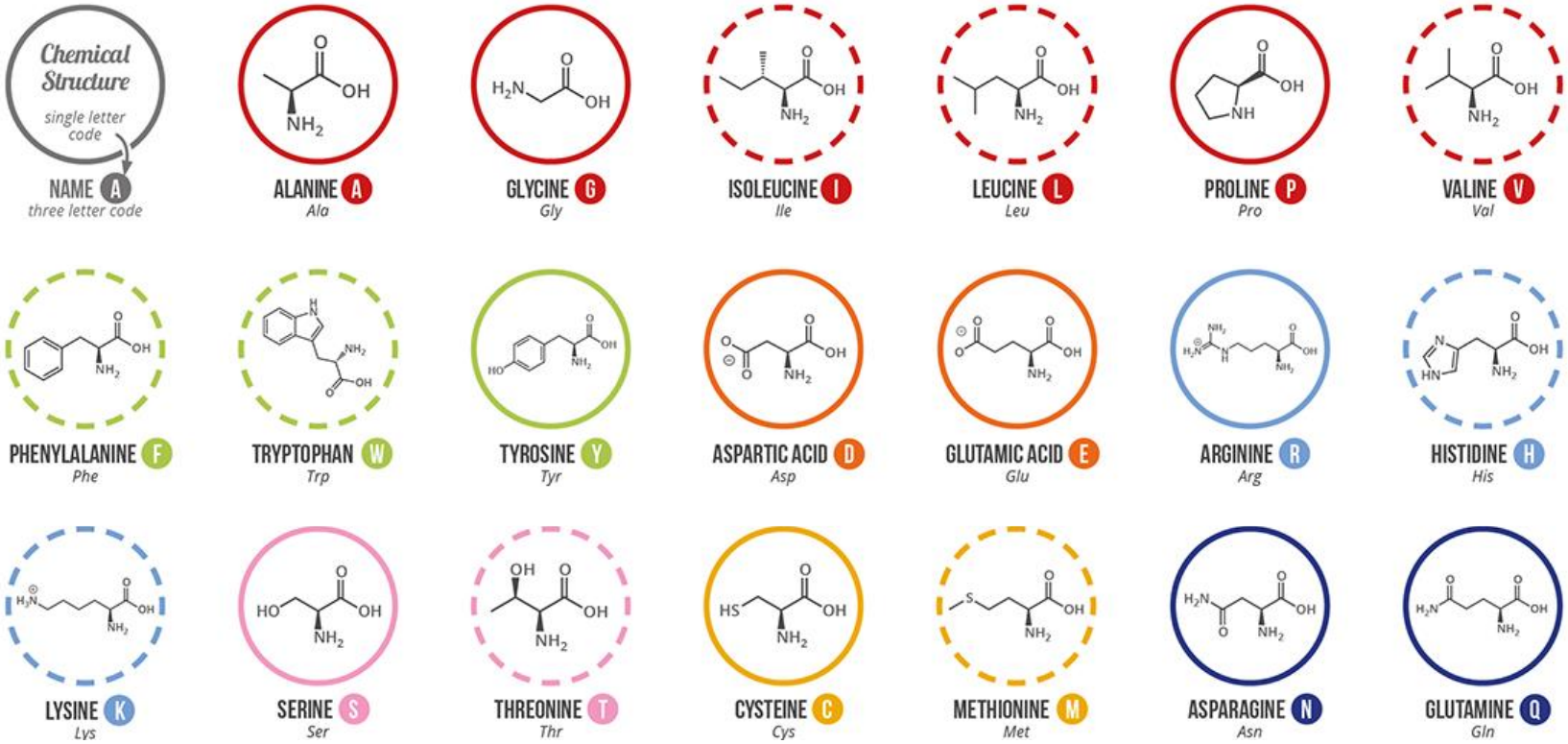
Unnatural Amino Acids

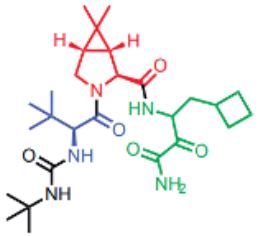
Synthesis to take us beyond the 20 standard amino acids



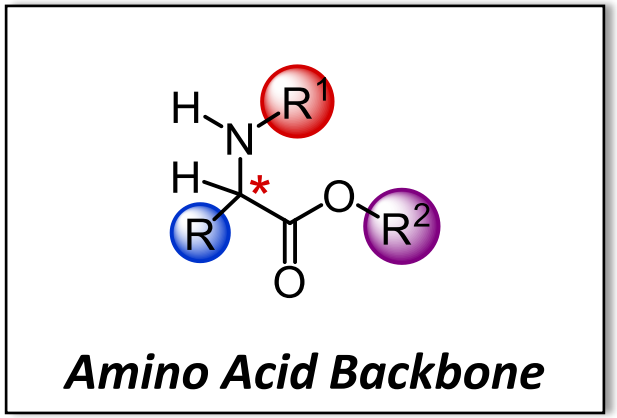
Brittany C. Haas
Sigman Lab

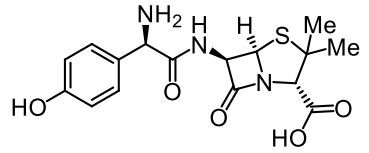
Synthesis Club
28 July 2021

Why Unnatural Amino Acids?



Boceprevir





Amoxicilin

Areas of Interest:

- Biology
- Protein Engineering
- Biochemistry/Enzymology
- Medicinal Chemistry
- Materials Science

Attraction:

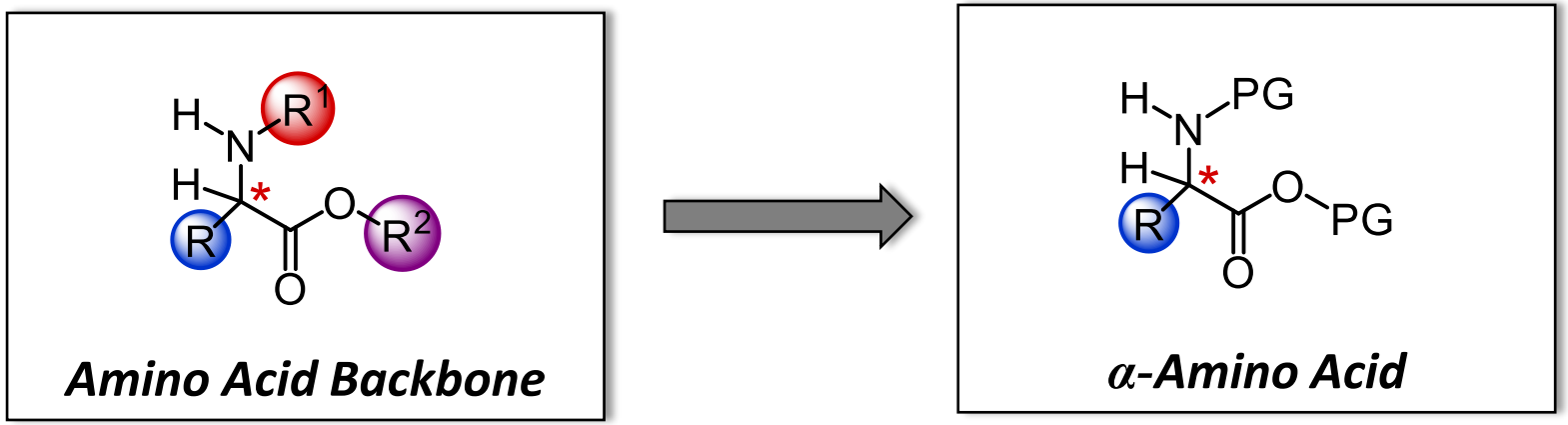
- Novel physiochemical properties
- New biological activity
- Determine protein properties
- Characterize molecular interactions
- Transform into β-amino alcohols

How to make UAA:

- Chemical reaction with SAA side chains
- Biological posttranslational modifications (PTMs)
- Synthetically

Gao, W.; Cho, E.; Liu, Y.; Lu, Y. *Front. Pharmacol.* **2019**, 10, 611, 1–8.

Why Unnatural Amino Acids?



Enantioselectively

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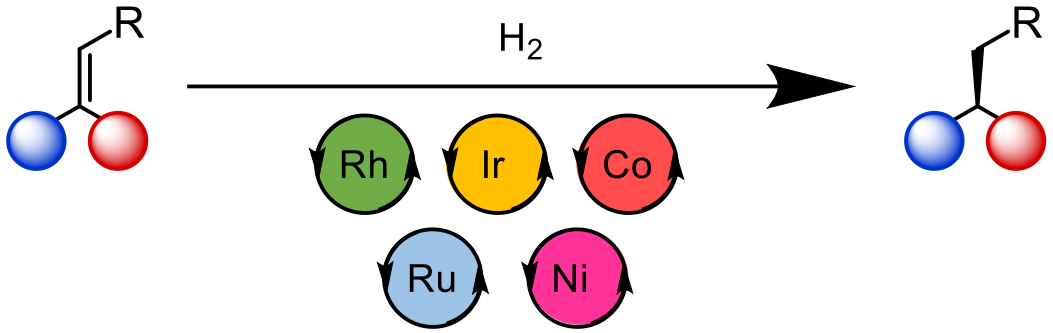
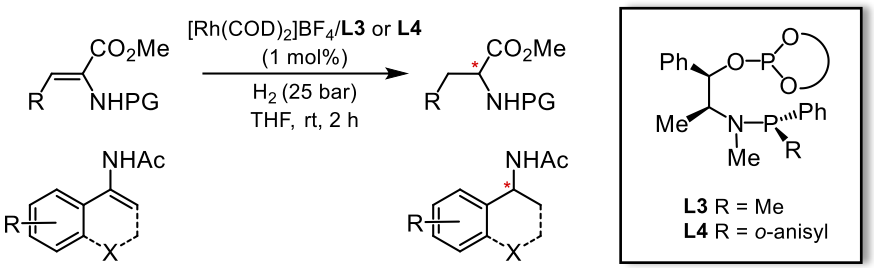
Synthetic Methods to UAA

Hydrogenation of olefins or imines

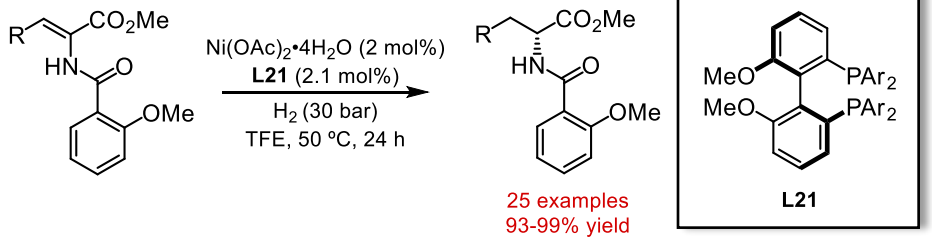




8 examples
96-99% conv.
60-99% ee

L3 R = Me
L4 R = *o*-anisyl

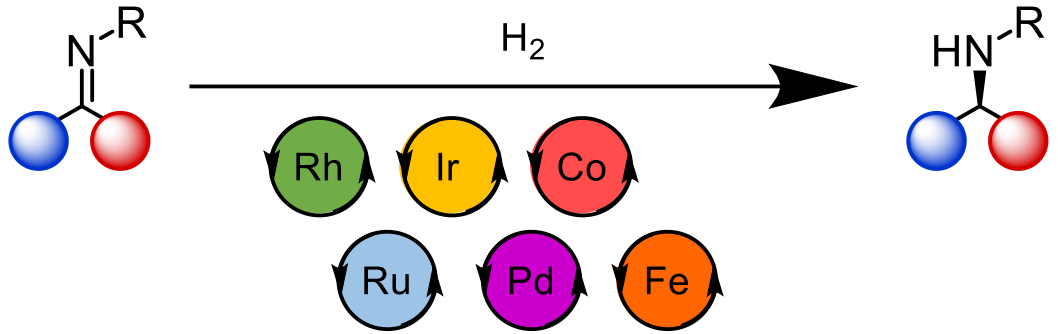
Biosca, M.; et. al. *J. Org. Chem.* **2020**, 85, 4730.

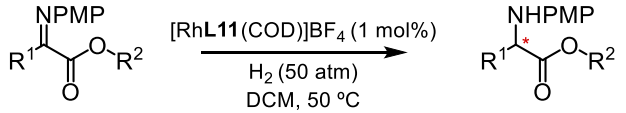


25 examples
93-99% yield
90-96%ee

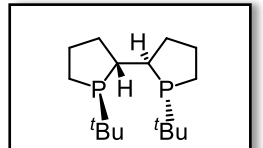
L21

Hu, Y.; et. al. *Angew. Chem. Int. Ed.* **2020,** 59, 5371.





15 examples
84-99% conv.
84-95% ee



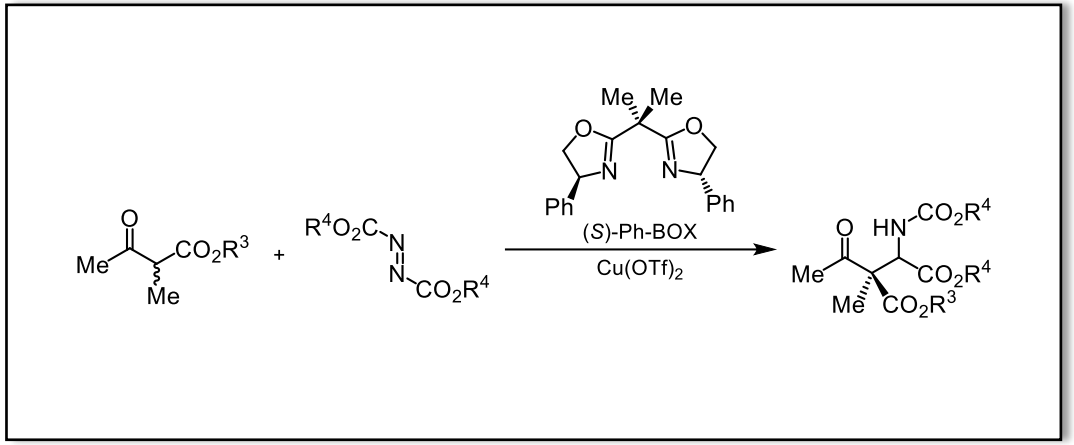
L11
(*S,S,R,R*)-TangPhos

Shang, G.; et. al. *Angew. Chem., Int. Ed*. **2006**, 45, 6360.

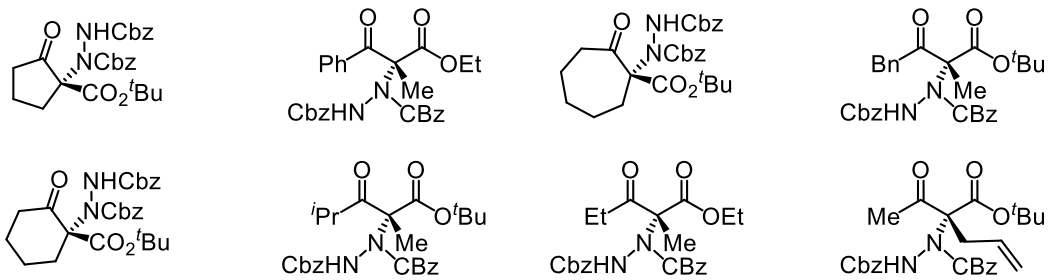
Ponra, S.; Boudet, B.; Phansavath,P.; Ratovelomanana-Vidal, V. *Synthesis* **2021**, 53, 193−214.
Abdine, R. A. A.; Hedouin, G.; Colobert, F.; Wencel-Delord, J. *ACS Catal*. **2021**, 11, 215−247.

Synthetic Methods to UAA

Electrophilic aminations of enolates



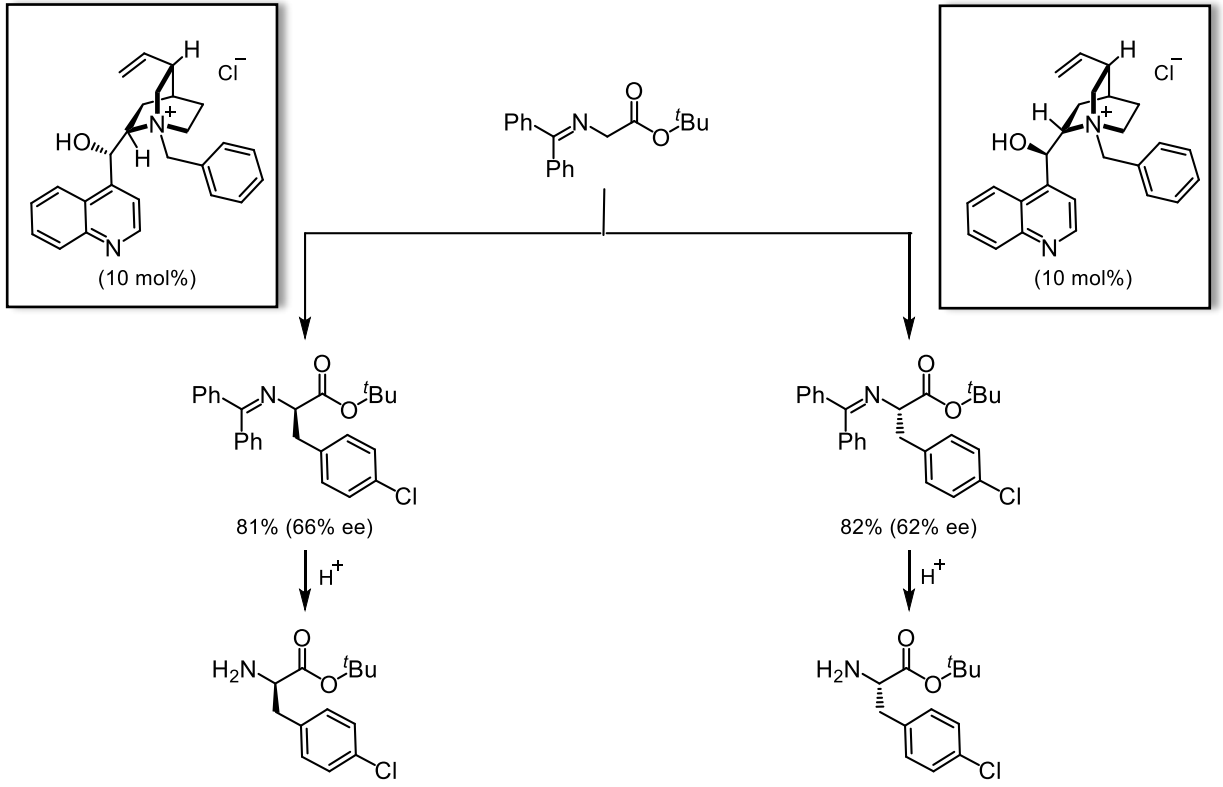
Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2003**, 42, 1367.



Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, 111, 1637−1656.

Synthetic Methods to UAA

Electrophilic alkylations of glycine derivatives

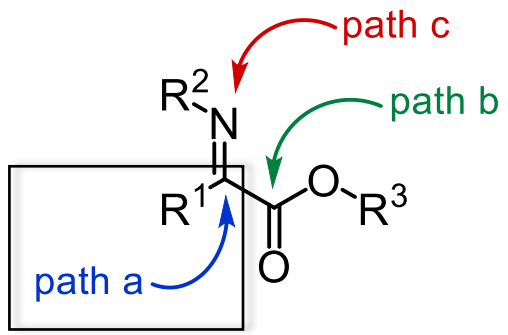


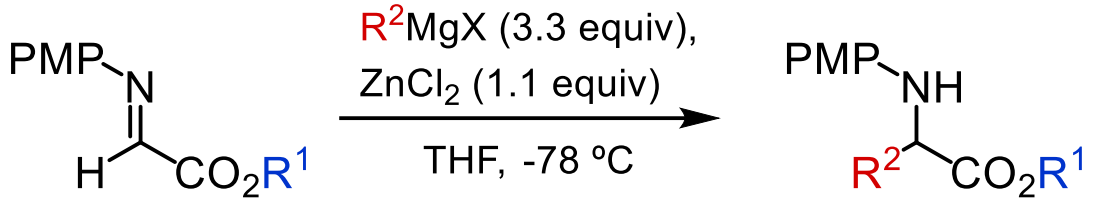
O'Donnell, M. J.; et. al. J. *Am. Chem. Soc*. **1989**,111, 2353.

Maruoka, K.; Ooi, T. *Chem. Rev*. **2003**, 103, 3013−3028.

Synthetic Methods to UAA

Nucleophilic additions to α-imino esters





Hatano, M.; et. al. *Org. Lett.* **2015**, 17 (10), 2412−2415.

Eftekhari-Sis, B.; Zirak, M. *Chem. Rev*. **2017**, 117, 8326−8419.

Case Study

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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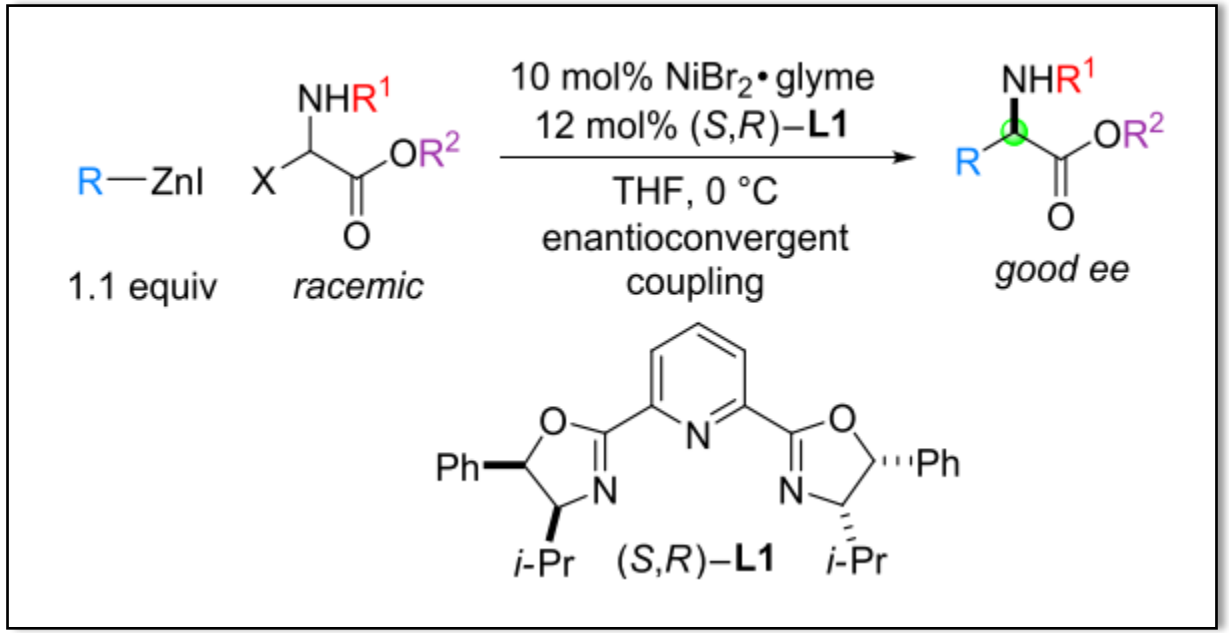
Communication

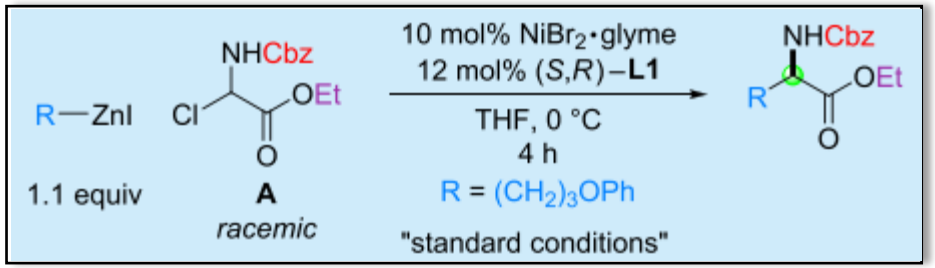
Asymmetric Synthesis of Protected Unnatural α-Amino Acids via Enantioconvergent Nickel-Catalyzed Cross-Coupling

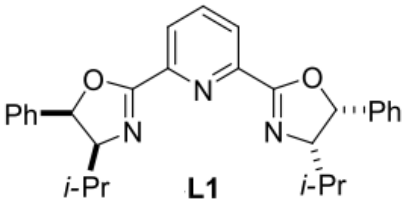
Ze-Peng Yang,[†] Dylan J. Freas,[†] and Gregory C. Fu*

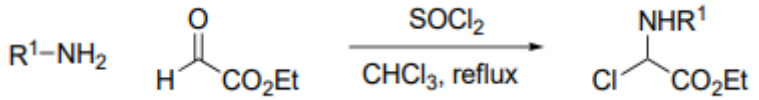


J. Am. Chem. Soc. **2021**, 143, 8614−8618.

Reaction Parameters







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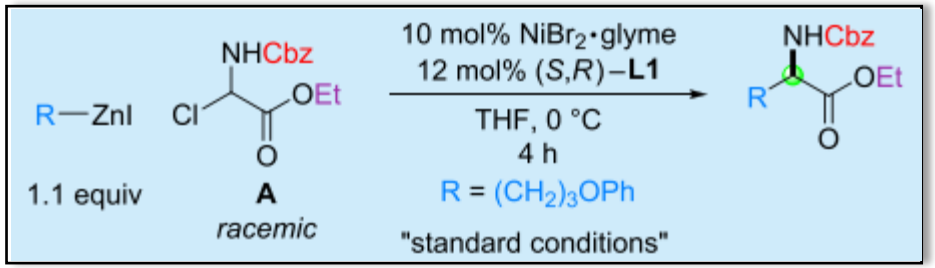

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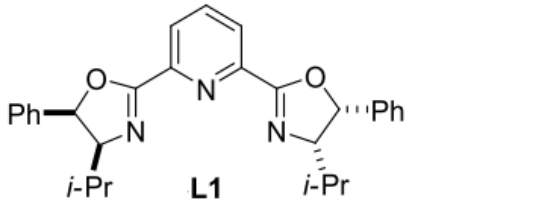

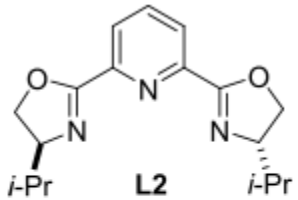

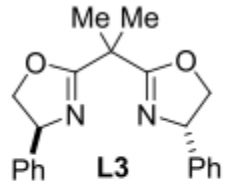

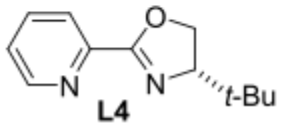

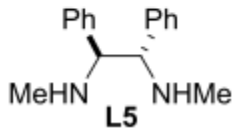

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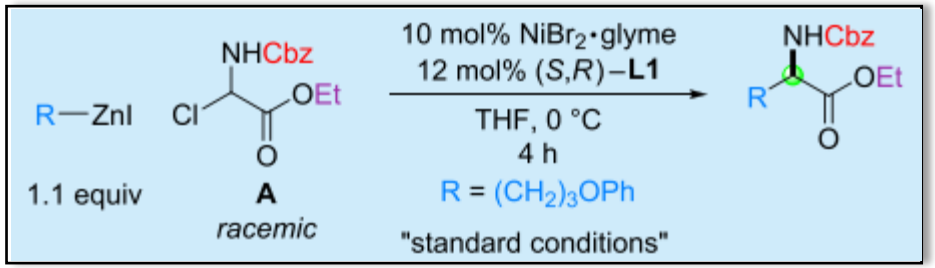

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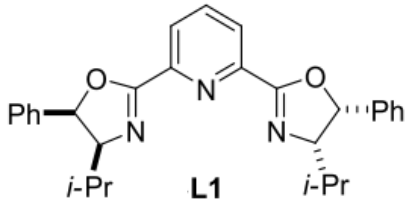

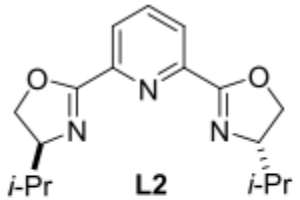

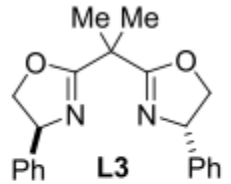

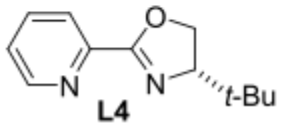

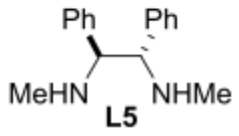

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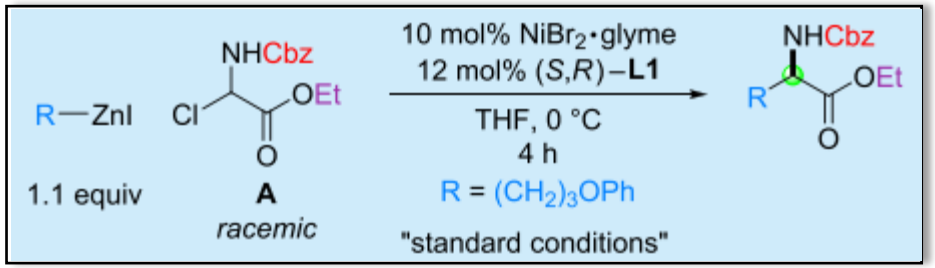

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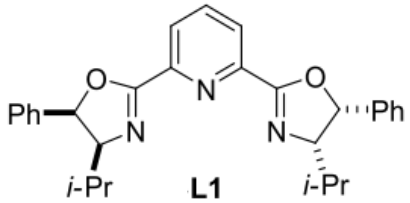

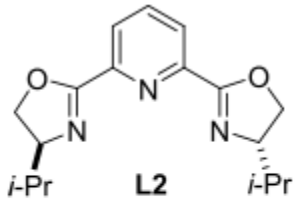

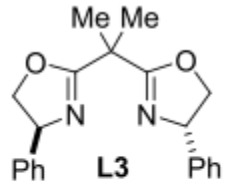

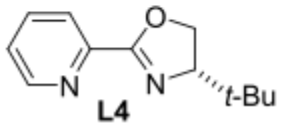

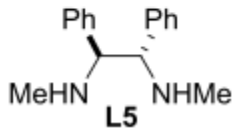

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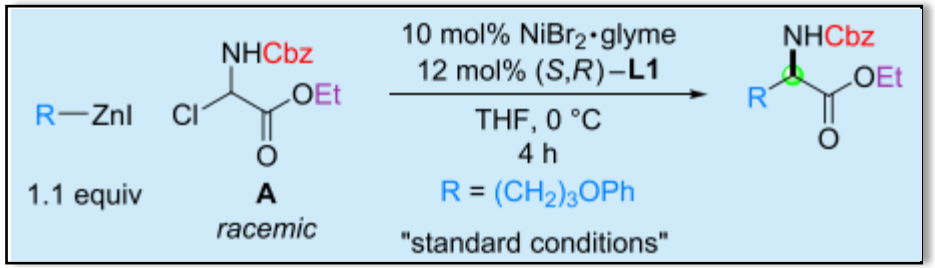

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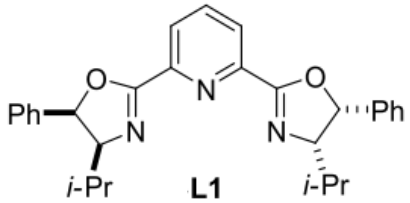
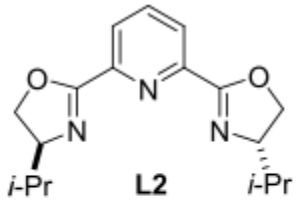
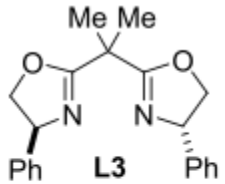
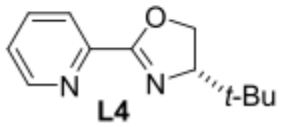
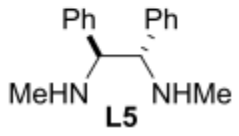




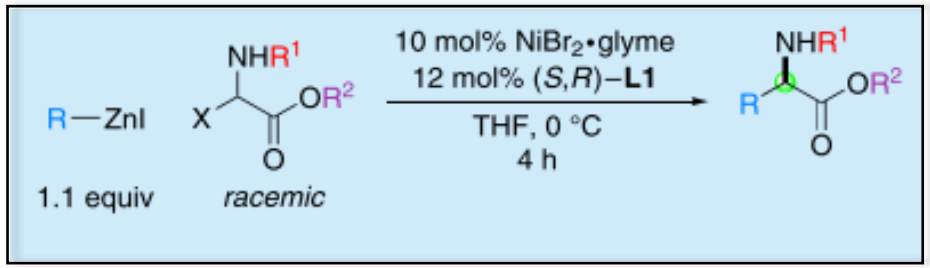


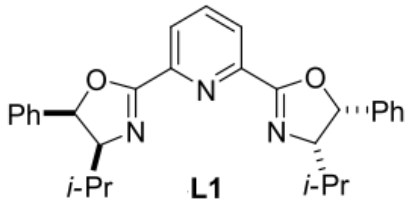




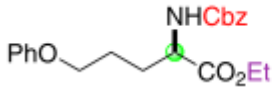
J. Am. Chem. Soc. **2021**, 143, 8614−8618.

Substrate Scope

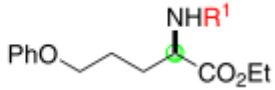




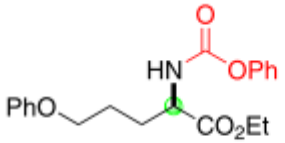
variation of N and O protecting groups



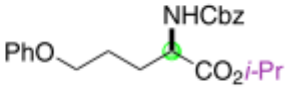
1, 83% yield, 97% ee
[gram scale (1.48 g):
83% yield, 97% ee]



R^1 = Boc **2**, 87% yield, 95% ee
Fmoc **3**, 73% yield, 94% ee
Alloc **4**, 70% yield, 96% ee



5, 74% yield, 96% ee



6, 89% yield, 97% ee

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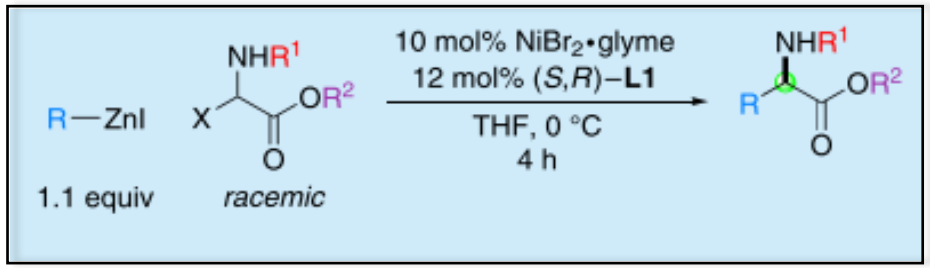
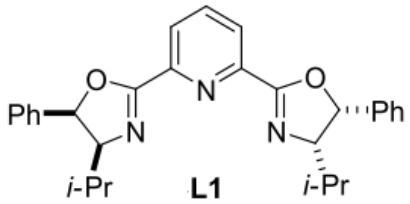
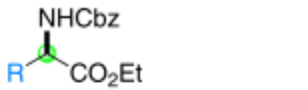
Substrate Scope

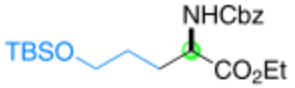




variation R-groups

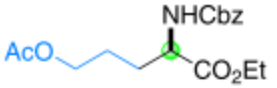


R = Me **7**, 76% yield, 91% ee
n-Pent **8**, 64% yield, 97% ee
$(CH_2)_2Ph$ **9**, 76% yield, 98% ee
$(CH_2)_2Cy$ **10**, 63% yield, 97% ee
i-Bu **11**, 65% yield, 99% ee

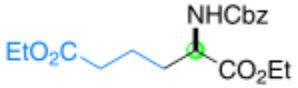


12, 80% yield, 97% ee

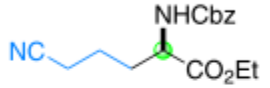
13, 75% yield, 96% ee



14, 81% yield, 95% ee



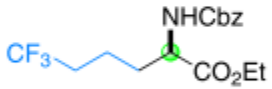
15, 79% yield, 95% ee



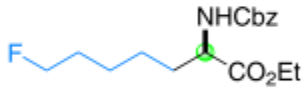
16, 90% yield, 90% ee

17, 75% yield, 97% ee

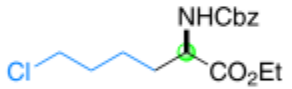
18, 81% yield, 97% ee



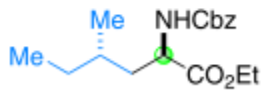
19, 81% yield, 96% ee



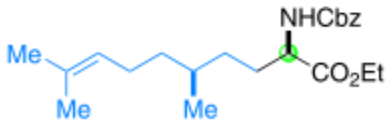
20, 74% yield, 96% ee



21, 78% yield, 97% ee



22, (*S*,*R*)–**L1**: 61% yield, 99:1 dr
[**23**, (*R*,*S*)–**L1**: 64% yield, 1:99 dr]



24, (*S*,*R*)–**L1**: 65% yield, 99:1 dr
[**25**, (*R*,*S*)–**L1**: 63% yield, 1:99 dr]

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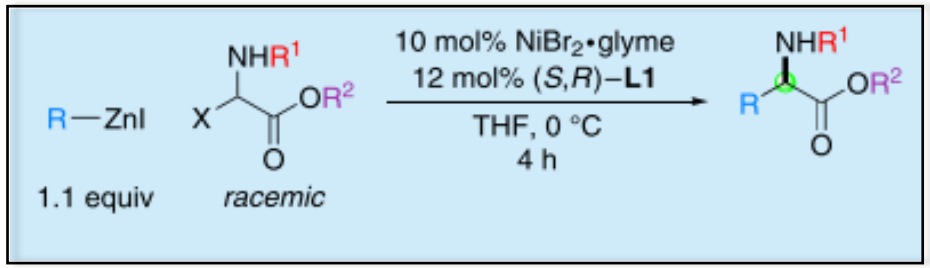
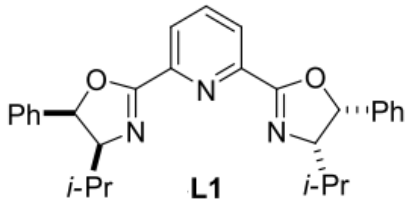
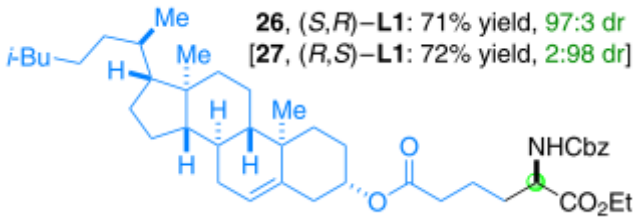
Substrate Scope

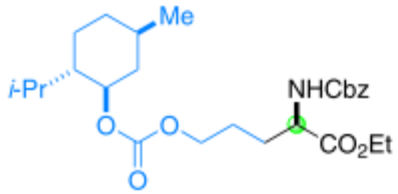




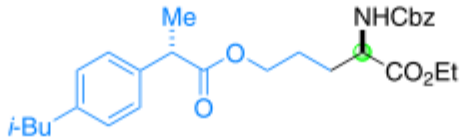
variation R-groups



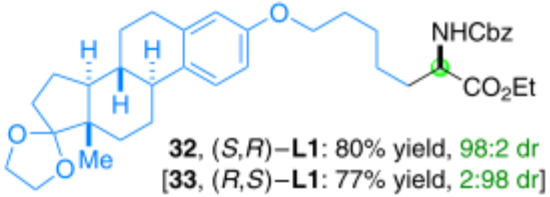
26, (*S*,*R*)–**L1**: 71% yield, 97:3 dr
[**27**, (*R*,*S*)–**L1**: 72% yield, 2:98 dr]



28, (*S*,*R*)–**L1**: 60% yield, 98:2 dr
[**29**, (*R*,*S*)–**L1**: 61% yield, 2:98 dr]



30, (*S*,*R*)–**L1**: 87% yield, 99:1 dr
[**31**, (*R*,*S*)–**L1**: 83% yield, 1:99 dr]



32, (*S*,*R*)–**L1**: 80% yield, 98:2 dr
[**33**, (*R*,*S*)–**L1**: 77% yield, 2:98 dr]

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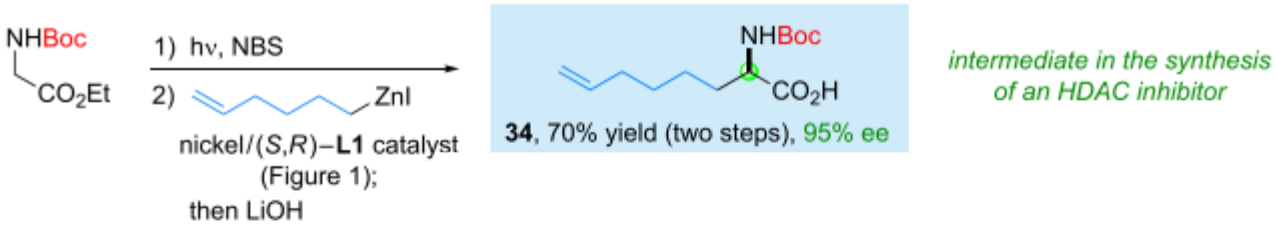
Practical Applications



intermediate in the synthesis of an HDAC inhibitor

Synthetic Steps

Previous Route	*This Method*
4	2

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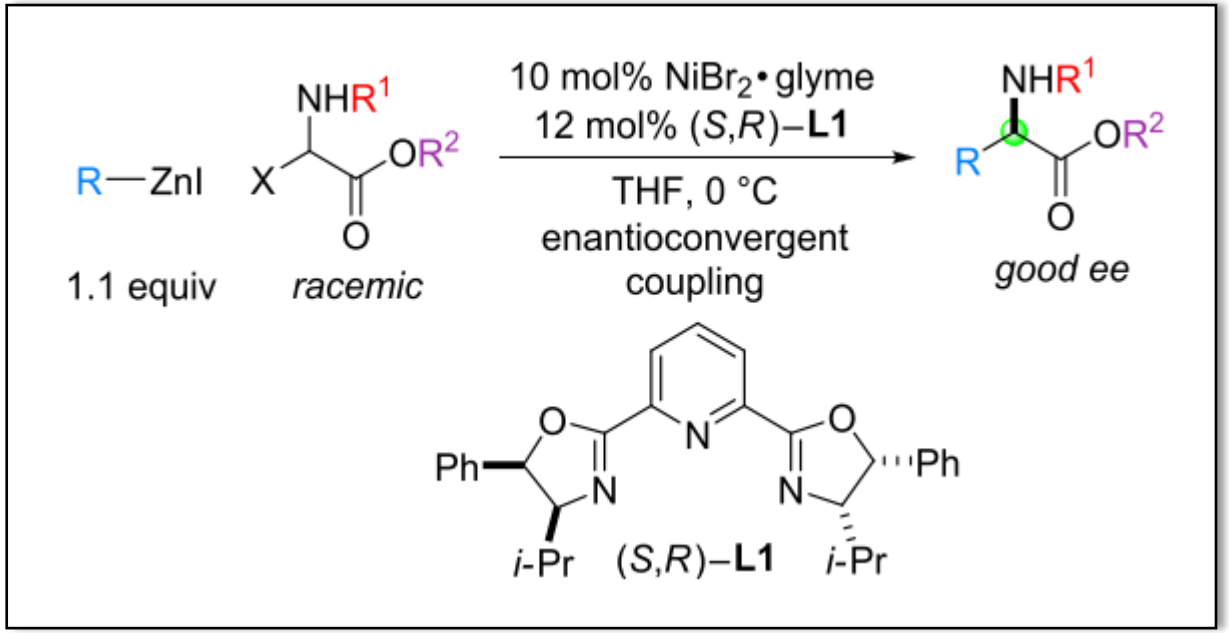
Case Study Conclusions



Method for the asymmetric synthesis of protected unnatural α-amino acids
via nickel-catalyzed enantioconvergent cross-couplings of
readily available racemic alkyl halides with alkylzinc reagents

+ Uses Ni
+ Mild conditions
  + Air and moisture tolerant
+ Diverse functional group compatibility
– Mechanistic discussion lacking

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