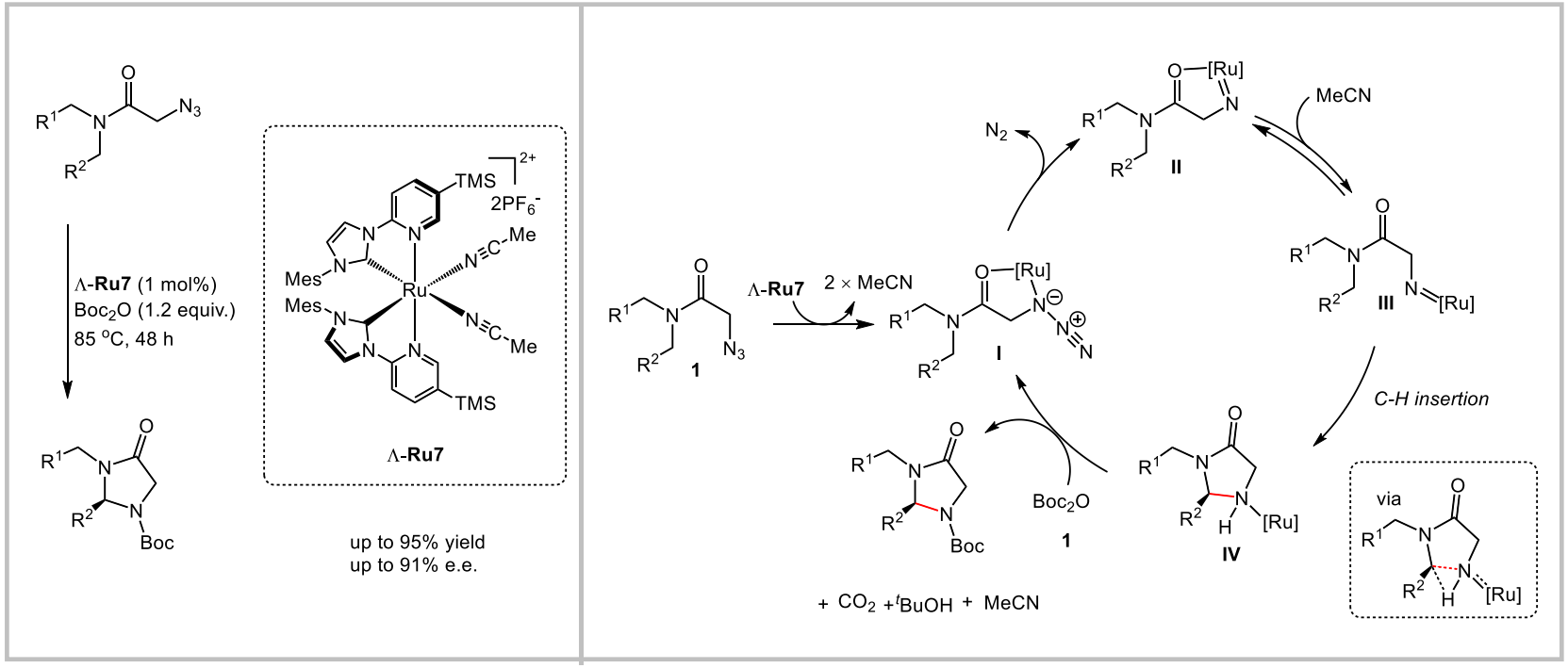
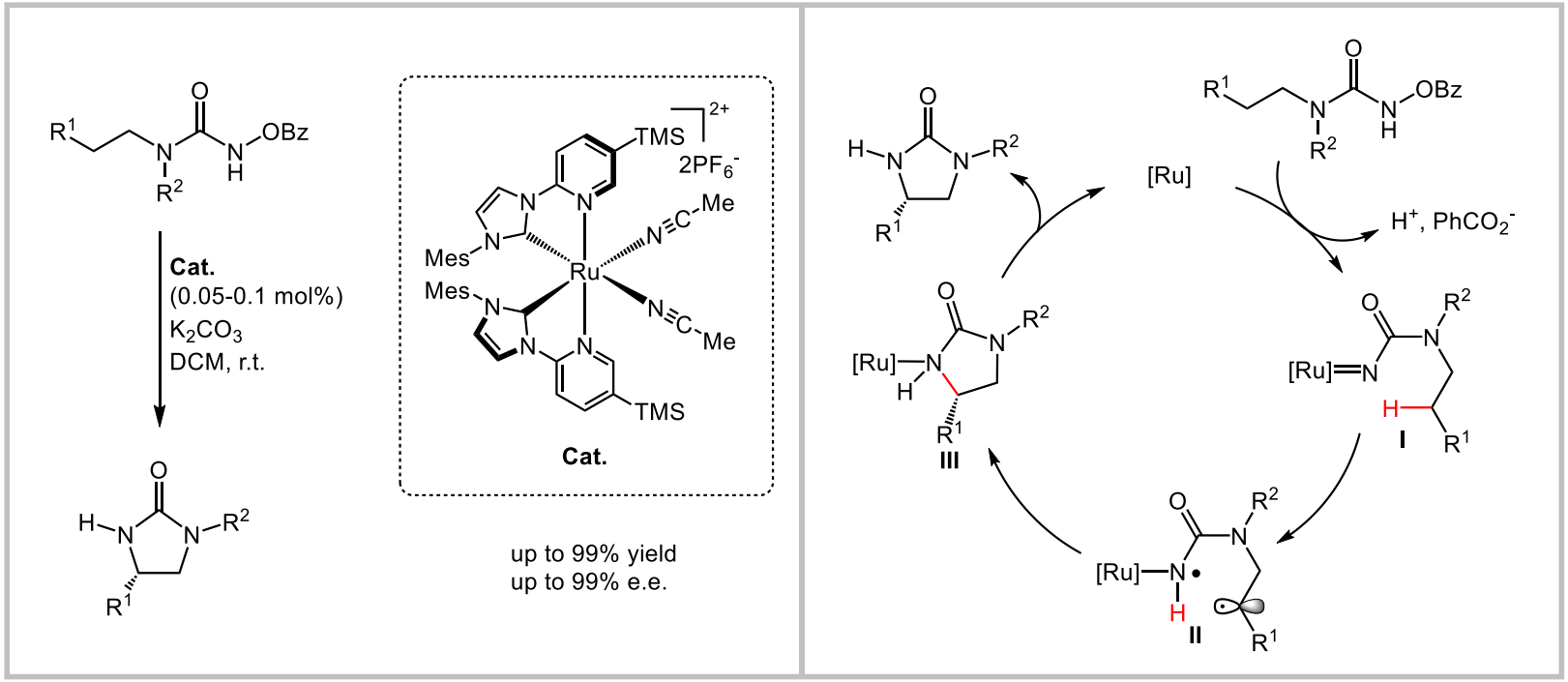
The Former Work in Their Group



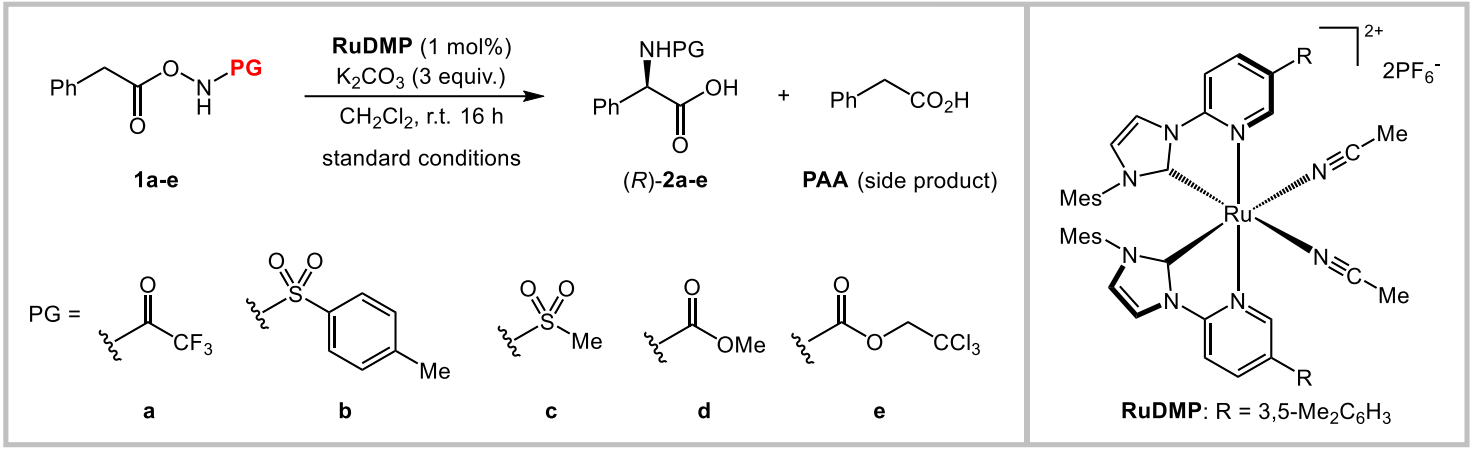
Zhou, Z.; Chen, S.; Qin, J.; Houk, K. N.; Meggers, E. *Angew. Chem. Int. Ed.* **2019**, *58*, 1088.

The Former Work in Their Group



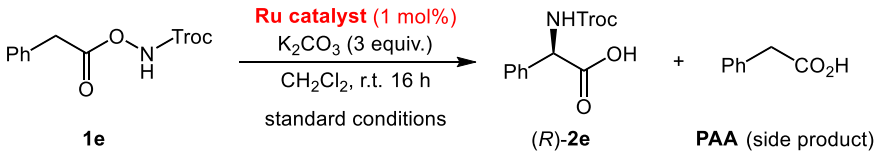
Zhou, Z.; Tan, Y.; Meggers, E. *Chem* **2020**, *6*, 2024.

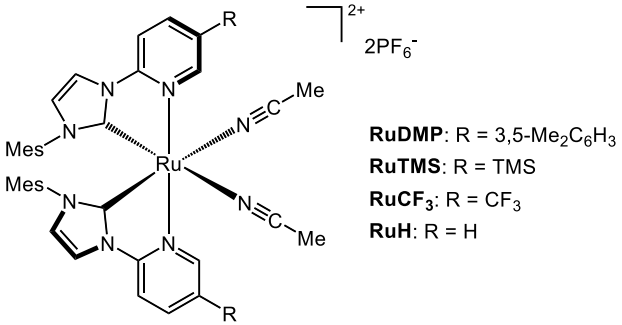
Reaction Conditions Optimization-N-Protecting Group



Entry	PG	Conversion (%)	Yield of 2 (%)	Yield of PAA (%)	e.e. of 2 (%)
1	$COCF_3$ (**a**)	0	/	/	/
2	Ts (**b**)	37	<5	23	n.d.
3	Ms (**c**)	50	<5	25	n.d.
4	CO_2Me (**d**)	100	86	12	89
5	Troc (**e**)	100	93	4	95

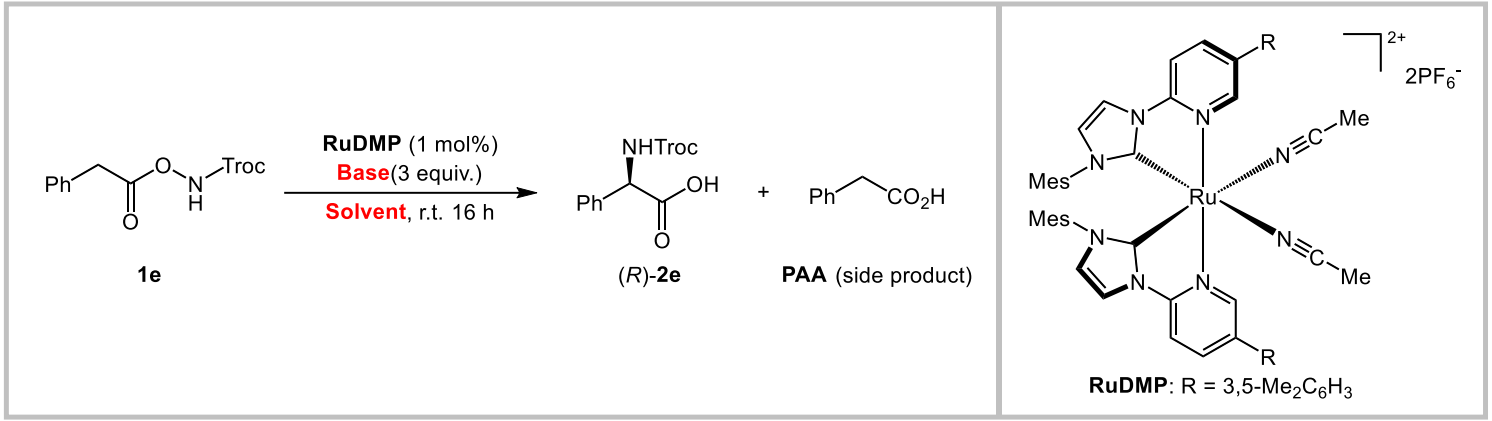
Reaction Conditions Optimization-Ru Catalyst





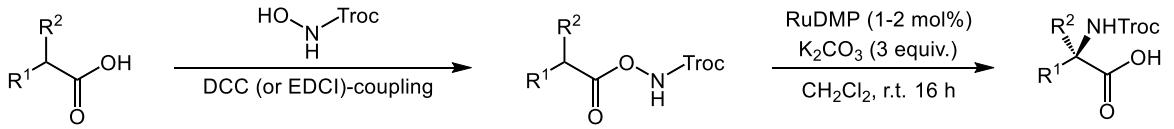
Entry	Ru catalyst	Conversion (%)	Yield of 2 (%)	Yield of PAA (%)	e.e. of 2 (%)
1	**RuDMP**	**100**	**93**	**4**	**95**
2	**RuTMS**	98	80	9	92
3	**$RuCF_3$**	19	6	5	90
4	**RuH**	100	85	9	92

Reaction Conditions Optimization-Base and Solvent

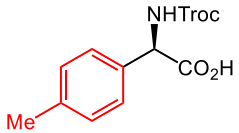


Entry	Base	Solvent	Conversion (%)	Yield of 2 (%)	Yield of PAA (%)	e.e. of 2 (%)
1	K_2CO_3	CH_2Cl_2	100	93	4	95
2	Na_2CO_3	CH_2Cl_2	99	87	5	95
3	Et_3N	CH_2Cl_2	100	25	73	95
4	K_2CO_3	THF	94	15	75	82
5	K_2CO_3	MeOH	96	0	64	/

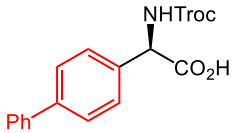
Substrate Scope



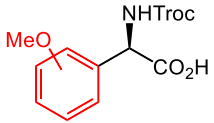
Carboxylic acids | Azanyl esters | α-Amino acids



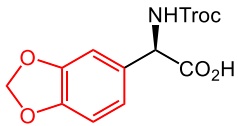
3
86%, 97% e.e.



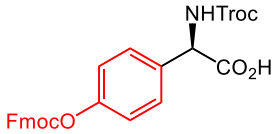
4
86%, 95% e.e.



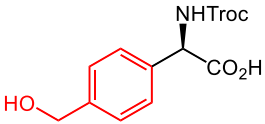
5 (*para*), 96%, 96% e.e.
6 (*meta*), 87%, 96% e.e.
7 (*ortho*), 79%, 85% e.e.



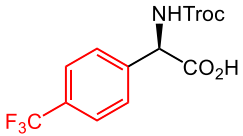
8
56%, 92% e.e.



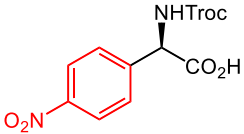
9
83%, 93% e.e.



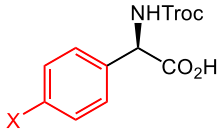
10
64%, 98% e.e.



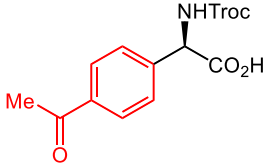
11
87%, 86% e.e.



12
73%, 92% e.e.

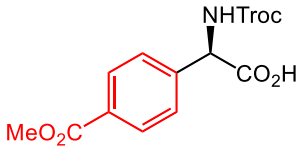


13, X = I, 91%, 94% e.e.
14, X = Br, 93%, 94% e.e.
15, X = Cl, 93%, 95% e.e.
16, X = F, 92%, 93% e.e.

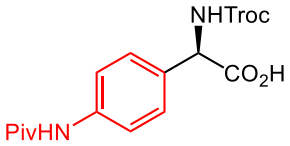


17
79%, 92% e.e.

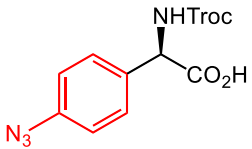
Substrate Scope



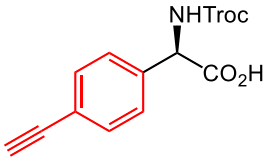
18
91%, 93% e.e.



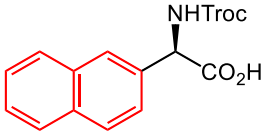
19
93%, 96% e.e.



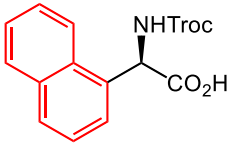
20
95%, 97% e.e.



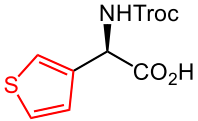
21
88%, 94% e.e.



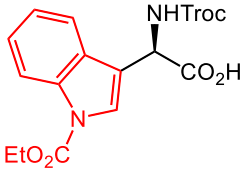
22
92%, 96% e.e.



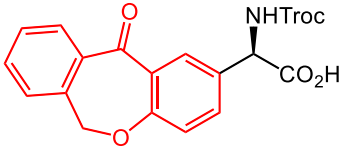
23
92%, 95% e.e.



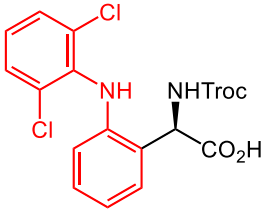
24
84%, 95% e.e.



25
77%, 90% e.e.

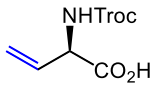


26
87%, 98% e.e.

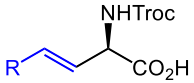


27
54%, 96% e.e.

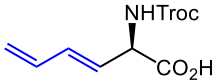
Substrate Scope



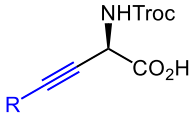
28
62%, 73% e.e.



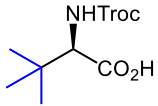
29, R = Et, 83%, 84% e.e.
30, R = ^{i}Pr, 88%, 81% e.e.
31, R = ^{n}Hex, 85%, 82% e.e.
32, R = ph, 88%, 82% e.e.



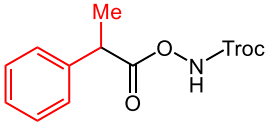
33
72%, 81% e.e.



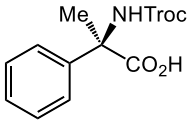
34[c], R = Ph, 46%, 62% e.e.
35[c], R = Et, 63%, 64% e.e.



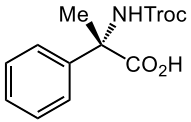
36[d]
20%, 90% e.e.



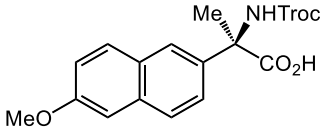
37
Azanyl ester



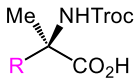
(*R*)-**38**
91%, 98% e.e.[f]
71%, 48% e.e.[e]



(*S*)-**38**[g]
34%, 28% e.e.



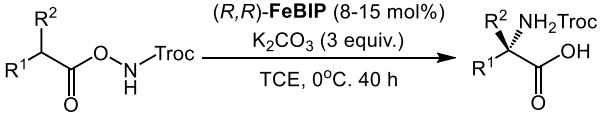
39
86%, 99% e.e.

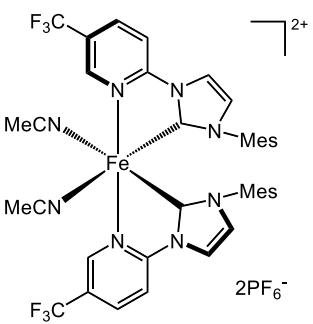


40
40[d,f], R = (*E*)-EtCH=CH, 77%, 87% e.e.
41[d,f], R = Et, 57%, 86% e.e.
42[d,f], R = cyclohexyl, 25%, 92% e.e.

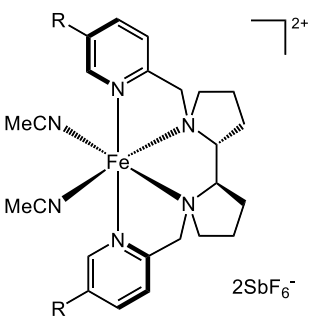
[c]$KHCO_3$ instead of K_2CO_3 as a base. [d]Λ-**RuH** (2–10 mol%) as the catalyst. [e]The reaction performed with racemic azanyl ester **37** afforded (*R*)-38 in 71% yield with 48% e.e. [f]Reaction performed with enantiopure (*S*)-azanyl ester. [g]Reaction performed with enantiopure (*R*)-azanyl ester.

Substrate Scope Catalyzed by Fe Catalyst

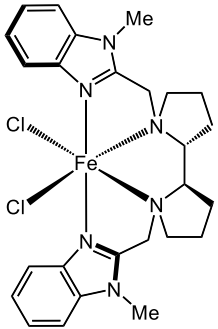




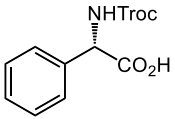
Δ-**Fe1**



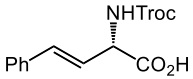
(*R,R*)-**Fe2**, R = H
(*R,R*)-**Fe3**, R = 2,6-$(CF_3)_2C_6H_3$



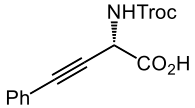
(*R,R*)-**FeBIP**



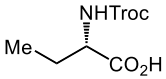
(*S*)-**2e**
Δ-**Fe1** (8 mol%), trace
(*R,R*)-**Fe2**, (8 mol%), 91%, 15% e.e.
(*R,R*)-**Fe3**, (8 mol%), 75%, 10% e.e.
(*R,R*)-**FeBIP**, (8 mol%), 95%, 91% e.e.



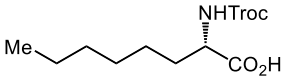
(*S*)-**32**
44%, 86% e.e.



(*S*)-**34**
13%, 44% e.e.

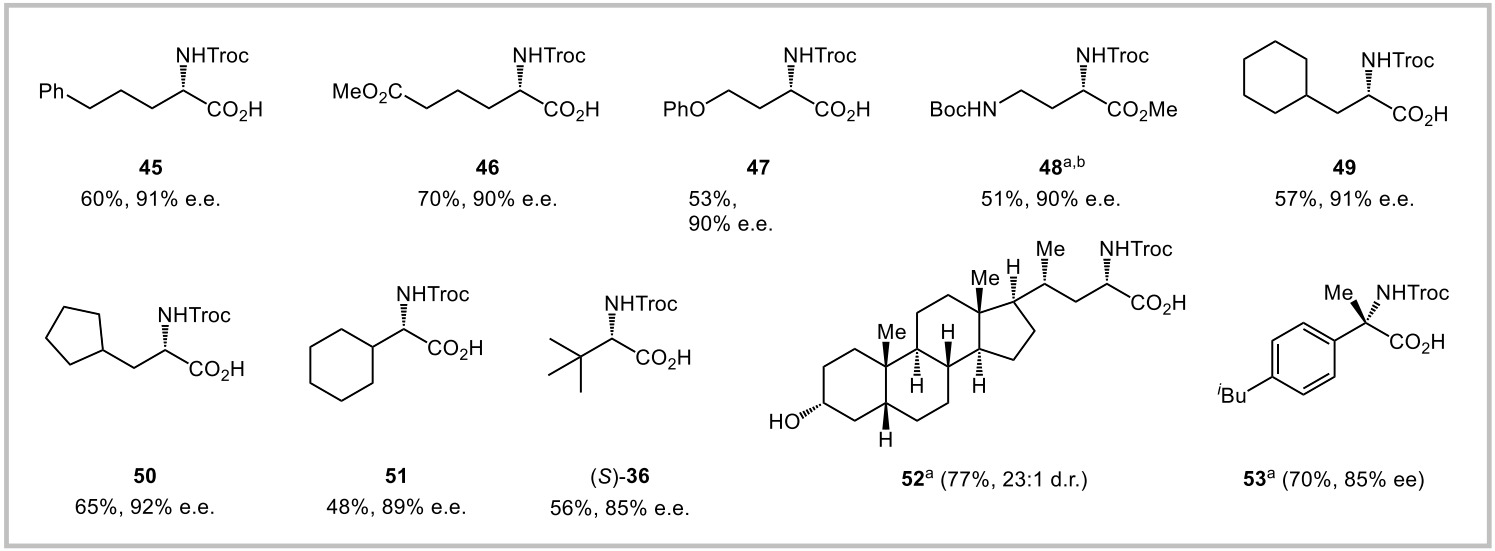


43
62%, 91% e.e.



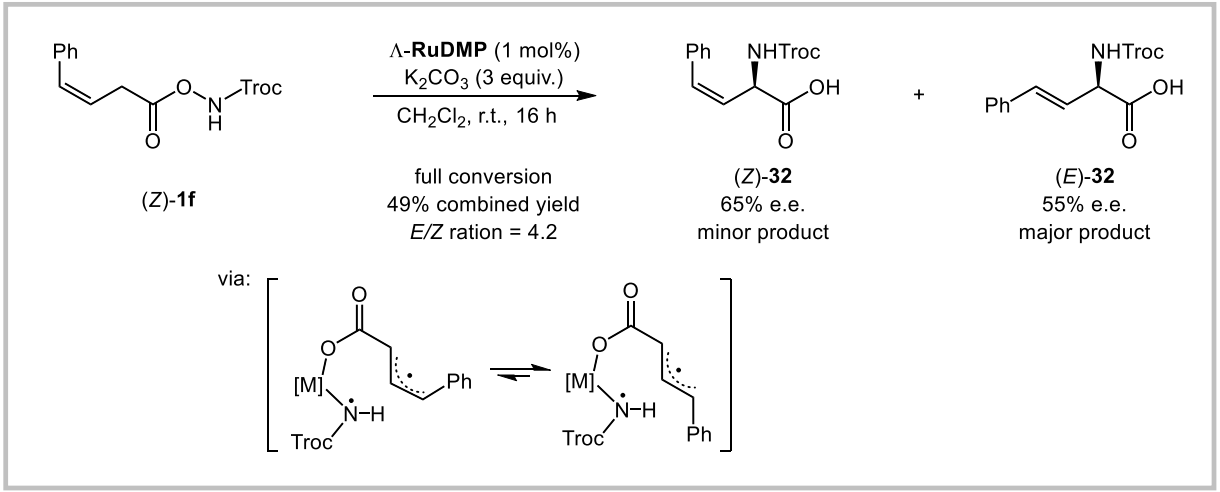
44
72%, 92% e.e.

Substrate Scope Catalyzed by Fe Catalyst

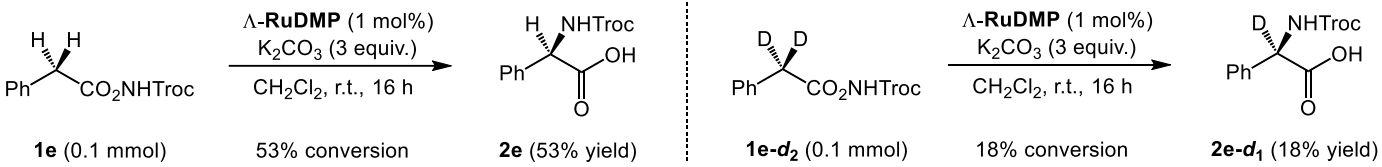


[a]Reaction performed at room temperature (25 °C) for 16 h.
[b]Isolated after conversion to the methyl ester. d.r., diastereomeric ratio.

Control Experiment



Control Experiment

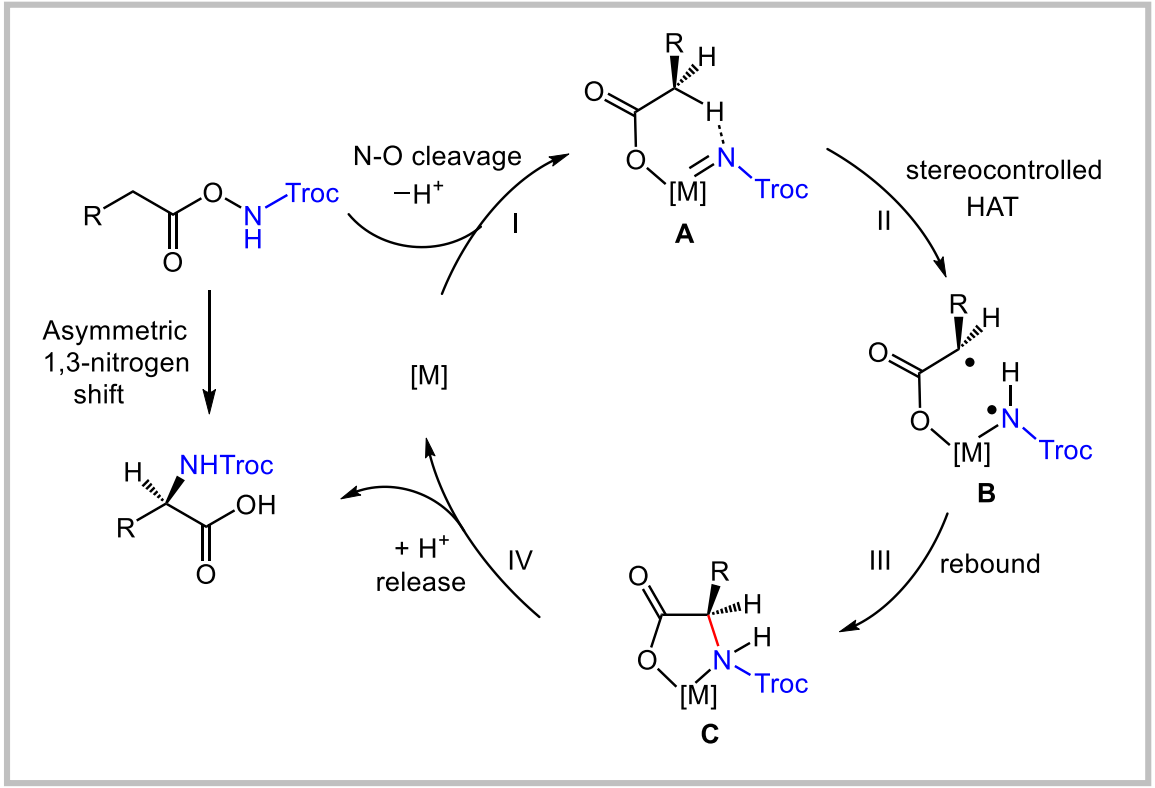


1e (0.1 mmol) | 53% conversion | **2e** (53% yield)

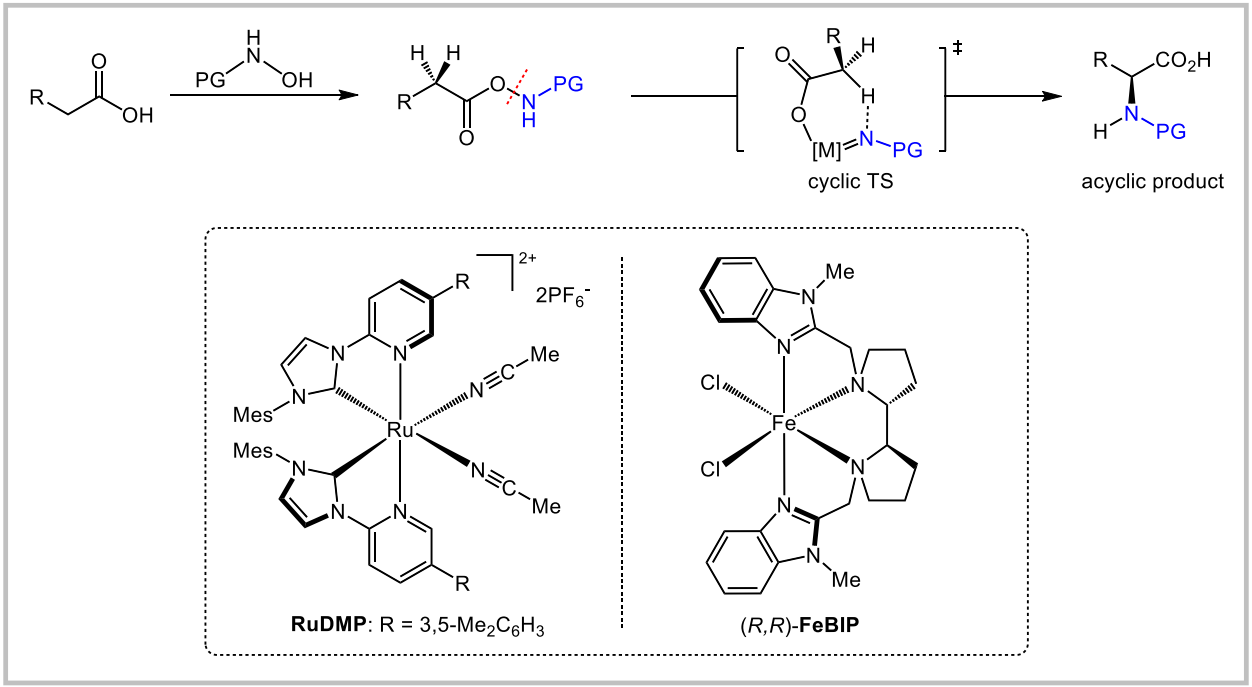
1e-d_2 (0.1 mmol) | 18% conversion | **2e-d_1** (18% yield)

KIE = 2.9

Reaction Mechanism



Summary



Writing Strategies-Introduction Part

Strategies for the synthesis of α-amino acids

↓

Current development of the first method

↓

Limitation of the first method

- ✓ A direct and straightforward strategy for the synthesis of optically active α-amino acids is the catalytic enantioselective introduction of an amino group in the α-position of readily available carboxylic acids.
- ✓ A number of methods for direct asymmetric C(sp^3)-H aminations have been reported and typically exploit the acidity of the C-H group next to a carbonyl functionality for electrophilic aminations *via* enolate intermediates.
- ✓ However, most existing methods use aldehydes, ketones or dicarbonyl compounds as starting materials instead of more desirable but less acidic carboxylic acid derivatives. To further complicate matters, the electrophilic amination reagents employed are usually diazo compounds, which lead to amination products that cannot be easily converted to the target α-amino acids.

Writing Strategies-Introduction Part

Current development of the second method

Limitation of the second method

Importance of Developing new method

- ✓ The insertion of nitrenes into C-H bonds provides a more tunable alternative platform for C(sp^3)-H aminations because the reactivity of nitrenes can be controlled by transition metal coordination. In addition, milder reaction conditions can often be used. Much progress has been made employing chiral transition metal catalysts for the enantioselective conversion of prochiral C(sp^3)-H bonds into C-N bonds by nitrene insertion.
- ✓ However, intermolecular nitrene insertion reactions suffer from problems with regioselectivity and enantioselectivity. Although this is not the case for intramolecular C(sp^3)-H amination reactions, in which well-defined intramolecular cyclic transition states allow exquisite regio- and stereocontrol, such intramolecular C-H nitrene insertions are typically ring-closing reactions and therefore lack general applicability.
- ✓ Thus, the catalytic enantioselective synthesis of acyclic amines by catalytic enantioselective C(sp^3)-H nitrene insertion remains a challenge, and its application to the synthesis of chiral α-amino acids would be highly desirable.

Writing Strategies-Introduction Part

Introduction of the new method

- ✓ In this article we introduce a strategy that combines the advantages of intramolecular (regio- and stereocontrol *via* intramolecular cyclic transition state) and intermolecular C-H nitrene insertion chemistry (more general, acyclic products) by covalently connecting a nitrene precursor to a carboxylic acid functionality. After O-N bond cleavage and binding of both fragments to the catalyst, an intramolecular cyclic transition state facilitates a stereocontrolled C(sp^3)-H amination. This reaction constitutes an unprecedented stereocontrolled 1,3-migratory nitrene C-H insertion and is applied to the catalytic asymmetric synthesis of α-amino acids.

Writing Strategies-Conclusion Part

Summary of this work

- ✓ We report the catalytic enantioselective synthesis of chiral α-amino acids by an enantioselective 1,3-migratory nitrene C(sp^3)-H insertion. The method is based on a unique stereocontrolled 1,3-nitrogen shift from one carboxylic acid oxygen to the α-carbon.

Advantage of the current method

- ✓ Our method employs abundant and easily accessible carboxylic acids as starting materials. Ligation to a nitrene precursor, followed by intramolecular C-H cleavage through an intramolecular cyclic transition state, ensures high regio- and stereocontrol in the synthesis of non-racemic chiral α-amino acids. Chiral ruthenium and iron catalysis jointly provide a very broad scope, enabling rapid access to optically active α-amino acids with aryl, allyl, propargyl (ruthenium catalysis) and non-activated alkyl (iron catalysis) side chains, including α-disubstituted amino acids by stereoretentive (ruthenium catalysis) or enantioconvergent (iron catalysis) C-H amination.

Writing Strategies-Conclusion Part

Advantage of the current method

- ✓ The high functional group tolerance of this method also permits the enantioselective late-stage amination of carboxylic-acid-containing drugs and natural products. The Troc-protected amino acids obtained through this protocol can be used directly in synthesis with the Troc group being selectively removable under mild conditions *via* a reductive Grob fragmentation.

Outlook of this work

- ✓ This strategy will expedite the synthesis of unnatural α-amino acids, which are important building blocks of peptidomimetic drugs, as well as engineered proteins and enzymes with modulated properties.

Representative Examples

We **commenced** our study with carboxylic acid derivatives **1a-e** in which the nitrogen bears different electron-withdrawing protecting groups, which is established to be beneficial for generating electrophilic nitrene intermediates.（开始…）

This strategy will **expedite** the synthesis of unnatural α-amino acids, which are important building blocks of peptidomimetic drugs, as well as engineered proteins and enzymes with modulated properties**.** (加速…）

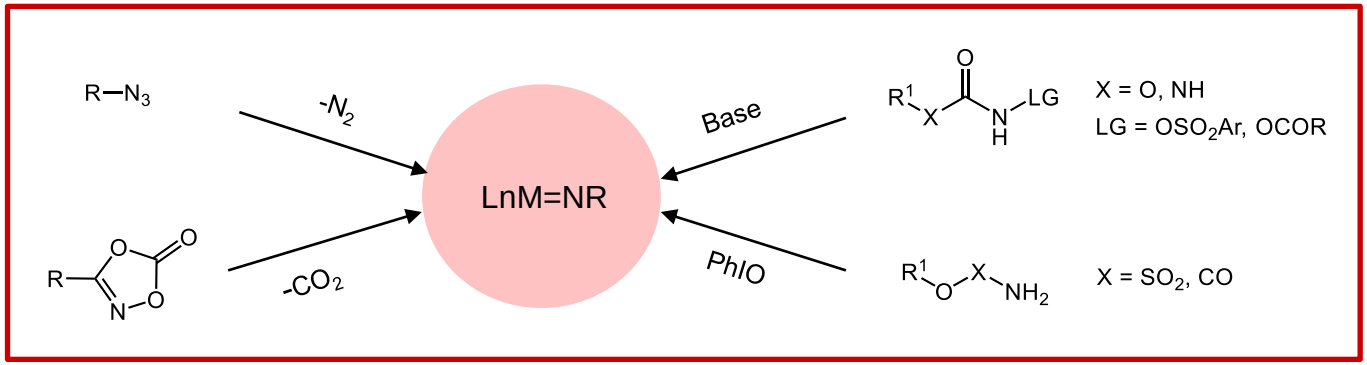
Importantly, catalysts of this class **feature** two vacant coordination sites adjacent to each other (coordination sites of the two labile acetonitrile, highlighted in red), which is essential for the envisioned mechanistic design. （以…为特色）

What We Learn from This Article

1. Synthesis of chiral amino acids is a subject worthy of being investigated in a long term.

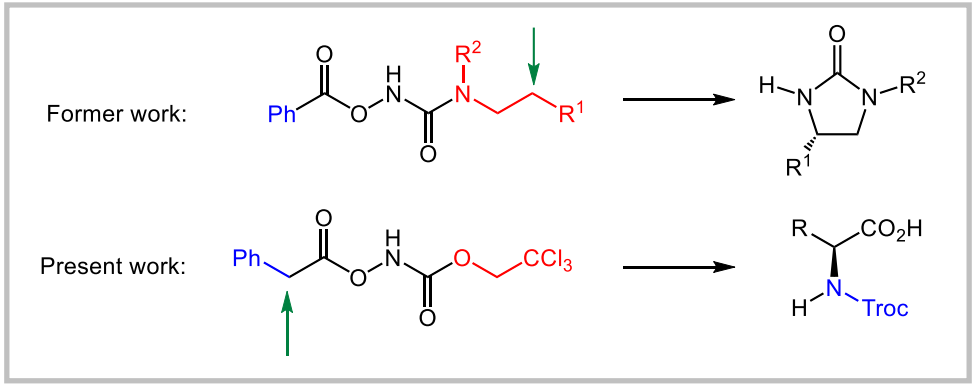
transamination, reductive amination, amination of α-position of carboxylic acids

2. Methods to produce nitrenoid



What We Learn from This Article

3. The importance of the substrate design



Knowledgement

Thanks for your attentions!