Literature Report 2

Catalyst-Controlled Regiodivergent and Enantioselective Formal Hydroamination of *N,N*-Disubstituted Acrylamides to α-Tertiary-α-Aminolactam and β-Aminoamide Derivatives

Reporter: Hao-Dong Chen
Checker: Qing-Xian Xie
Date: 2023-6-5

Wang, S. Shi, L. Chen, X.-Y. Shu, W. *Angew. Chem. Int. Ed.* **2023**, *62,* e202303795

CV of Dr. Wei Shu

Research:

- Green catalytic chemistry
- Visible photocatalytic chemistry
- First-row transition metal catalysis

Background:

- **2001-2005** B.S., Nankai University
- **2005-2010** Ph.D., Shanghai Institution of Organic Chemistry
- **2010-2018** Postdoctoral, Massachusetts Institute of Technology
  Postdoctoral, Princeton University
  Postdoctoral, University of Zurich
- **2018-now** Associate Professor to Professor, SUSTech

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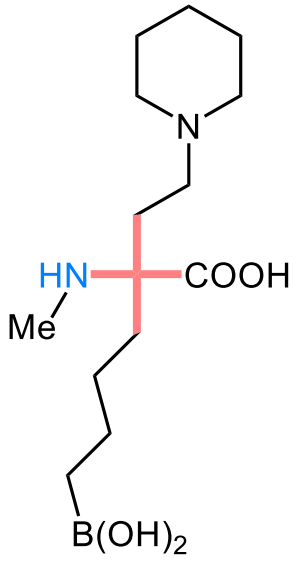
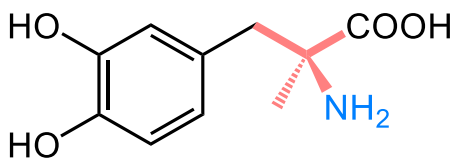
Introduction

Selected Molecular Containing Chiral α-Tertiary-α-Aminoacid, β-Aminoacid Derivatives



potent arginase inhibitor



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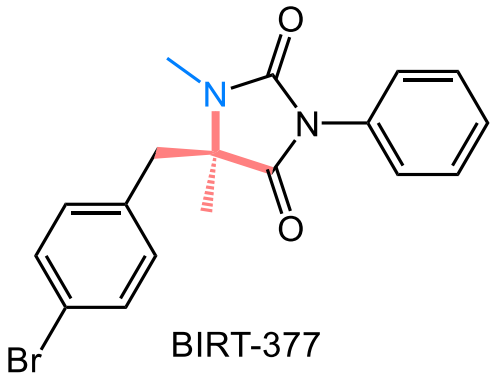

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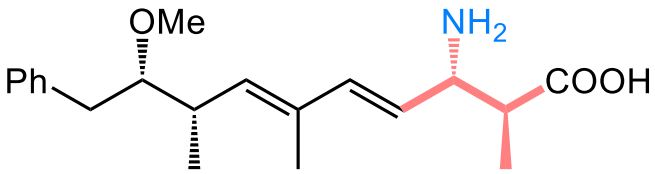

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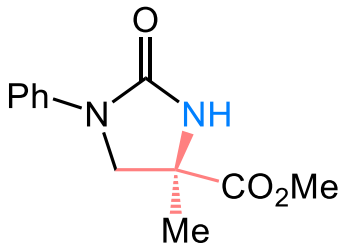

selective androgen receptor modulators

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Markovitz, D. C.; Fernstrom, J. D. *et al. Science* **1977**, *197*, 1014
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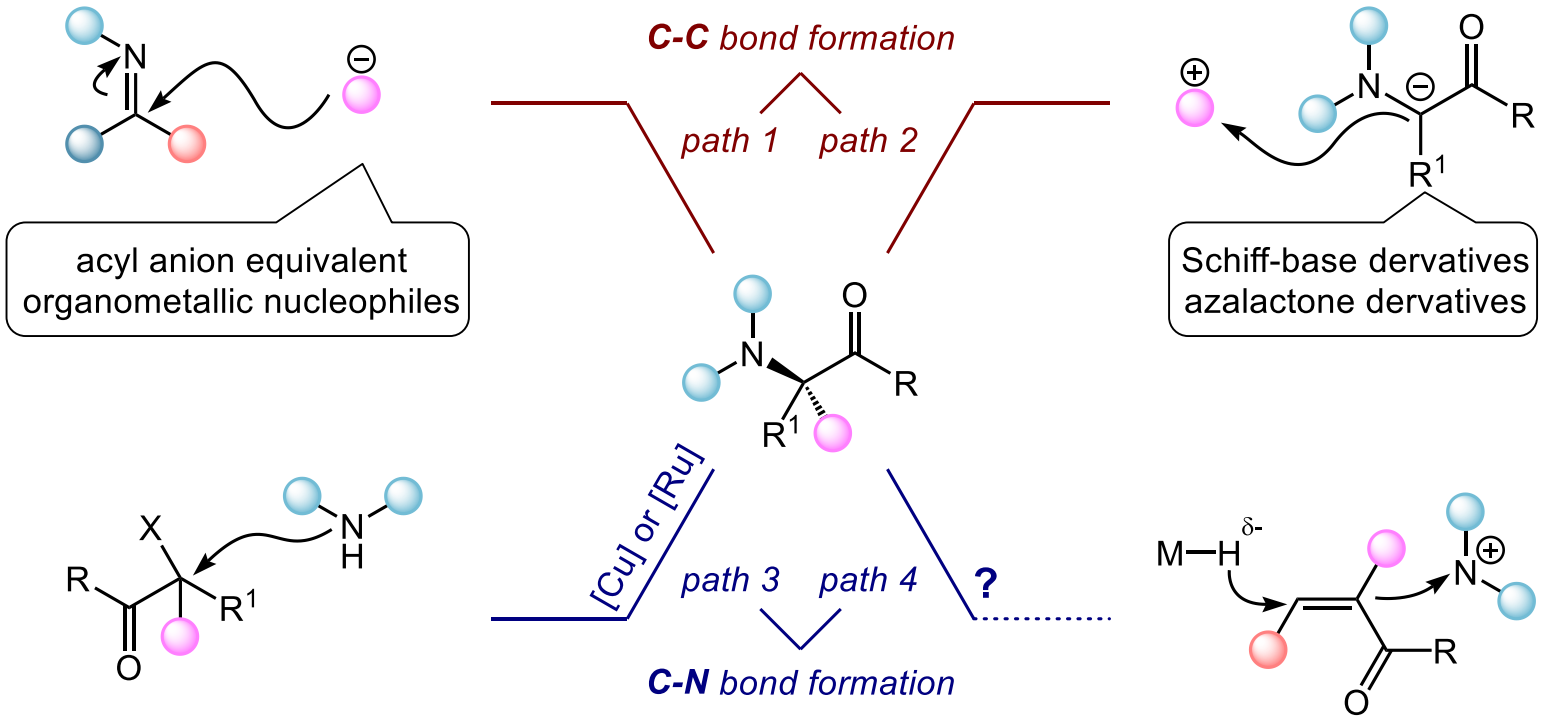
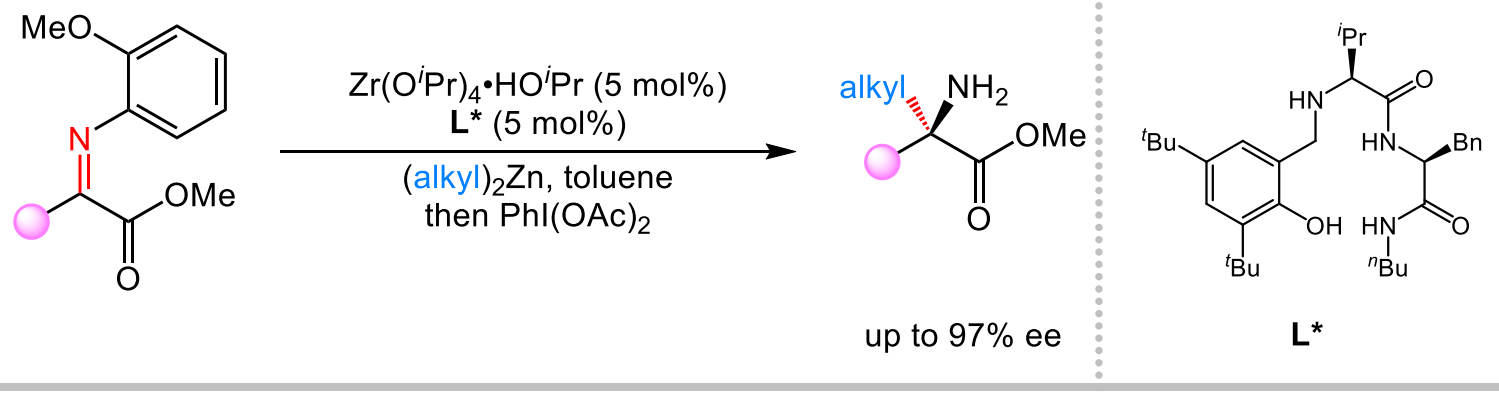
Introduction

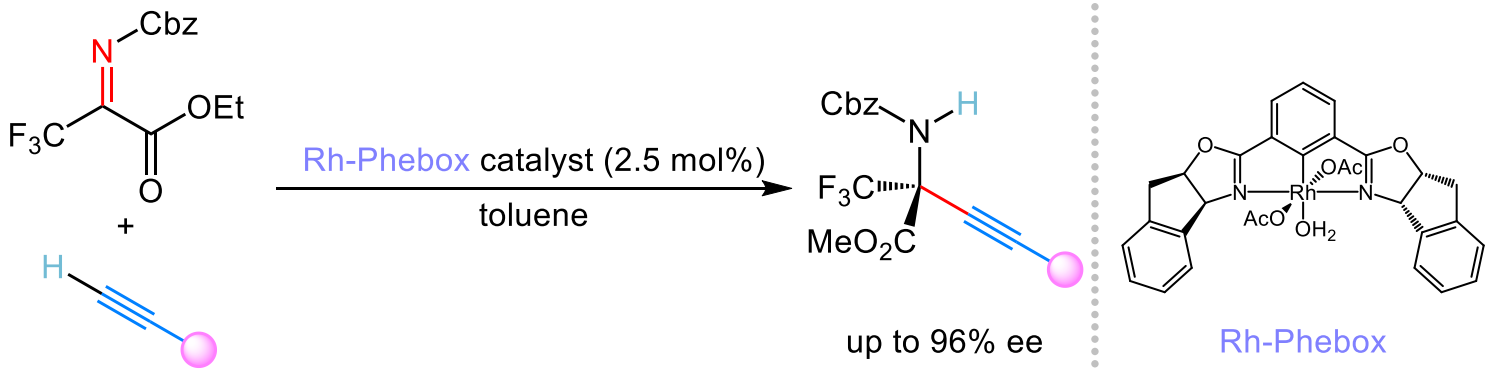
α-Tertiary-α-Aminoacid Derivatives Synthesis via C-C or C-N Bond Formation



Introduction

Synthesis of α-Tertiary-α-Aminoacid Derivatives via C-C Bond Formation





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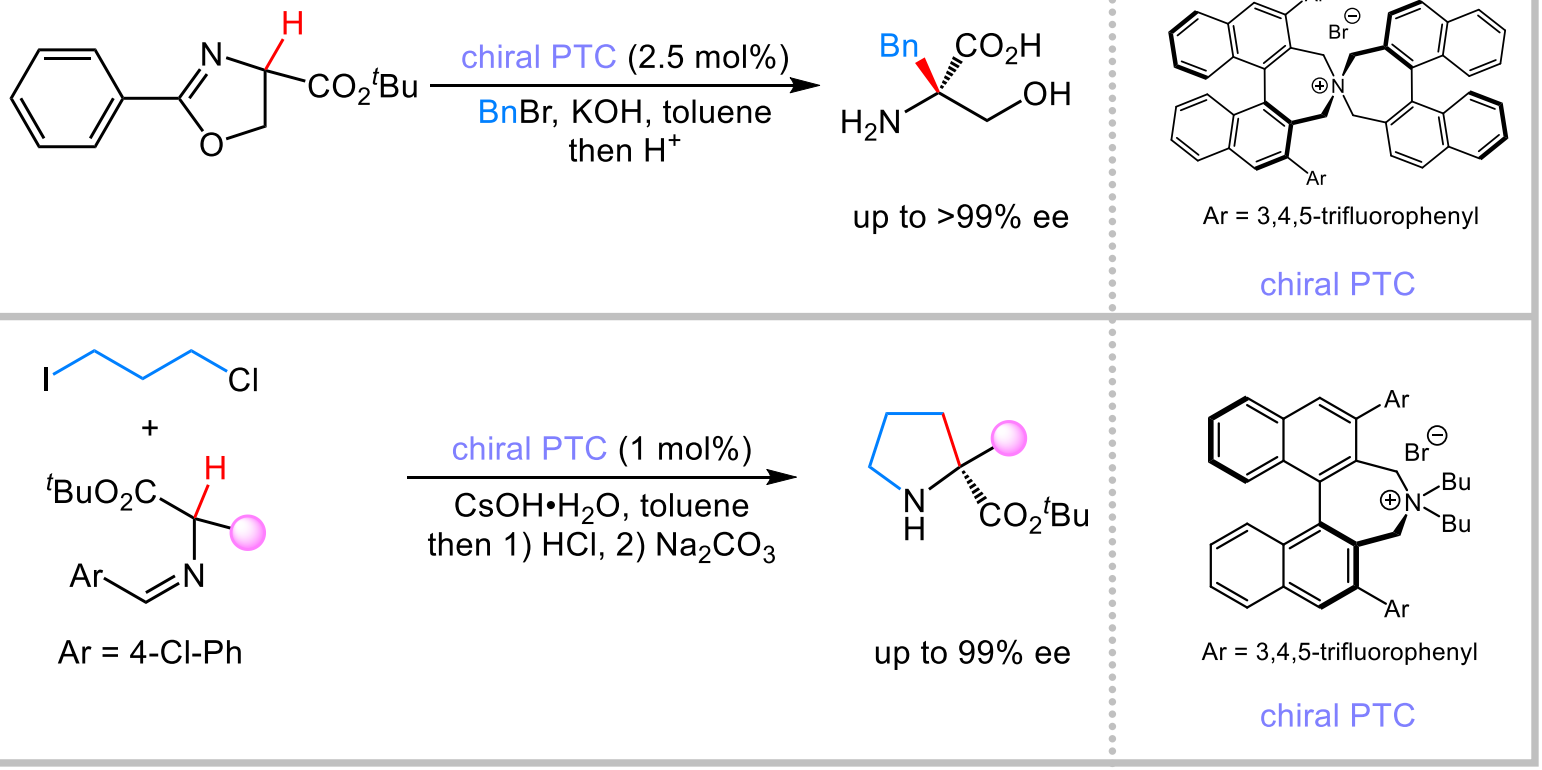
Introduction

Synthesis of α-Tertiary-α-Aminoacid Derivatives via C-C Bond Formation



Jew, S.-s.; Lee, Y.-J.; Park, H.-g. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 2382

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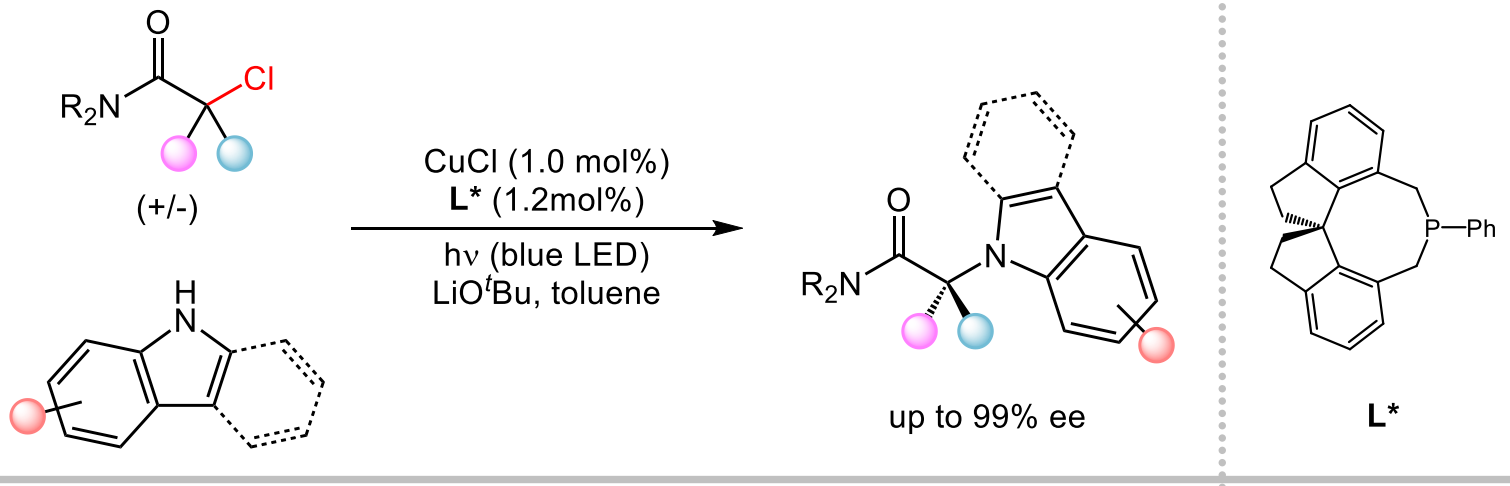
Introduction

Synthesis of α-Tertiary-α-Aminoacid Derivatives via C-N Bond Formation

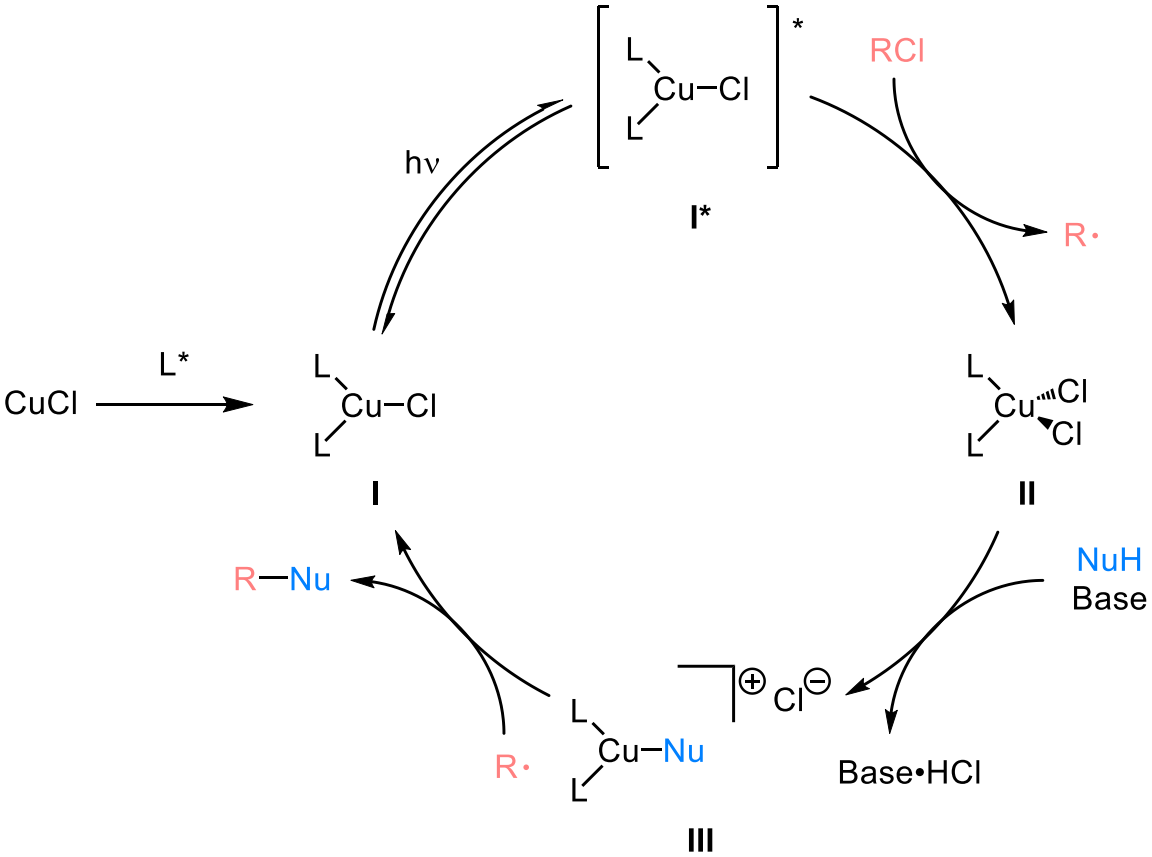


Kainz, Q. M.; Peters, J. C. Fu, G. C. *et al. Science* **2016**, *351*, 681

Cho, H.; Peters, J. C. Fu, G. C. *et al. J. Am. Chem. Soc.* **2022**, *144*, 4550

Introduction

Synthesis of α-Tertiary-α-Aminoacid Derivatives via C-N Bond Formation



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Cho, H.; Peters, J. C. Fu, G. C. *et al. J. Am. Chem. Soc.* **2022**, *144*, 4550

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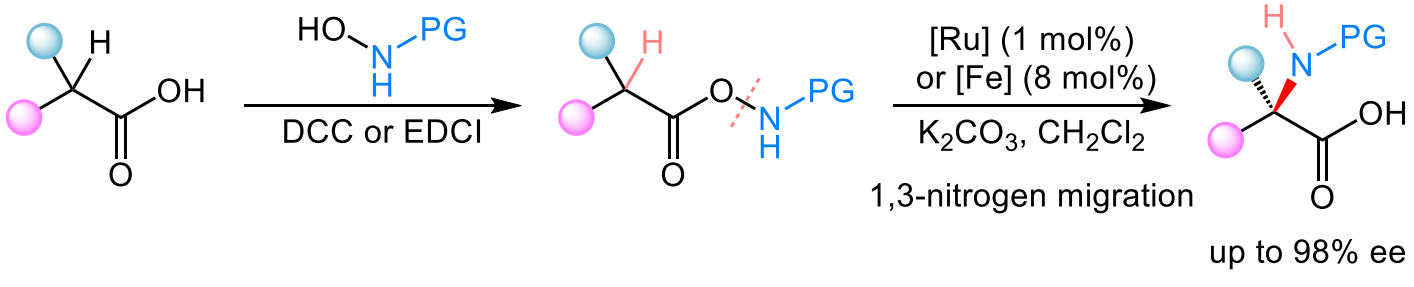
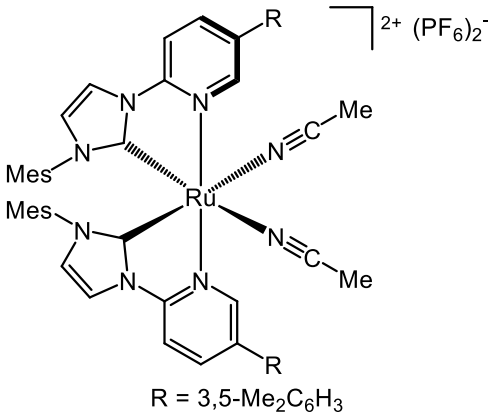
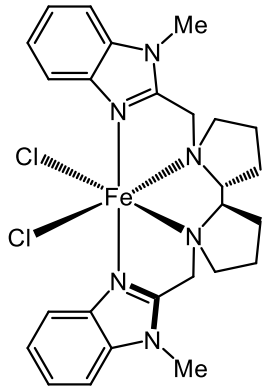




[Ru] = Λ-**RuDMP**

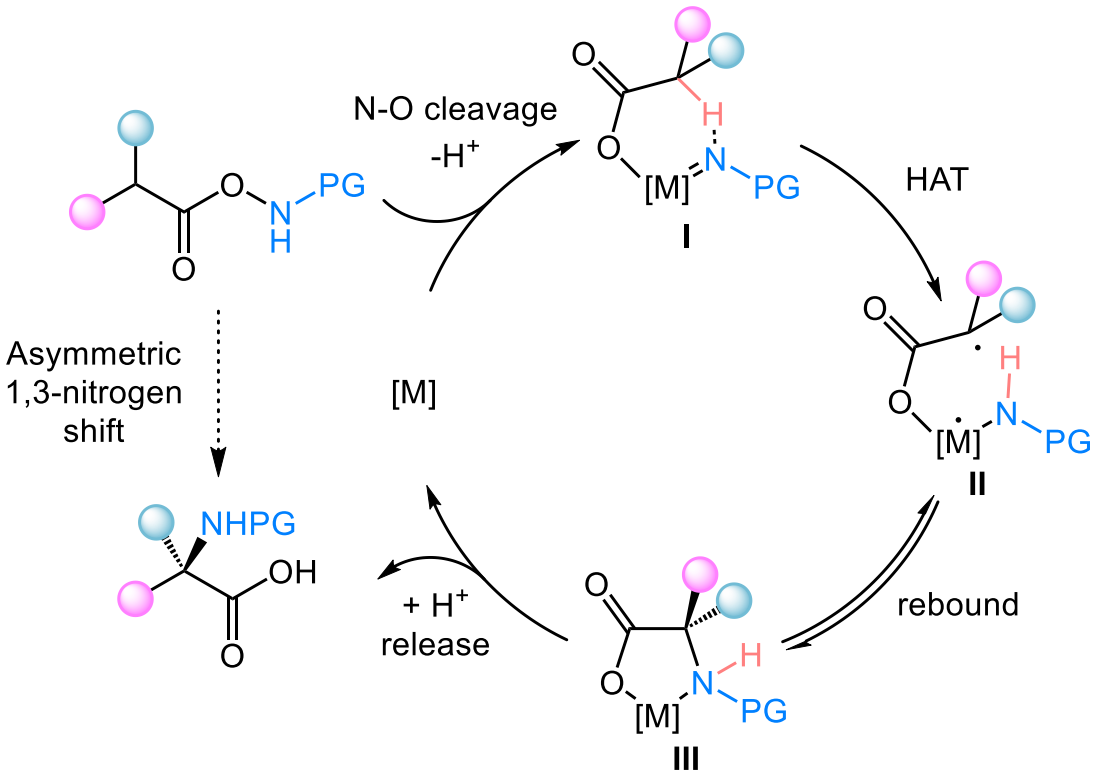


[Fe] = (*R*,*R*)-**FeBIP**

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

Introduction

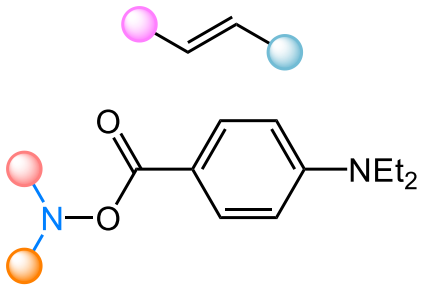
Synthesis of α-Tertiary-α-Aminoacid Derivatives via C-N Bond Formation



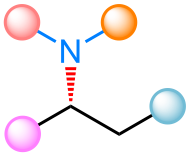
Ye, C.-X.; Chen, S.; Meggers, E. *et al. Nat. Chem.* **2022**, *14*, 566

Introduction

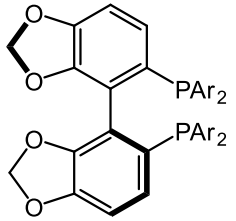
CuH-Catalyzed Hydroamination of Alkenes



$Cu(OAc)_2$ (5 mol%)
L* (5.5 mol%)
$(MeO)_2MeSiH$, THF

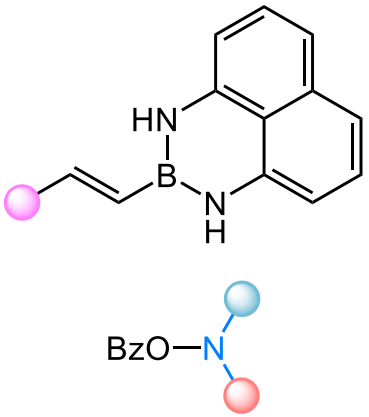


up to 99% ee

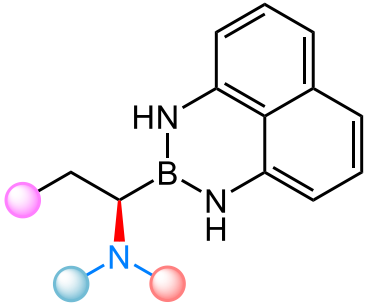


Ar = 3,5-^{t}Bu$_2$-4MeOC$_6$H$_2$

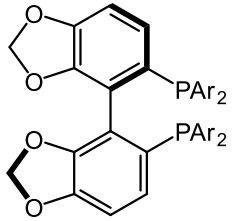
L*



$Cu(OAc)_2$ (10 mol%)
L* (10 mol%)
PMHS, LiO^tBu, THF



up to 98% ee



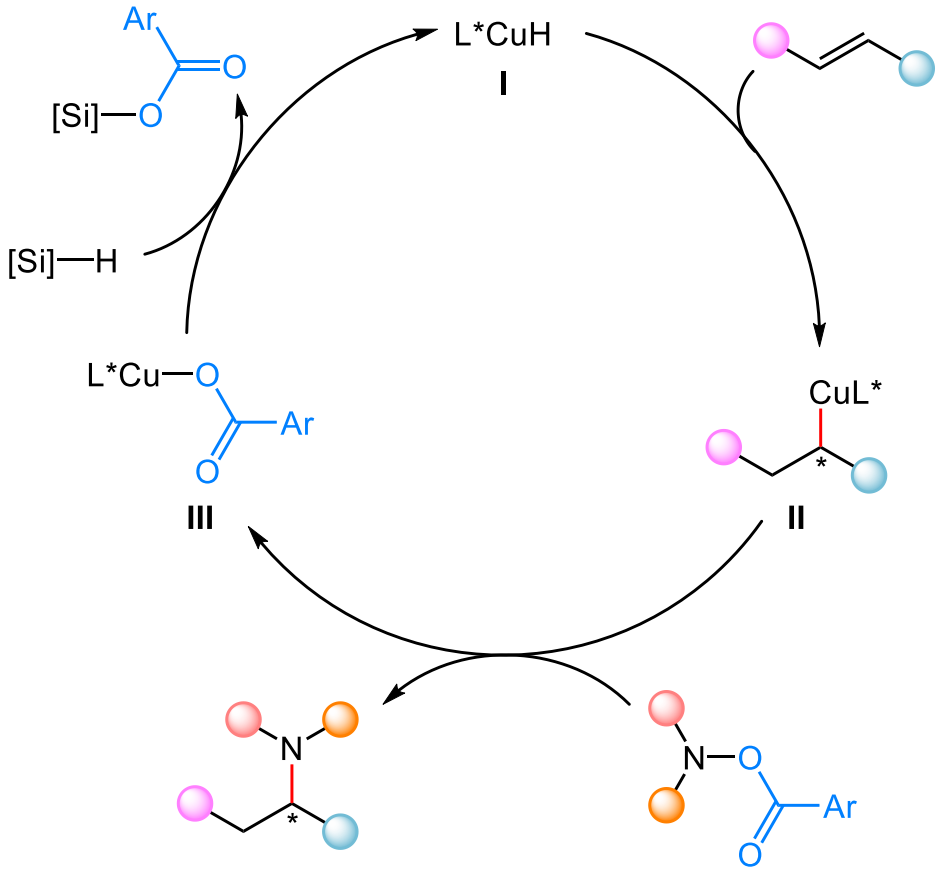
Ar = 3,5-^{t}Bu$_2$-4MeOC$_6$H$_2$

L*

Yang, Y.; Shi, S.-L.; Buchwald, S. L. *et al. Science* **2015**, *349*, 62
Nishikawa, D.; Hirano, K.; Miura, M. *et al. J. Am. Chem. Soc.* **2015**, *137*, 15620

Introduction

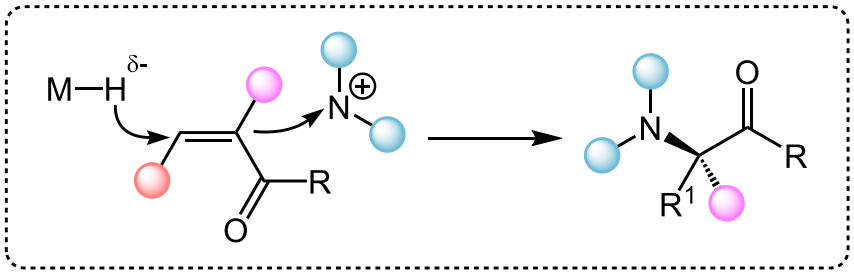
CuH-Catalyzed Hydroamination of Alkenes

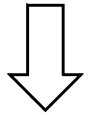


Yang, Y.; Shi, S.-L.; Buchwald, S. L. *et al. Science* **2015**, *349*, 62

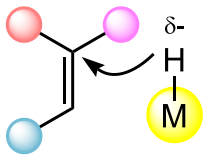
Project Synopsis

Regiodivergent and Enantioselective Formal Hydroamination





challenge



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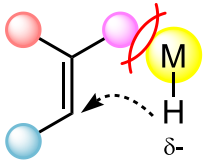

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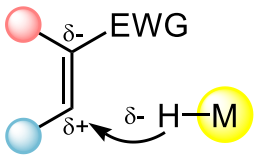

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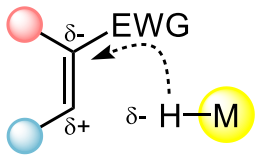
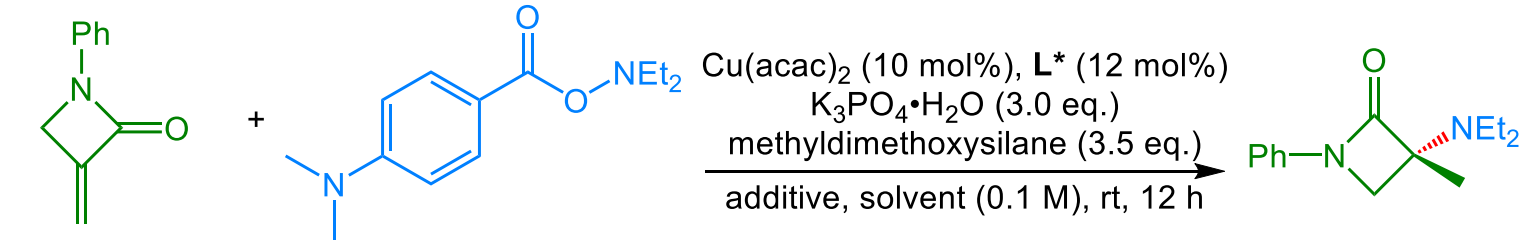


disfavored

Optimization of Reaction Conditions

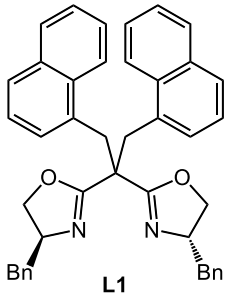
Optimization of Reaction Conditions



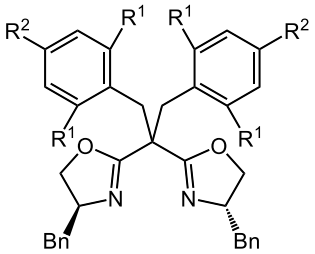
1a (0.10 mmol) **2a** (0.11 mmol) **3a**

entry	L*	addictive	solvent	**3a** yield (ee)/%
1	**L1**	none	PhMe	4 (79)
2	**L2**	none	PhMe	8 (83)
3	**L3**	none	PhMe	8 (77)
4	**L4**	none	PhMe	5 (54)
5	**L5**	none	PhMe	8 (78)
6	**L2**	H_2O (1.5 eq.)	PhMe	42 (89)
7	**L5**	Hacac (1.5 eq.)	PhMe	45 (91)
8[a]	**L2**	Hacac (1.5 eq.)	*o*-xylene	60 (91)
9[a, b]	**L2**	Hacac (1.5 eq.)	*o*-xylene	65 (90)

[a] ^{i}PrOH (2.0 eq.) was added. [b] [Cu] (5 mol%) and ligand (6 mol%) were used and reaction time was 24 h.



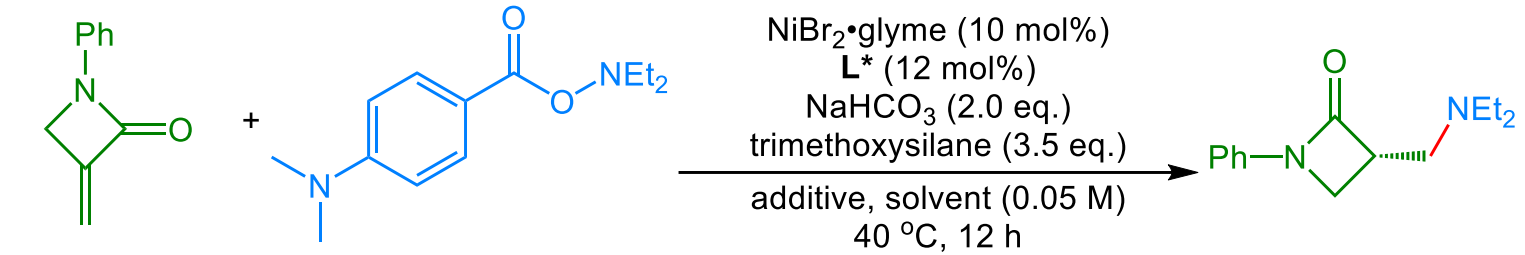
L1



L2 R^1 = Me, R^2 = H
L3 R^1 = R^2 = Me
L4 R^1 = H, R^2 = Cl
L5 R^1 = R^2 = Et

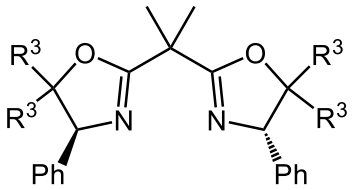
Optimization of Reaction Conditions

Optimization of Reaction Conditions

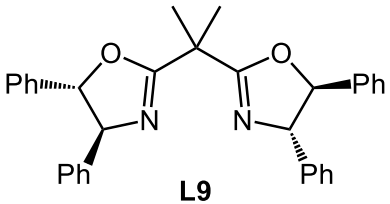


1a (0.15 mmol) **2a** (0.10 mmol) **4a**

entry	L*	addictive	solvent	**4a** yield (ee)/%
1	**L2**	Hacac (1.5 eq.)	*o*-xylene	/
2	**L6**	^{t}BuOH (4.0 eq.)	Et_2O	36 (92)
3	**L7**	^{t}BuOH (4.0 eq.)	Et_2O	40 (93)
4	**L8**	^{t}BuOH (4.0 eq.)	Et_2O	46 (86)
5	**L9**	^{t}BuOH (4.0 eq.)	Et_2O	63 (94)
6	**L9**	none	Et_2O	56 (94)
7	**L9**	^{t}BuOH (4.0 eq.)	PhMe	23 (95)
8	**L9**	^{t}BuOH (4.0 eq.)	DMF	N.D.



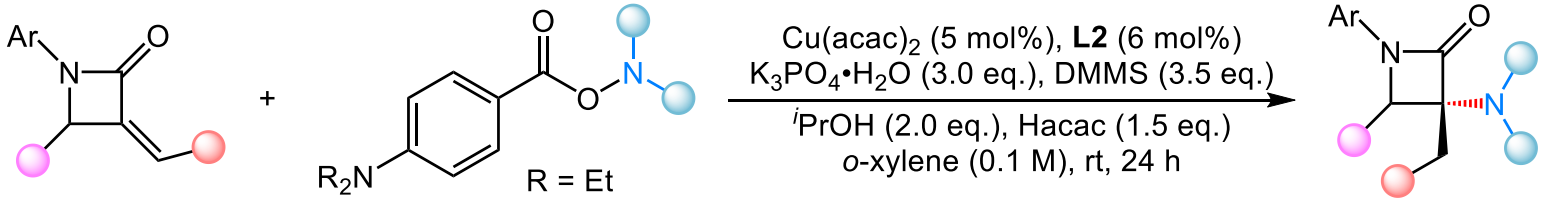
L6 R^3 = H
L7 R^3 = Ph
L8 R^3 = ^{n}Pr



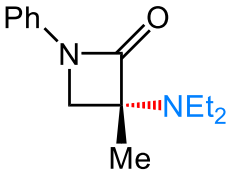
L9

Substrate Scope

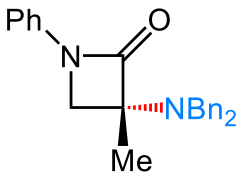
Scope of α-Methylene-β-Lactams



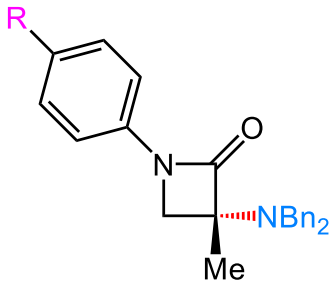
1 (0.20 mmol) **2** (0.22 mmol) **3**



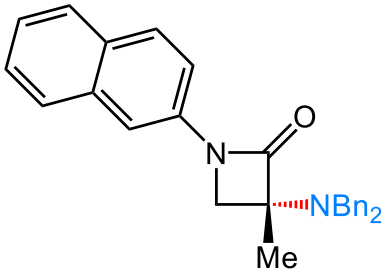
3a, 65%, 90% *ee*[a]



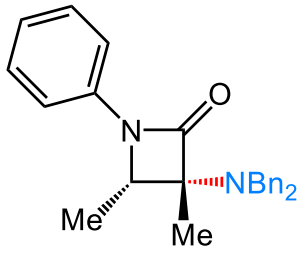
3b, 95%, 89% *ee*



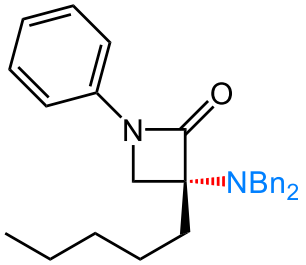
3c, R = Cl, 77%, 86% *ee*
3d, R = Br, 83%, 84% *ee*
3e, R = I, 74%, 84% *ee*
3f, R = OMe, 70%, 90% *ee*
3g, R = SMe, 68%, 90% *ee*



3h, 96%, 85% *ee*



3i, 54%, 68% *ee*
95:5 *dr*

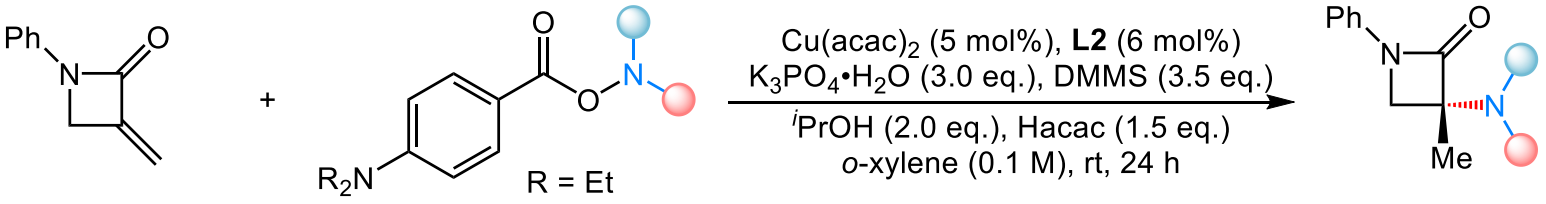


3j, 37%, 87% *ee*[b]

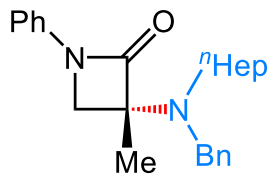
[a] R = Me. [b] **2** (1.5 eq.), $Cu(acac)_2$ (10 mol%), **L2** (12 mol%) and DMMS (5.0 eq.) was used, reacted for 40 h.

Substrate Scope

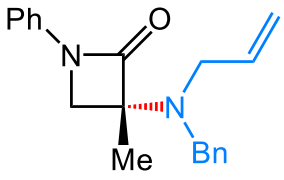
Scope of The Amination Reagents



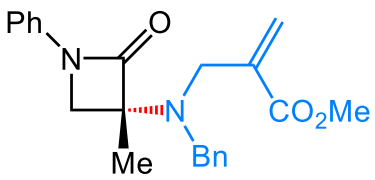
1 (0.20 mmol) **2** (0.22 mmol) **3**



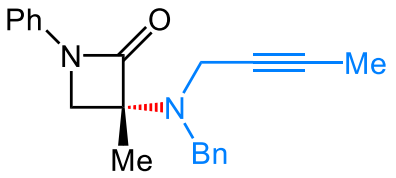
3k, 70%, 88% *ee*



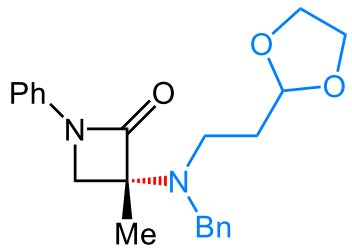
3l, 66%, 87% *ee*



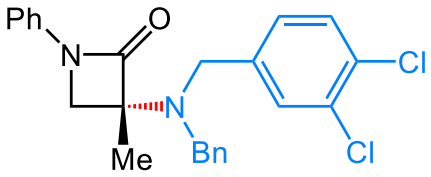
3m, 67%, 87% *ee*



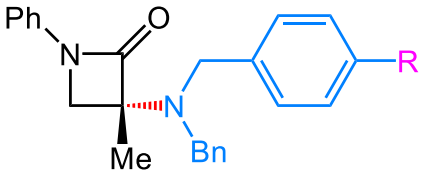
3n, 62%, 84% *ee*



3o, 77%, 89% *ee*



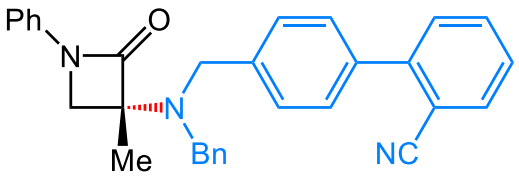
3p, 81%, 87% *ee*



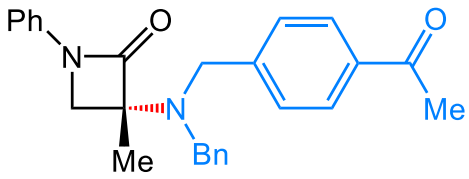
3q, R = Br, 83%, 89% *ee*
3r, R = I, 85%, 88% *ee*
3s, R = CF_3, 82%, 86% *ee*
3t, R = CN, 90%, 89% *ee*

Substrate Scope

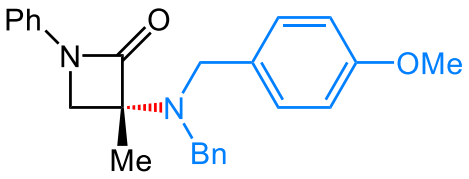
Scope of The Amination Reagents



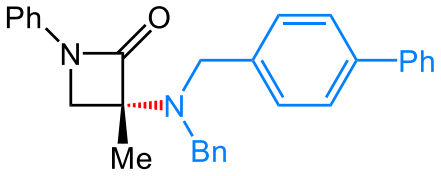
3u, 73%, 88% *ee*



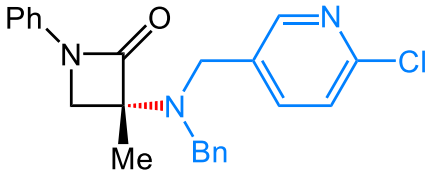
3v, 73%, 89% *ee*



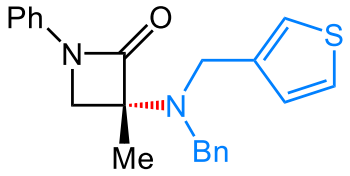
3w, 77%, 90% *ee*



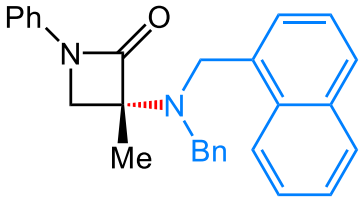
3x, 89%, 84% *ee*



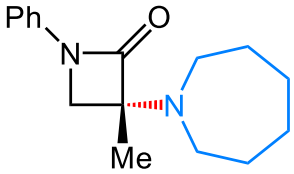
3y, 85%, 88% *ee*



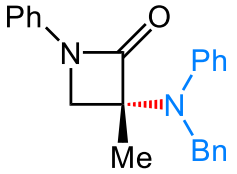
3z, 76%, 90% *ee*



3aa, 79%, 90% *ee*



3ab, 51%, 84% *ee*[a, b]

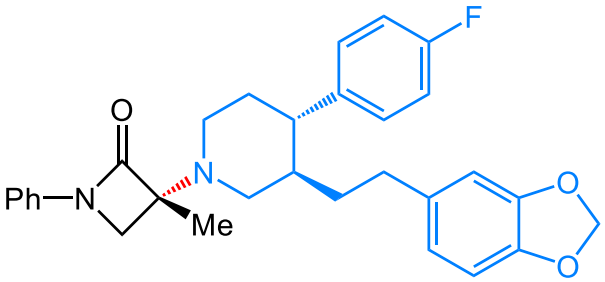


3ac, 66%, 88% *ee*

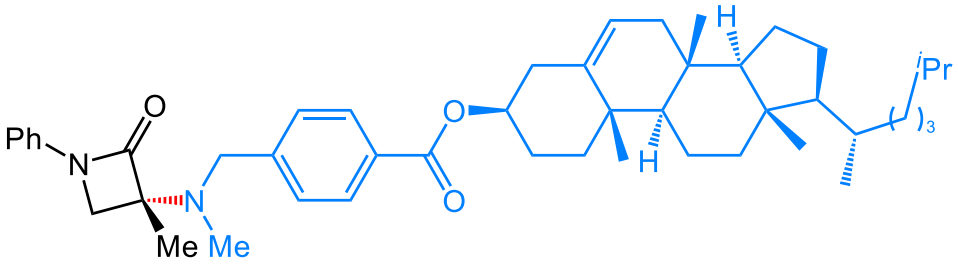
[a] R = Me. [b] Hacac (0.5 eq.) was used.

Substrate Scope

Scope of The Amination Reagents



3ad, From Paroxetine
47%, 91:9 *dr*[a,b]

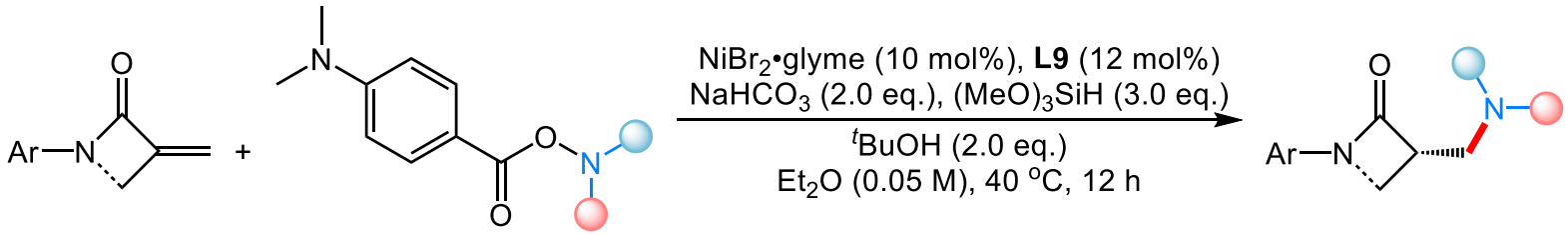


3ae, From Cholesterol
56%, 92:8 *dr*

[a] R = Me. [b] Hacac (0.5 eq.) was used.

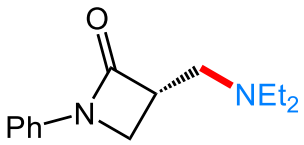
Substrate Scope

Scope of The Amination Reagents

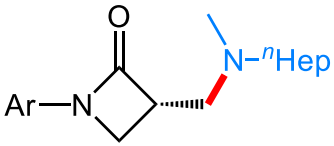


1 (0.30 mmol) **2** (0.20 mmol) **4**

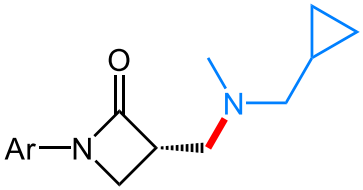
Ar = 4-CNC_6H_4



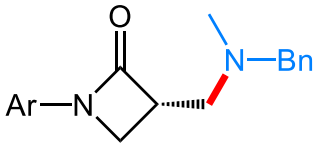
4a, 63%, 95% *ee*



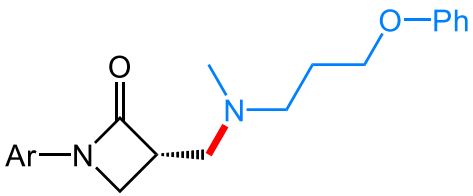
4b, 61%, 92% *ee*



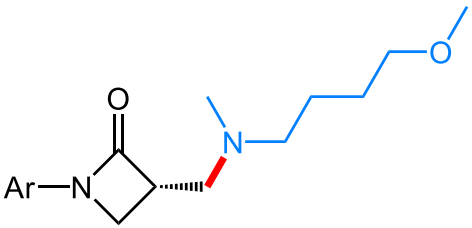
4c, 54%, 92% *ee*



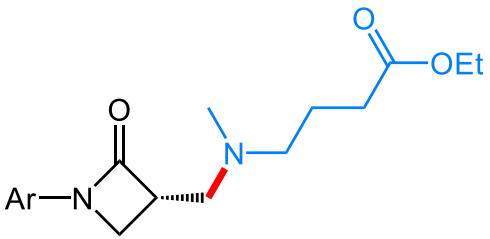
4d, 48%, 92% *ee*



4e, 63%, 92% *ee*



4f, 54%, 91% *ee*

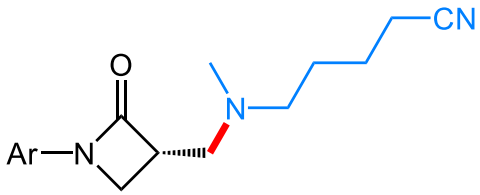


4g, 50%, 92% *ee*

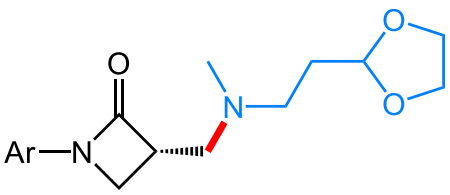
Substrate Scope

Scope of The Amination Reagents

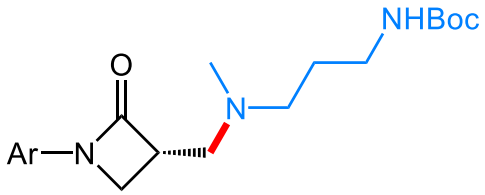
Ar = 4-CNC$_6$H$_4$



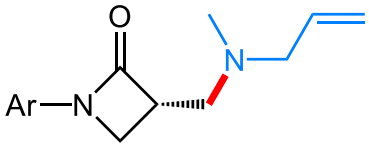
4h, 49%, 92% *ee*



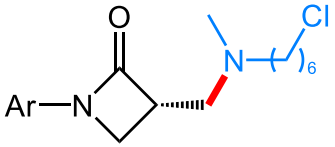
4i, 60%, 92% *ee*



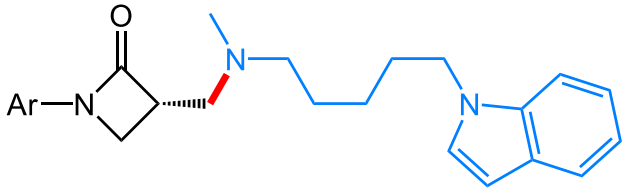
4j, 66%, 95% *ee*



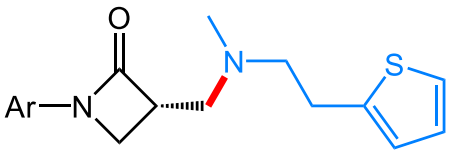
4k, 43%, 92% *ee*



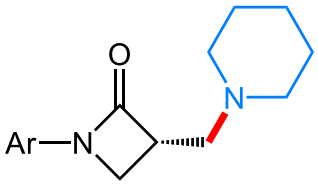
4l, 47%, 92% *ee*



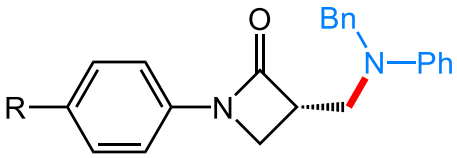
4m, 46%, 92% *ee*



4n, 65%, 91% *ee*



4o, 55%, 92% *ee*

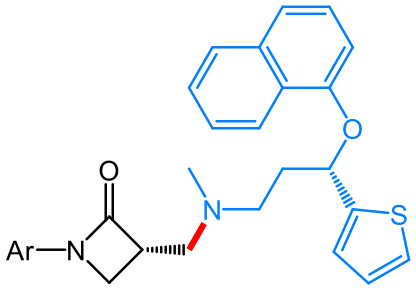


4p, R = H, 51%, 94% *ee*
4q, R = CN, 46%, 90% *ee*

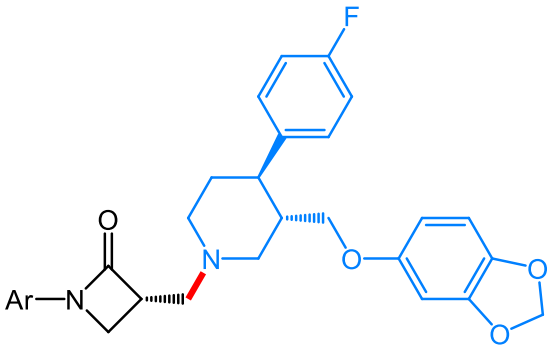
Substrate Scope

Scope of The Amination Reagents

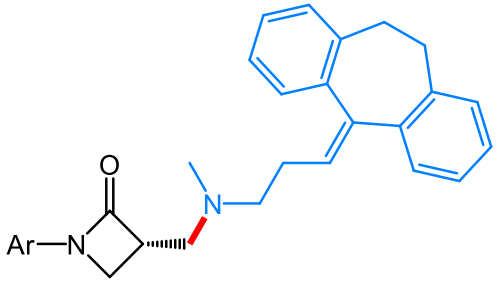
Ar = 4-CNC_6H_4



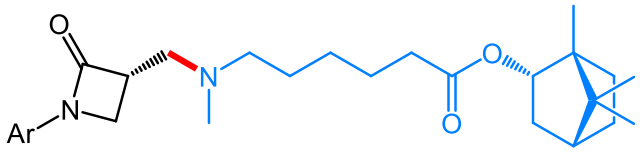
4r, From Duloxetine
70%, 96:4 *dr*



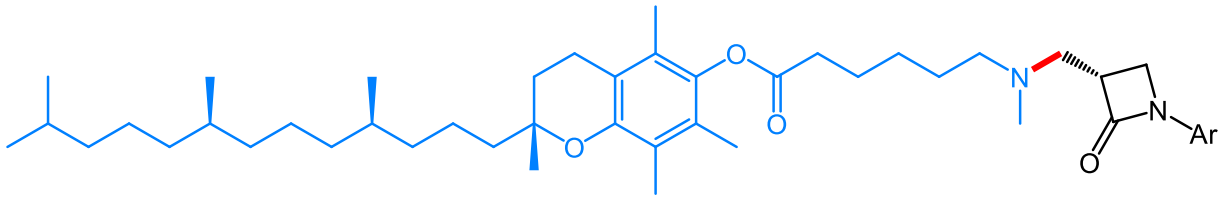
4s, From Paroxetine
30%, 98:2 *dr*



4t, From Nortriptyline
58%, 93% *ee*



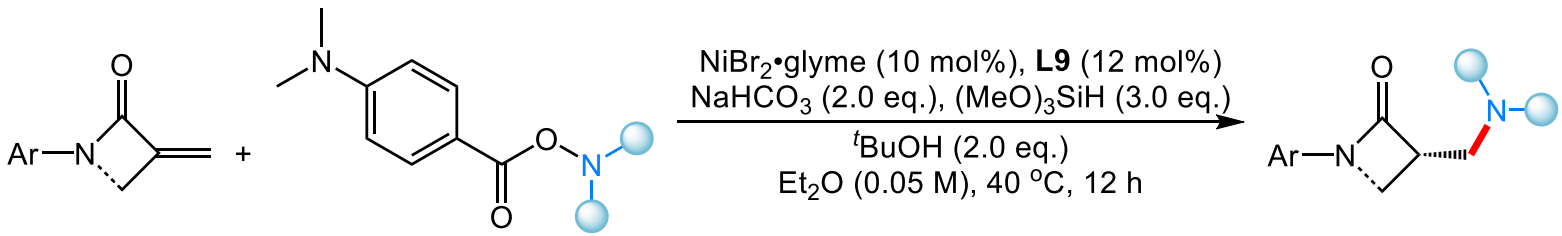
4u, From (-)- Borneol
40%, 96:4 *dr*



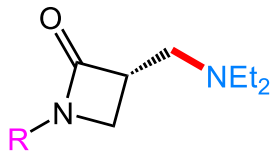
4v, From Vitamin El
63%, 97:3 *dr*

Substrate Scope

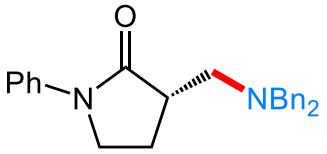
Scope of *N,N*-Acrylamides



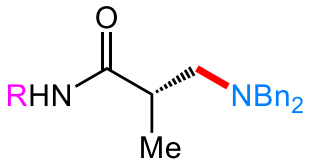
1 (0.30 mmol) **2** (0.20 mmol) **5, 6**



5a, R = *p*-$CF_3C_6H_4$, 70%, 92% *ee*
5b, R = *p*-CNC_6H_4, 70%, 92% *ee*
5c, R = *p*-ClC_6H_4, 62%, 93% *ee*
5d, R = *p*-BrC_6H_4, 55%, 92% *ee*
5e, R = *p*-IC_6H_4, 61%, 94% *ee*
5f, R = 3,5-$(CF_3)_2C_6H_3$, 64%, 92% *ee*
5g, R = *p*-$MeOC_6H_4$, 63%, 93% *ee*
5h, R = 2-Napthyl, 60%, 92% *ee*
5i, R = 1-Napthyl, 49%, 94% *ee*



5j, 60%, 99% *ee*



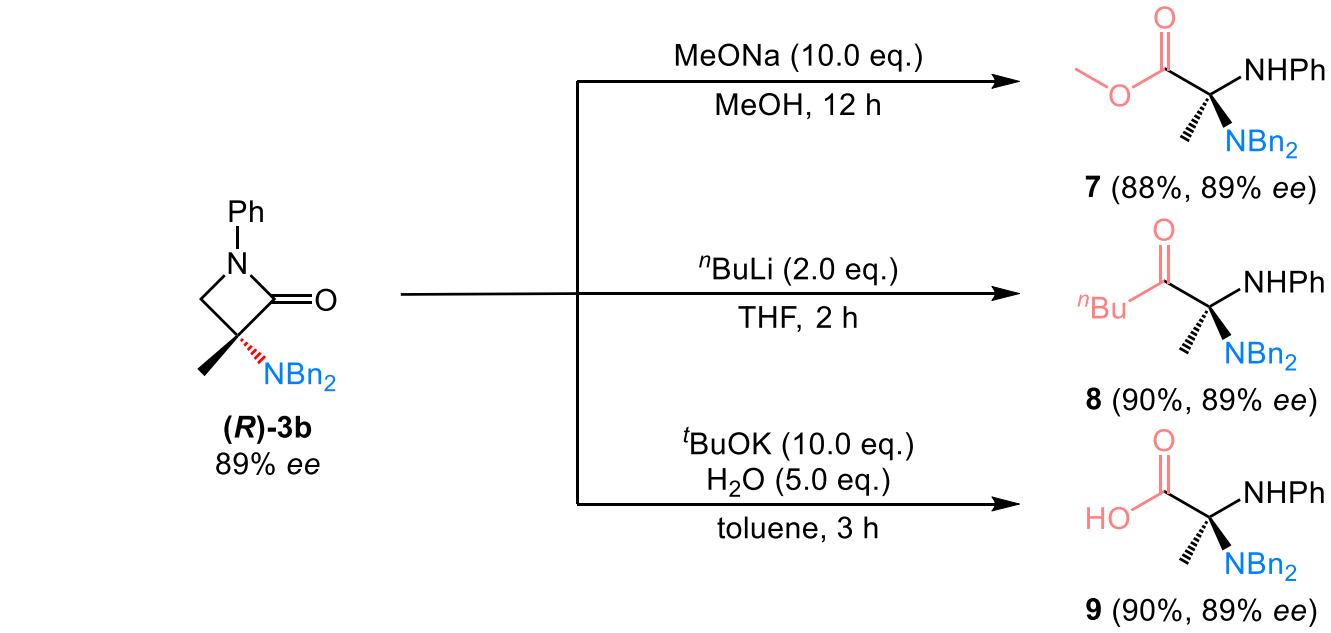
6[a]

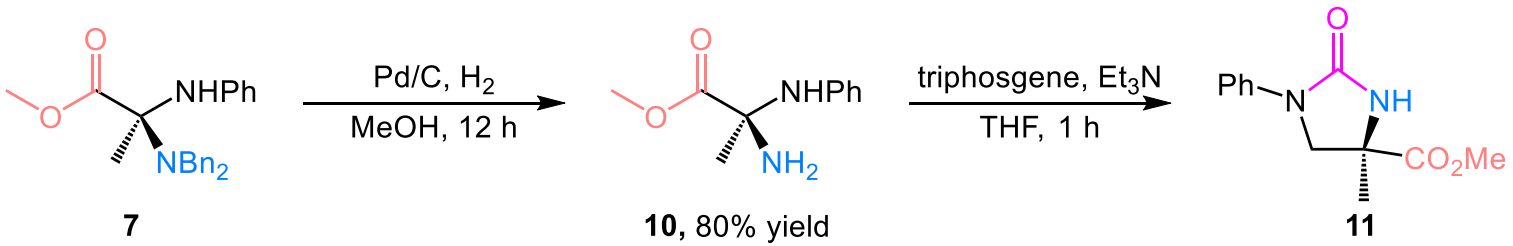
6a, R = Ph, 60%, 83% *ee*
6b, R = *p*-$MeOC_6H_4$, 50%, 78% (97%)[b] *ee*
6c, R = *p*-$^tBuC_6H_4$, 50%, 80% *ee*
6d, R = *m*-$^tBuC_6H_4$, 56%, 83% *ee*
6e, R = *p*-$CF_3C_6H_4$, 40%, 83% *ee*
6f, R = 2-Napthyl, 45%, 82% *ee*

[a] **L8** was used instead of **L9** with addition of NMP (10.0 eq.). [b] Enantiomeric excess after recrystallization.

Synthetic applications

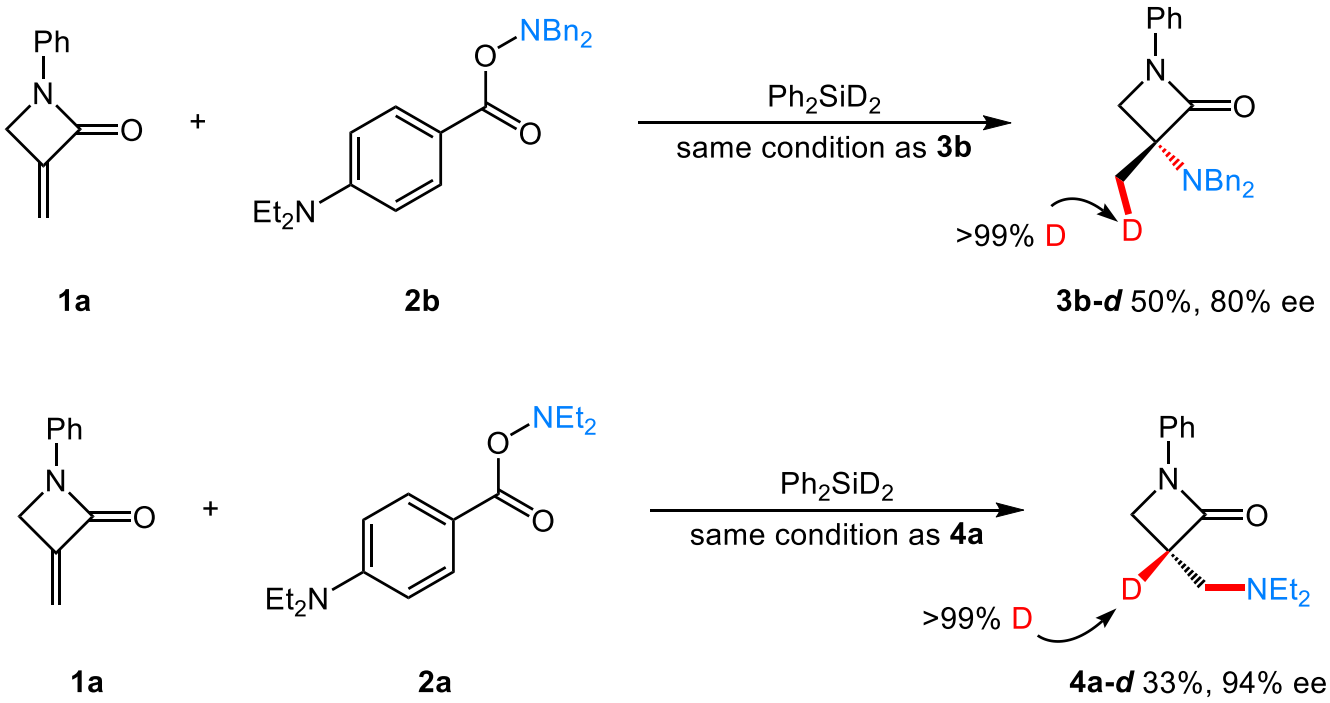
Synthetic Application



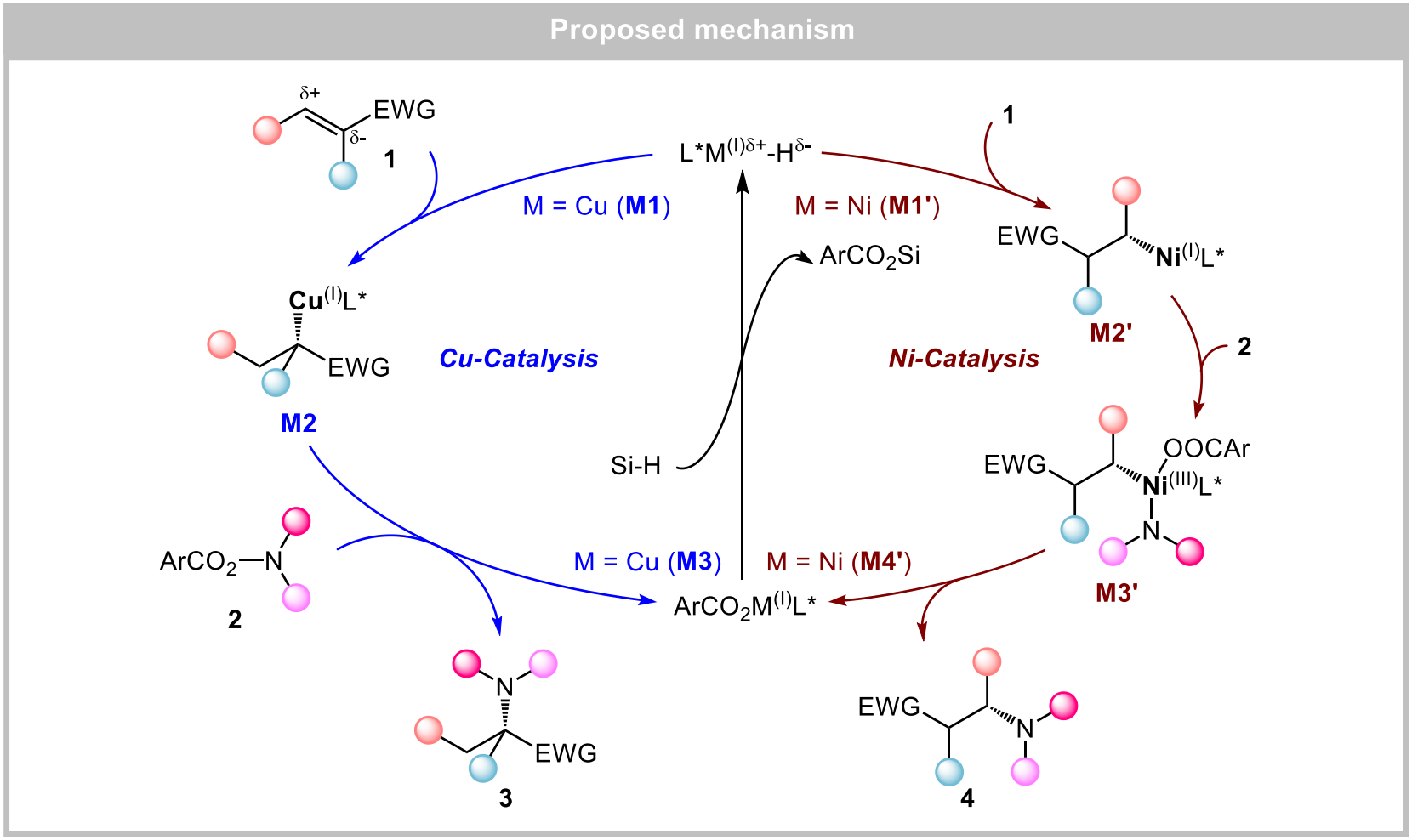


Mechanism

Mechanistic Studies

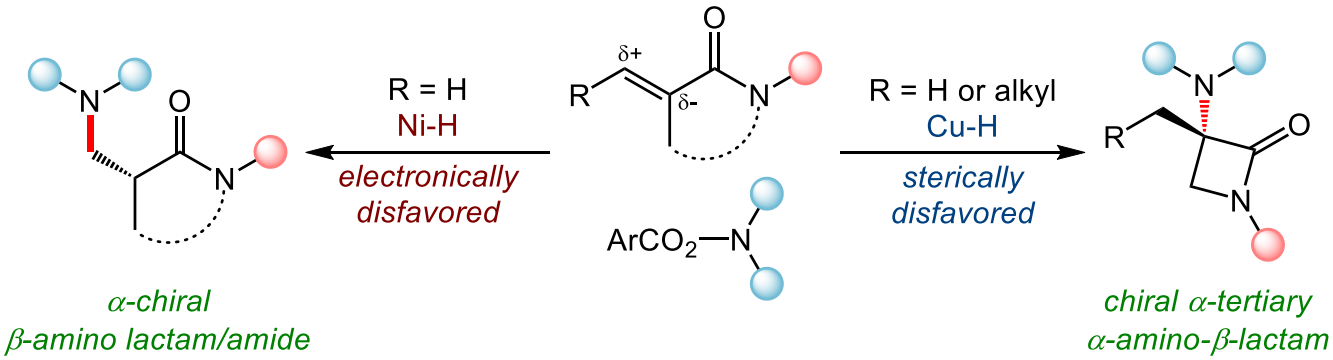


Mechanism


Proposed mechanism
δ+
EWG
δ-
1
L*M(I)δ+-Hδ-
1
M = Cu (M1)
M = Ni (M1')
ArCO2Si
EWG
Ni(I)L*
M2'
2
Cu(I)L*
EWG
Cu-Catalysis
Ni-Catalysis
M2
Si-H
EWG
OOCAr
Ni(III)L*
N
M3'
ArCO2—N
2
M = Cu (M3)
M = Ni (M4')
ArCO2M(I)L*
N
EWG
3
EWG
N
4

Summary

Regiodivergent and enantioselective formal hydroaminations



- catalyst-controlled divergent regioselectivity
- enantioselective C-N coupling with tertiary alkyls
- high enantioselsctivity
- high regioselectivity

Strategy for Writing The First Paragraph

The Importance of Unnatural α-Aminoacid and β-Aminoacid

Prior Art for Metal-Catalyzed Asymmetric C-N Bond Formation

The Limitations of Prior Works

- ✓ Enantiopure unnatural α-aminoacid and β-aminoacid derivatives constitute an important class of molecules, which serve as pervasive key substructures in peptides, pharmaceuticals, agrochemicals, and biologically active natural products.
- ✓ Recently, Fu developed a ground-breaking work on Cu-catalyzed C-N coupling of α-tertiary α-haloamides/nitriles with anilines to afford α-tertiary-α-aminonitriles/amides in good enantioselectivities…
- ✓ Metal-H catalyzed hydroamination of alkenes to construct C-N bond with tertiary carbon center remains unknown due to the kinetic and thermodynamic challenges as well as difficulties in regio- and enantioselectivity control…

Strategy for Writing The Last Paragraph

Summary of This Work

- ✓ In summary, catalyst-controlled regiodivergent and enantioselective formal hydroaminations of *N,N*-acrylamides have been achieved to deliver enantioenriched α-tertiary-α-amino-lactam and β-aminoamide derivatives in good yields and excellent levels of enantioselectivity.

Elucidate the Highlights of This Work

- ✓ Notably, both sterically-disfavored and electronically-disfavored formal hydroamina-tions have been realized by catalyst regulation. In addition, sterically congested enantio-enriched α-tertiary aliphatic amines have been obtained by formal hydroamination via C-N bond-forming from alkenes…

Representative Examples

- However, it remains an unmet challenge to achieve high enantioselectivity for dialkyl ketimines. (*adj.* 未满足的，未解决的，unresolved)
- Notably, chlorides, bromides and iodides were compatible in this copper catalytic process (3c, 3d and 3e), leaving chemical handles for further elaboration of α-tertiary-α-amino lactams. (为进一步处理留下余地，elaboration，细化， 精加工)
- Next, we carried out the reaction using deuterated silane (Ph_2SiD_2) under otherwise identical to standard conditions to shed light on the reaction process. (揭示，阐明)

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Thanks for your attention