Literature Report X

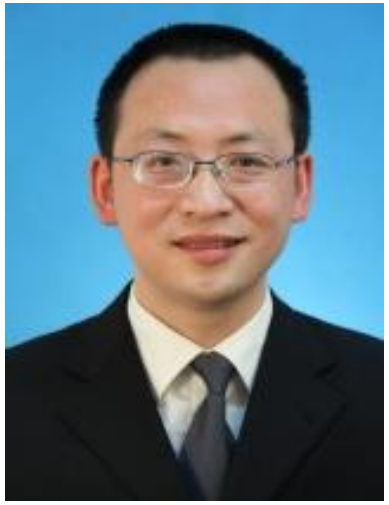
Trifluoroethanol-Assisted Asymmetric Propargylic Hydrazination to α-Tertiary Ethynylhydrazines Enabled by Sterically Confined Pyridinebisoxazolines

Reporter: Jian Chen
Checker: Han Wang
Date: 2025-06-16

Gong, Y.; Zhang, Z.; Liu, H.; Wang, T.; Jiang, M.; Zhou, F.; Wang, X.; Zhou, J.*

Nat. Commun. **2025**, *16*, 4571-4582

CV of Prof. Zhou Jian (周剑)



Research:

- Organic Synthesis
- Asymmetric Catalysis
- Green Chemistry
- Development of New Chiral Catalysts

Background:

- **1993-1997** B.S., Sichuan Normal University
- **1999-2004** Ph.D., Shanghai Institute of Organic Chemistry
- **2004-2005** Postdoc., The University of Tokyo
- **2005-2008** Postdoc., Max Planck Institute for Coal Research
- **2008-Present** Professor, East China Normal University

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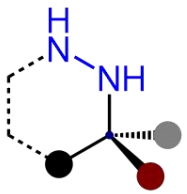
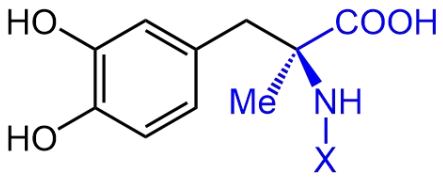
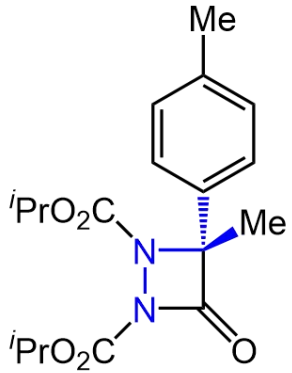
Selected Bioactive Molecules Containing Chiral α-Tertiary Hydrazine



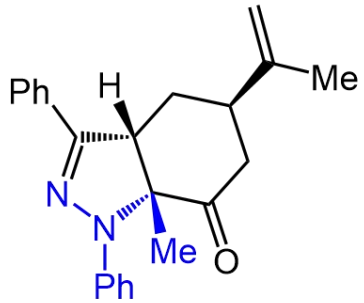
Privileged scaffolds



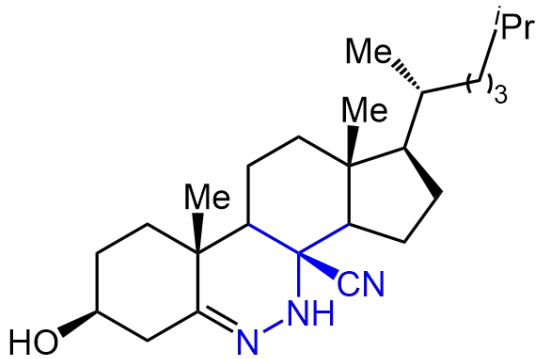
X = H, Methyldopa
X = NH_2, *L*-Carbidopa



Serine hydrolase



Antitumor



Antibacterial

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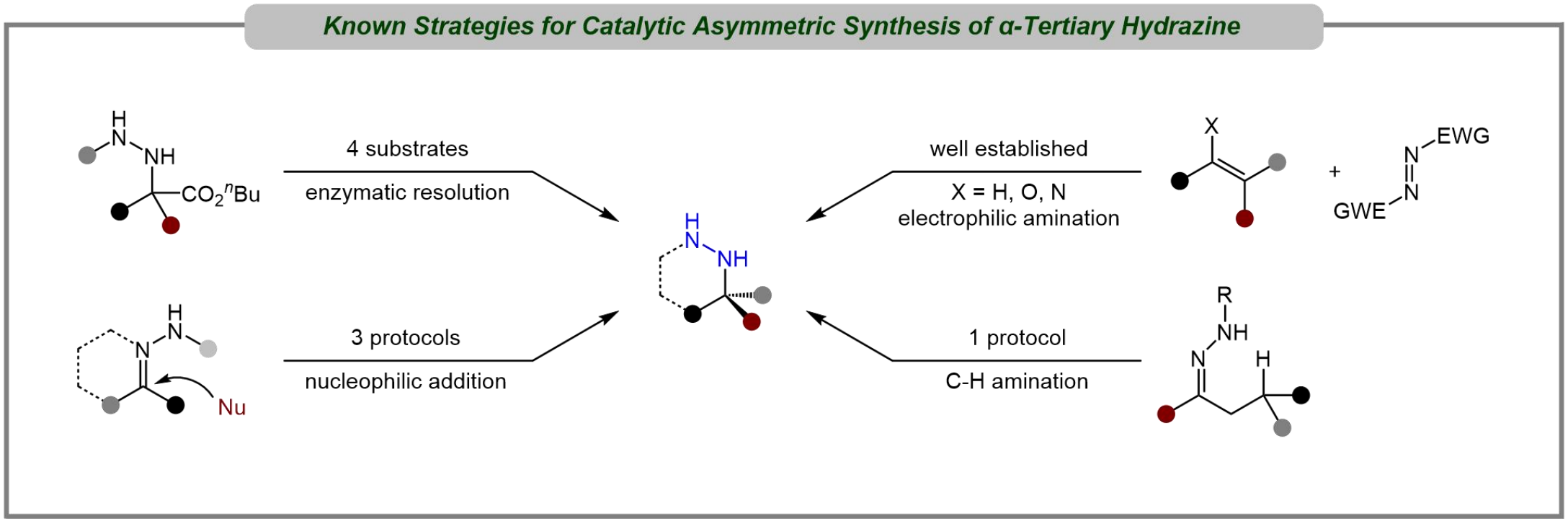

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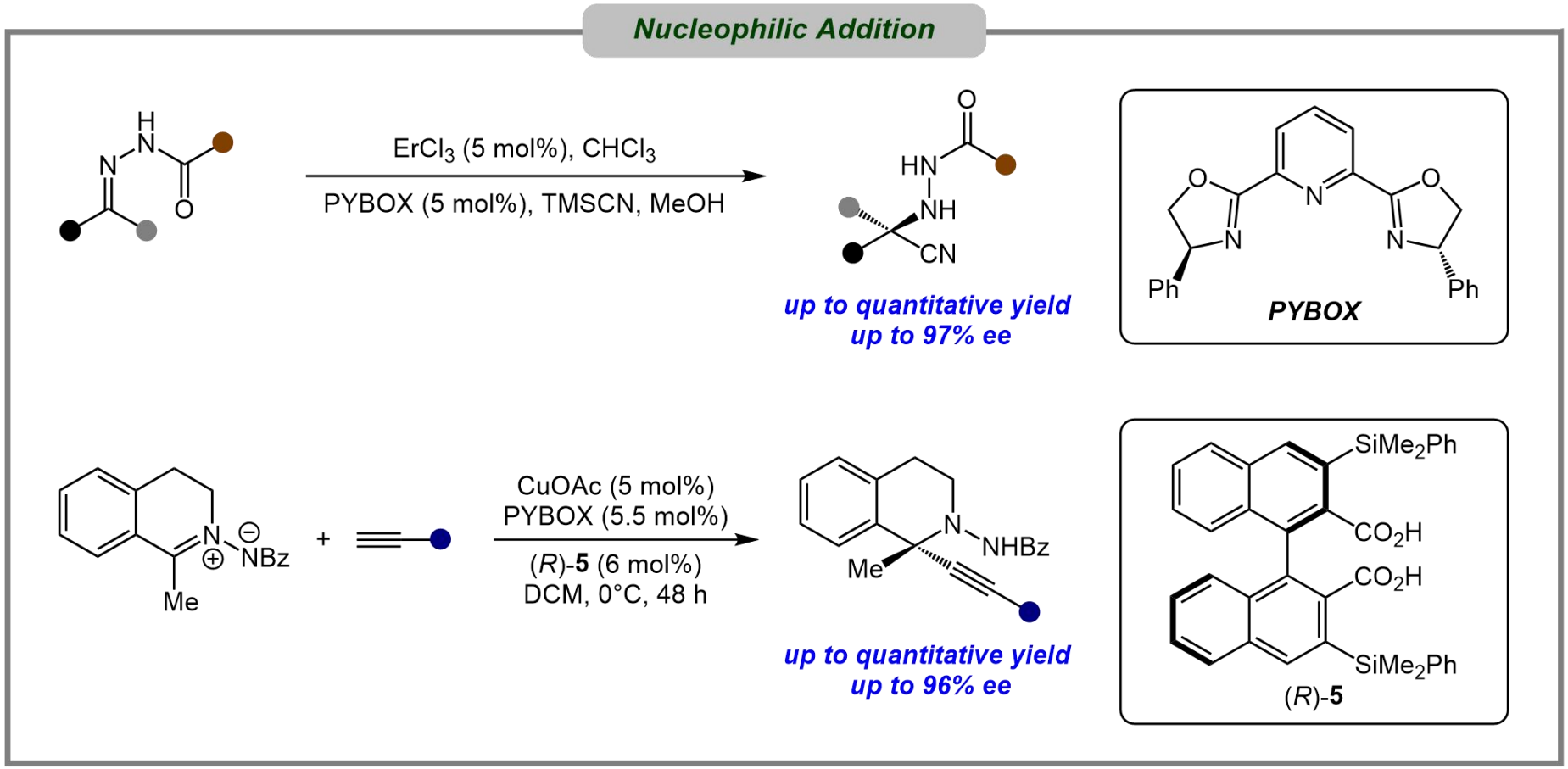

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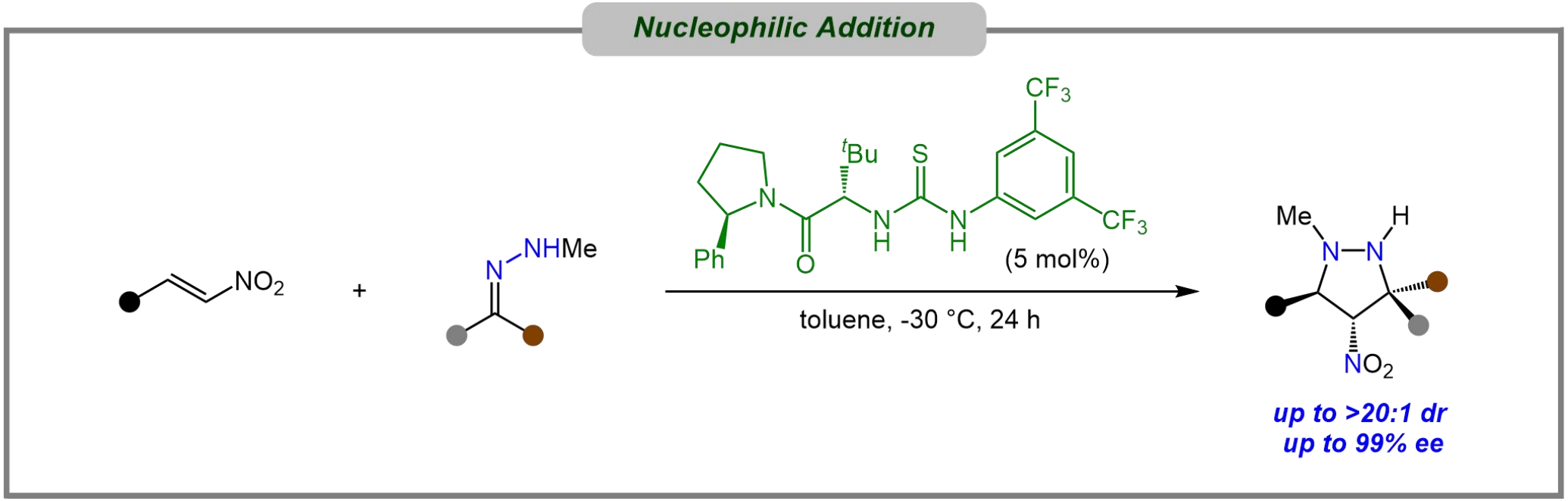
Introduction



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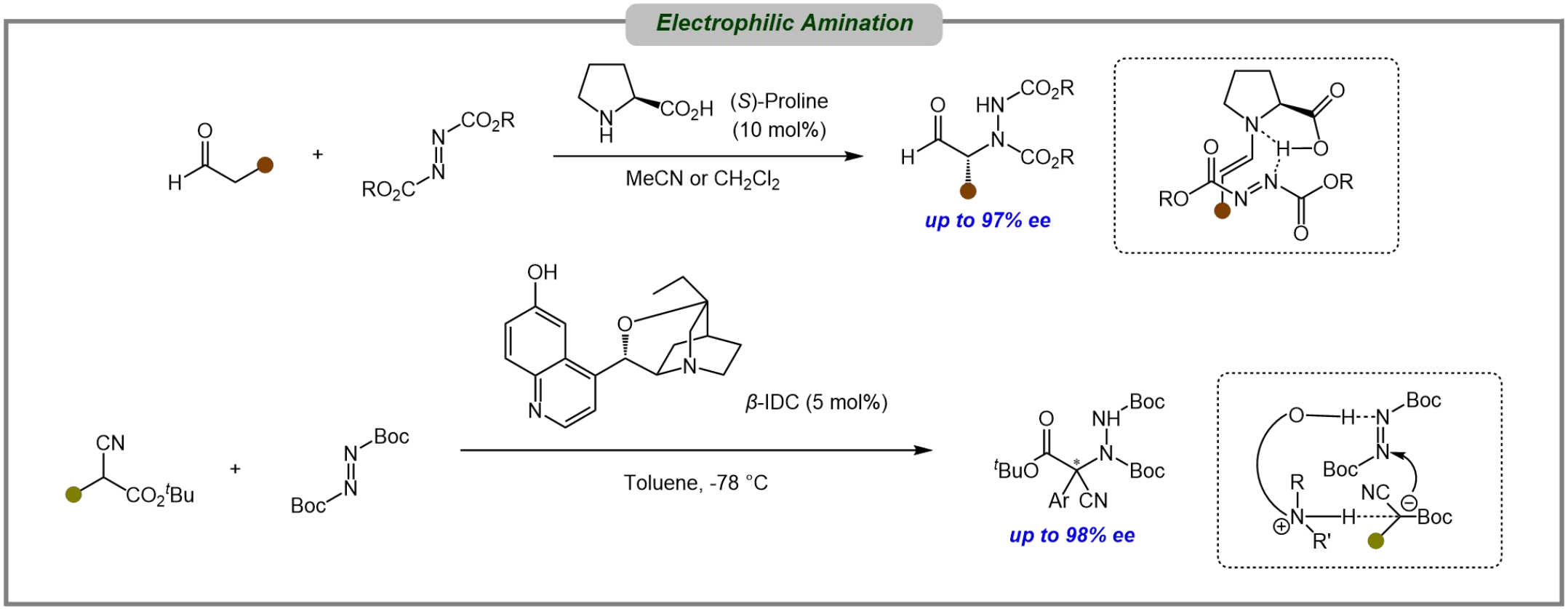

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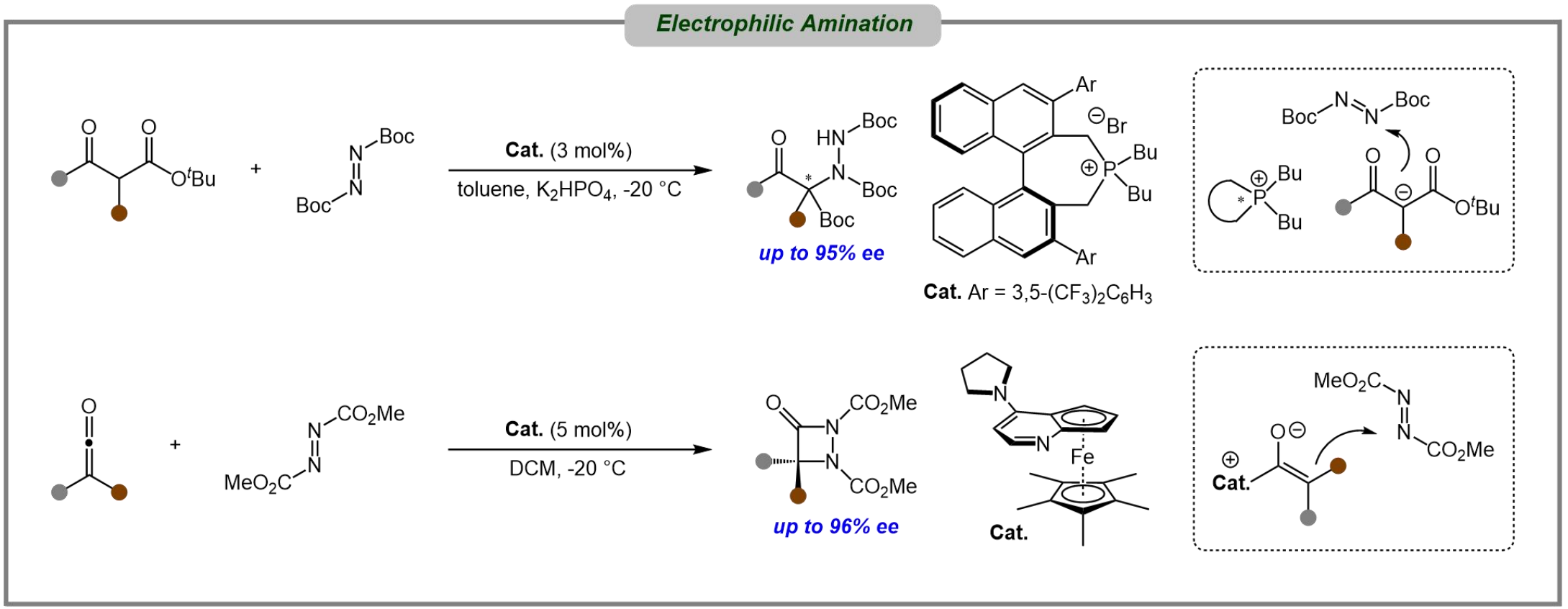

Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J.* *Synthesis* **2014**, *46*, 2983

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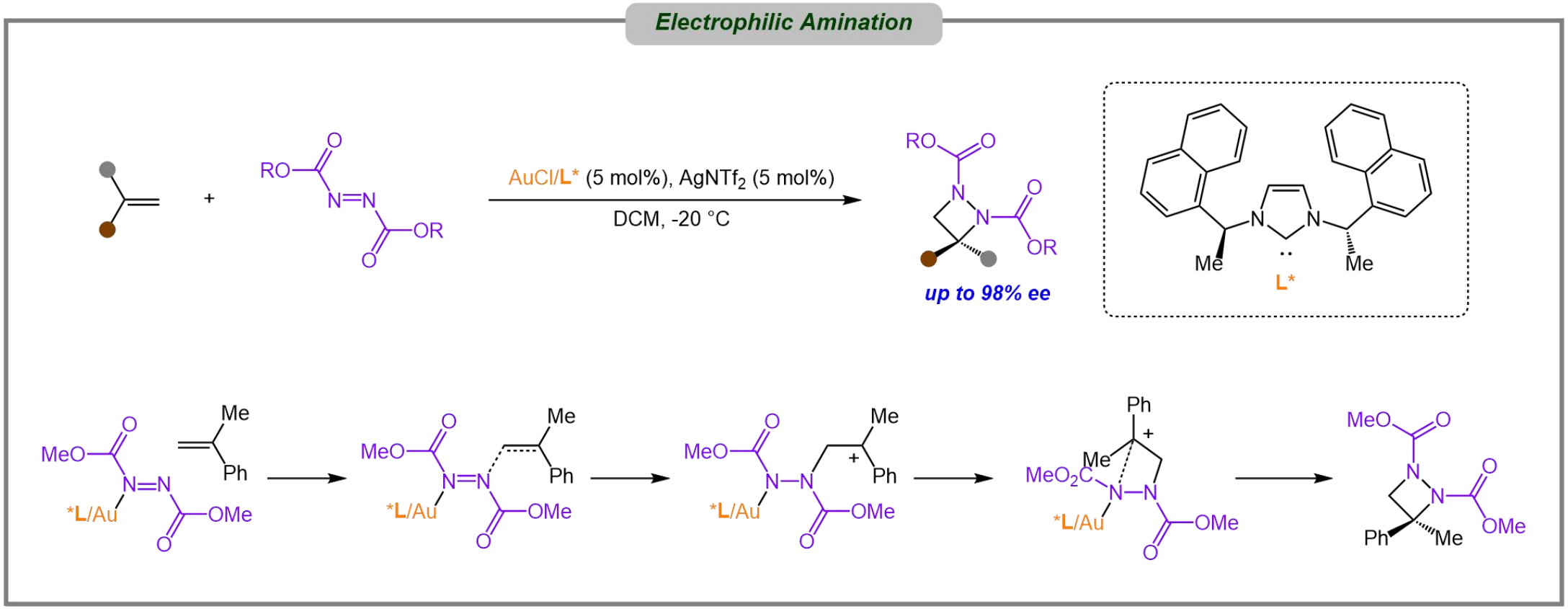

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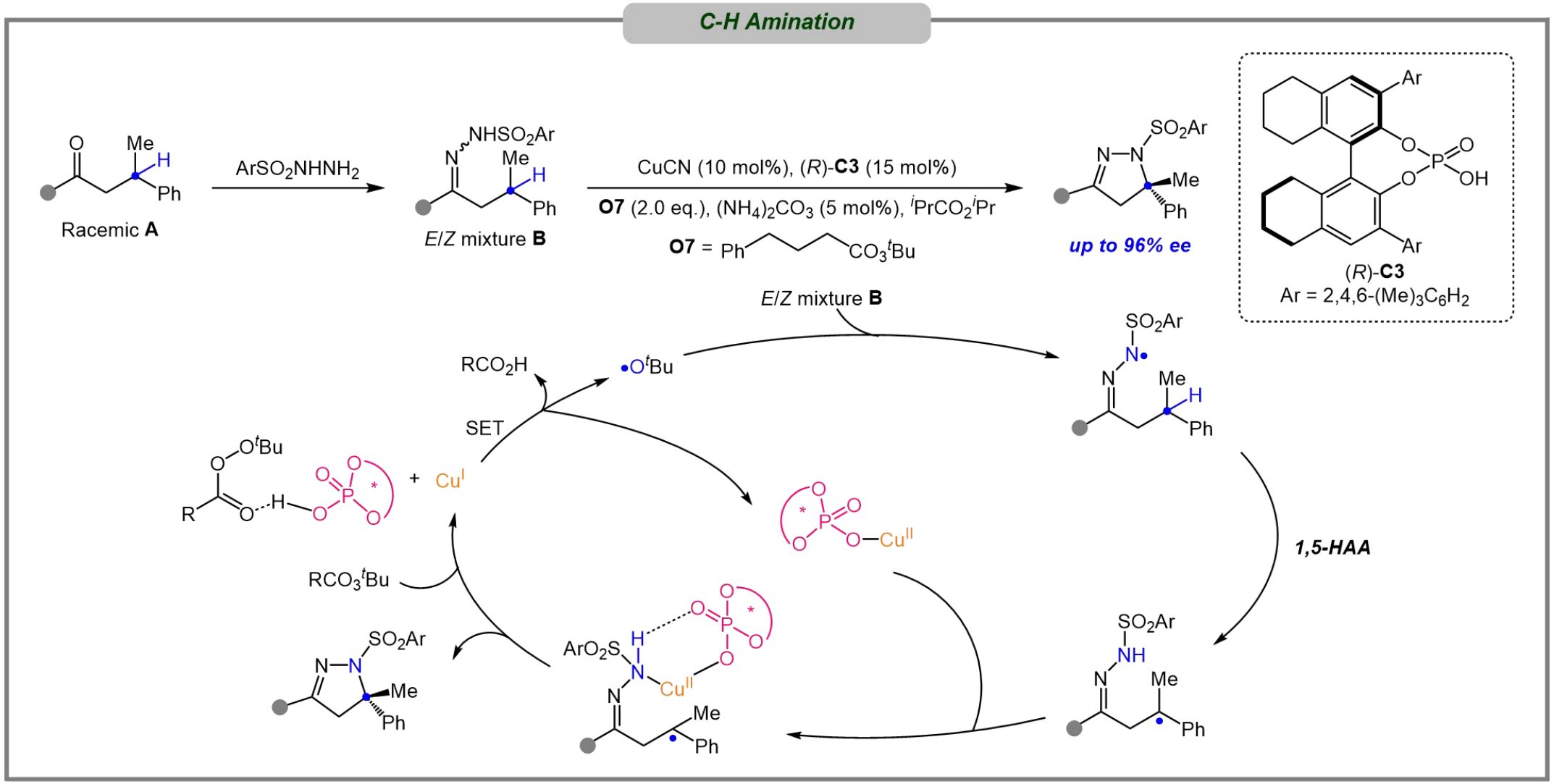
Introduction



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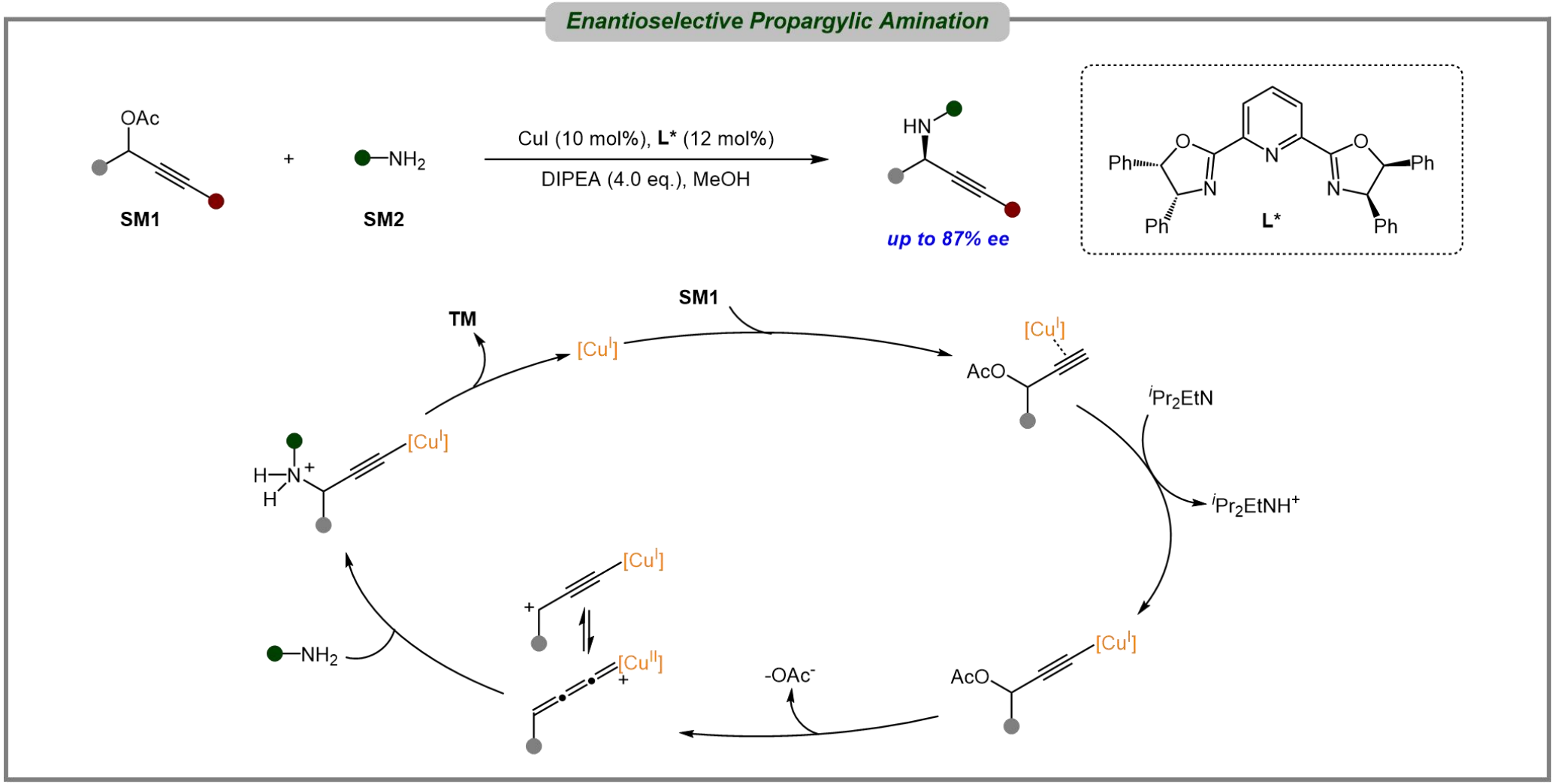
Introduction



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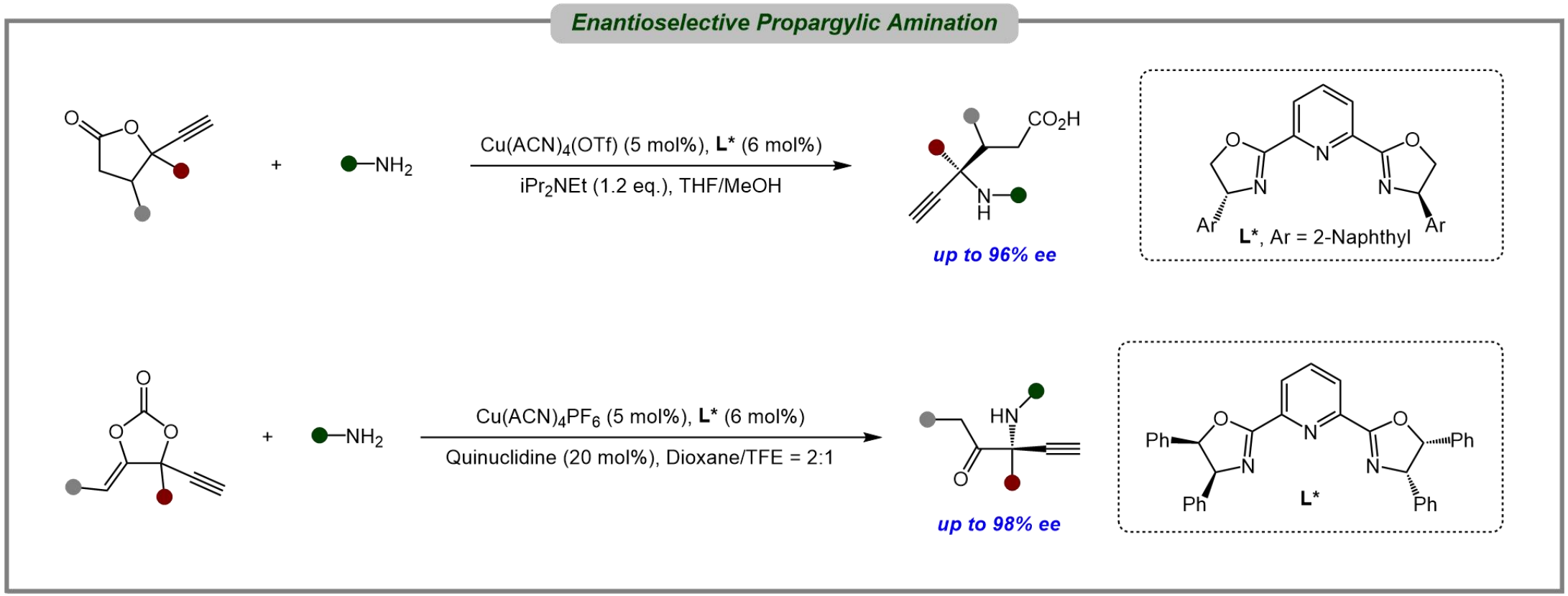

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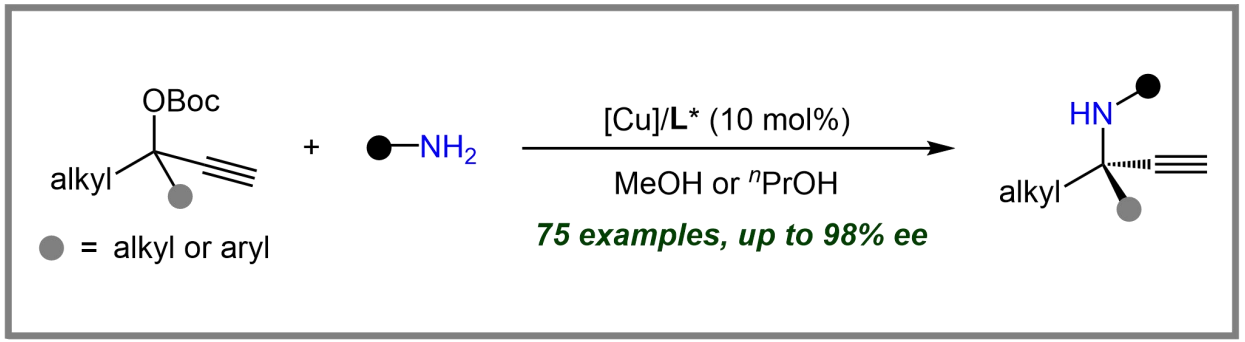
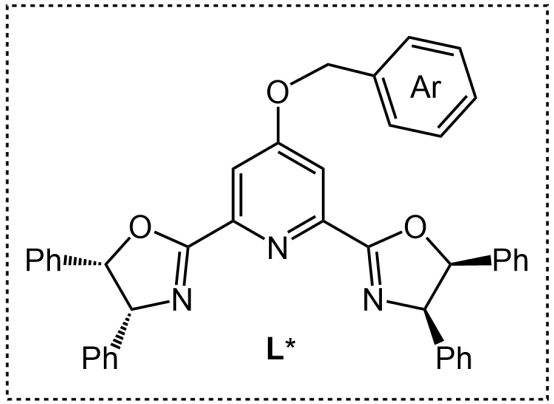
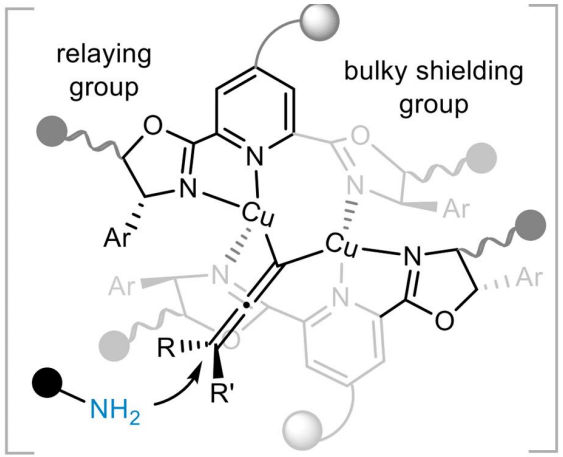
Introduction

Sterically Confined PYBOX-Enabled Cu(I)-Catalysed Propargylic Amination

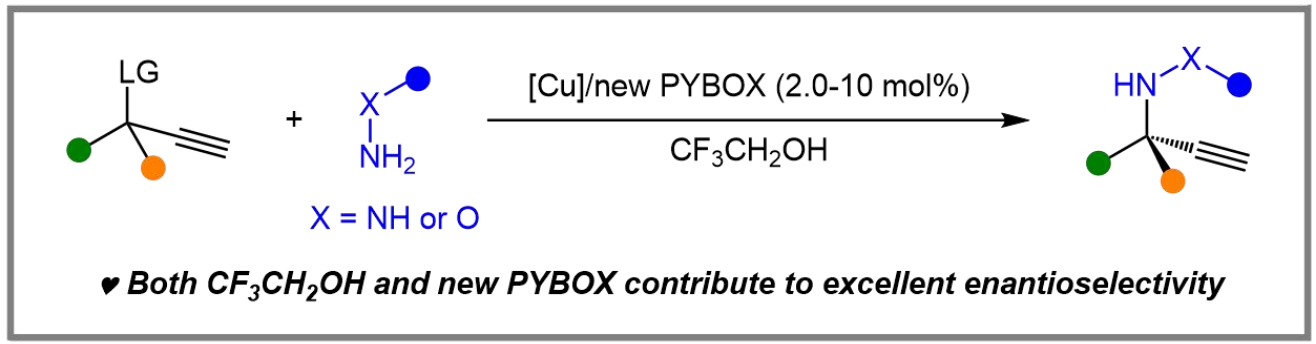




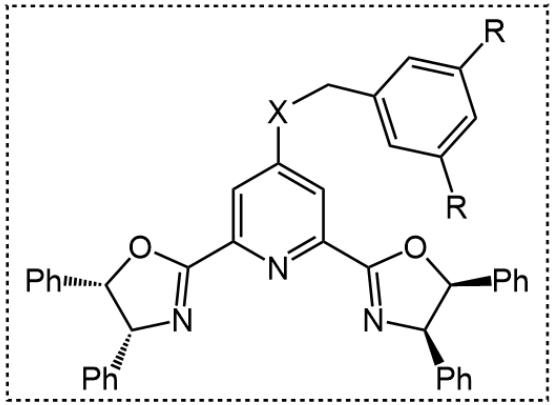


Zhang, Z.; Sun, Y.; Gong, Y.; Luo, H.; Zhou, J.* *Nat. Chem.* **2024**, *16*, 521-532

Project Synopsis



♥ ***Both CF_3CH_2OH and new PYBOX contribute to excellent enantioselectivity***



Challenges:

♥ ***Remote chiral center makes stereocontrol highly challenging***

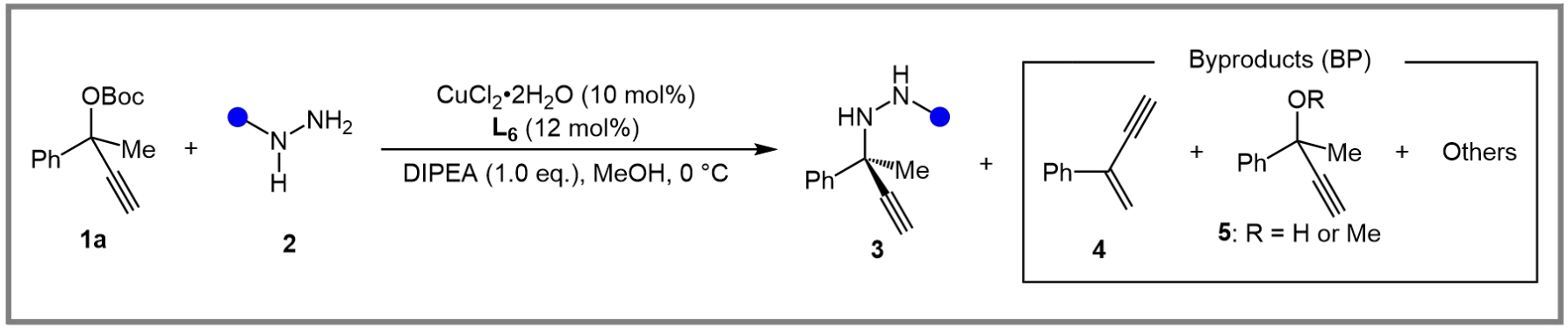
♥ ***Hydrazines are too nucleophilic, causing side reactions***

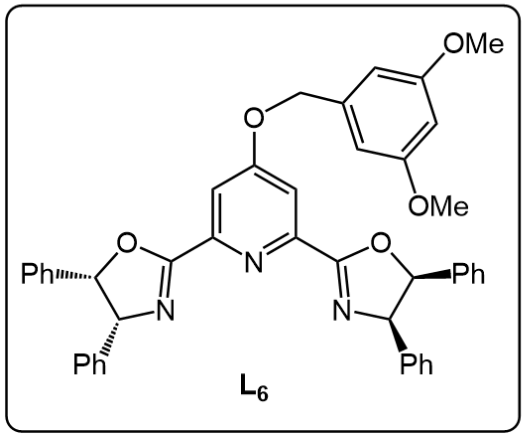
Strategies:

♥ ***Bulky PYBOX ligands improve remote stereocontrol efficiency***

♥ ***TFE solvent reduces hydrazine reactivity via hydrogen bonding***

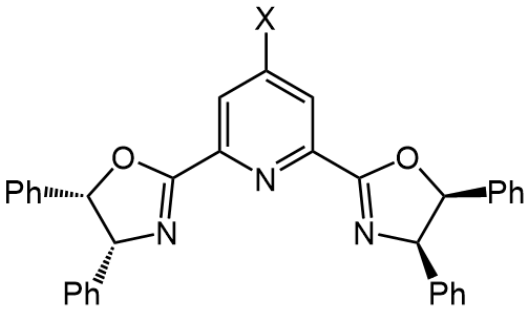
Optimization of Reaction Conditions

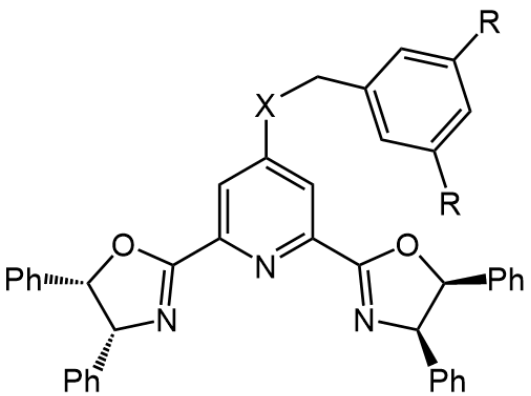




	$NH_2NH_2 \cdot HCl$	Bn, NH_2	Ph, NH_2	Ac, NH_2	Ts, NH_2	Ph, H, N, Ph	Bz, NH_2
RSM of **1a**	78%	-	-	58%	-	-	-
Product **3**	-	-	-	-	-	-	71%, 64% ee
BP **4**	11%	57%	58%	26%	66%	82%	15%
BP **5**	-	15%	5%	-	10%	1%	-
Others	11%	28%	37%	16%	24%	17%	14%

Optimization of Reaction Conditions





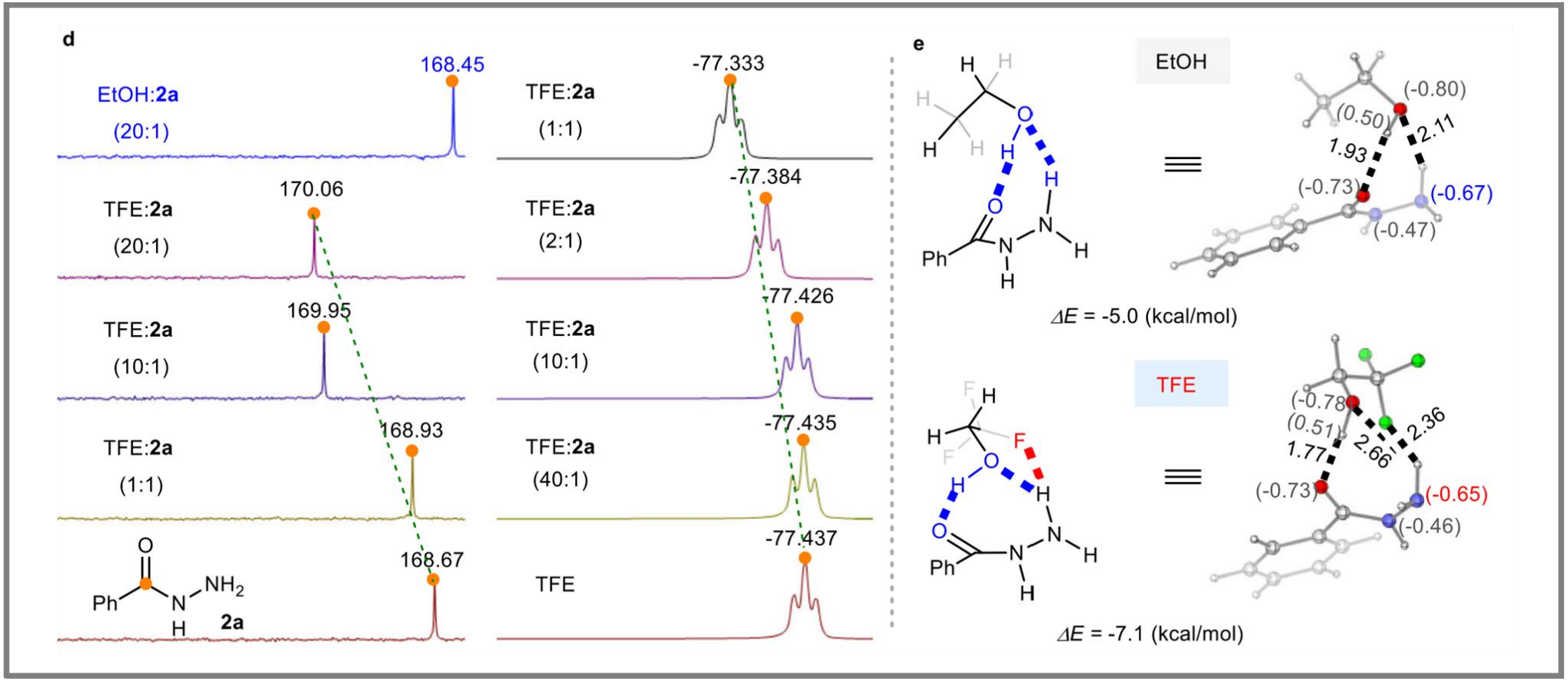
Ligand effect

L	X	R	Yield (%)	ee (%)
L_1	H	-	66	59
L_2	Cl	-	62	49
L_3	OBn	-	62	64
L_4	SBn	-	64	73
L_5	S	OMe	70	70
L_6	O	OMe	71	64
L_7	S	CF_3	60	66
L_8	O	CF_3	62	62
L_9	S	^{t}Bu	66	77
L_{10}	O	^{t}Bu	64	72

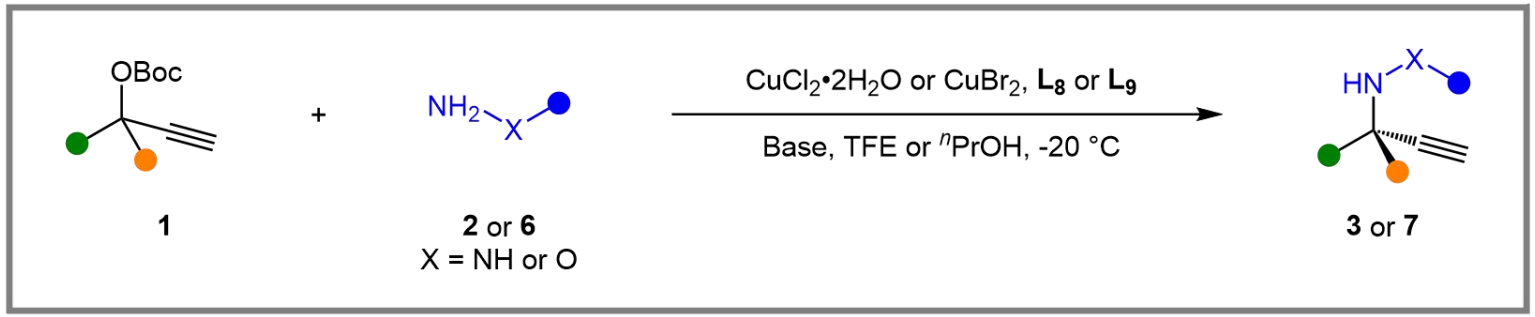
Solvent effect (with L_9)

Alcohols	Yield (%)	ee (%)
MeOH	66	77
EtOH	72	79
^{n}PrOH	68	66
^{i}PrOH	65	60
^{n}BuOH	65	64
FCH_2CH_2OH	87	82
F_2CHCH_2OH	87	87
TFE	93	90
TFE (-20 °C)	94	94
HIFP	ND	-

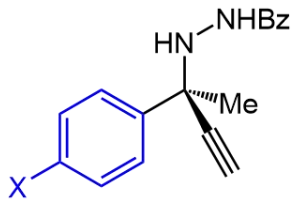
Optimization of Reaction Conditions



Substrate Scope

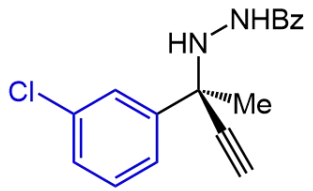


α-aryl propargylic esters

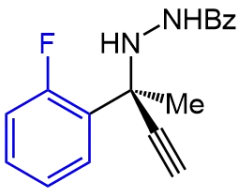


3a, X = H, 94%, 94% ee
3b, X = F, 92%, 90% ee
3c, X = Cl, 92%, 92% ee
3d, X = Br, 96%, 92% ee

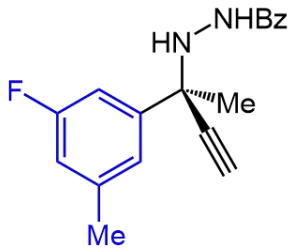
3e, X = I, 95%, 94% ee
3f, X = CF_3, 85%, 91% ee
3g, X = Me, 87%, 88% ee
3h, X = Ph, 87%, 90% ee



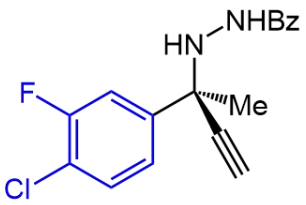
3i, 92%, 86% ee



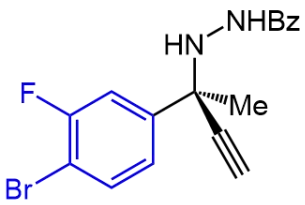
3j, 87%, 84% ee



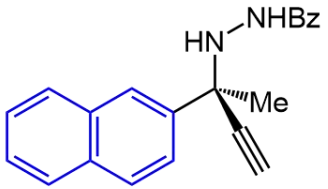
3k, 85%, 86% ee



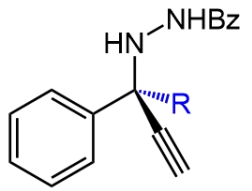
3l, 93%, 87% ee



3m, 90%, 90% ee



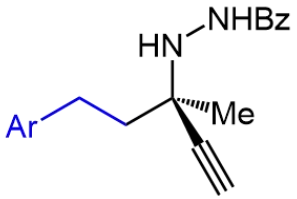
3n, 93%, 90% ee



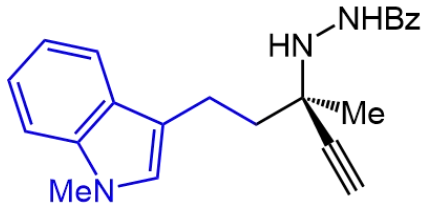
3o, R = Et, 84%, 80% ee
3p, R = ^{n}Pr, 86%, 74% ee
3q, R = ^{n}Bu, 80%, 78% ee

Substrate Scope

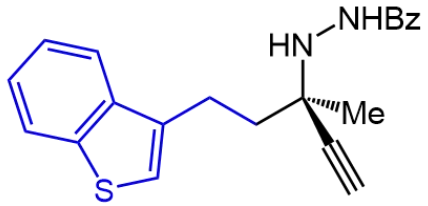
α-alkyl propargylic esters



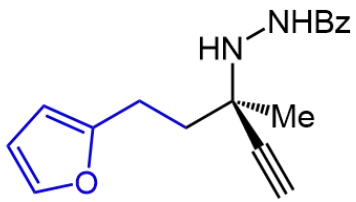
3r, Ar = Ph, 90%, 90% ee
3s, Ar = 4-MeC_6H_4, 80%, 91% ee
3t, Ar = 3-MeC_6H_4, 84%, 90% ee
3u, Ar = 4-BrC_6H_4, 92%, 84% ee
3v, Ar = 2-Naphthyl, 84%, 91% ee



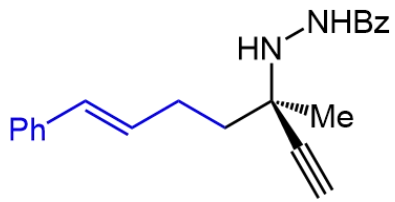
3w, 87%, 97% ee



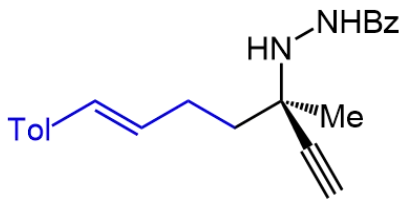
3x, 92%, 94% ee



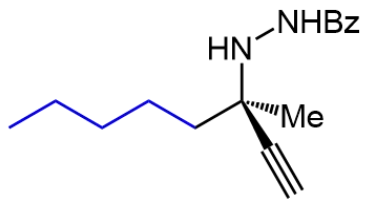
3y, 84%, 86% ee



3z, 89%, 90% ee



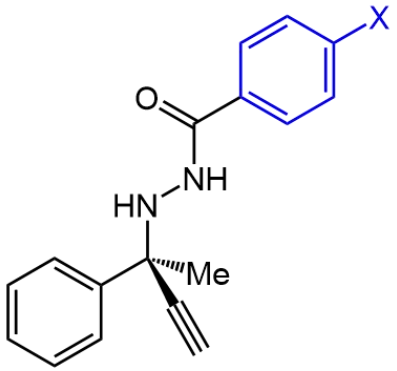
3aa, 90%, 90% ee



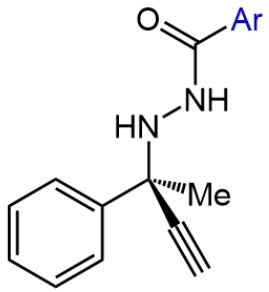
3ab 78%, 46% ee

Substrate Scope

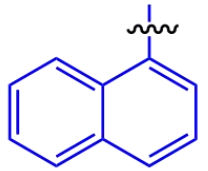
hydrazines and hydroxylamines



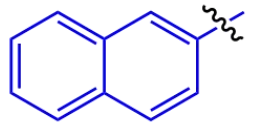
3ad, X = F, 99%, 92% ee
3ae, X = Br, 96%, 92% ee
3af, X = Me, 80%, 94% ee
3ag, X = ^{t}Bu, 91%, 93% ee
3ah, X = OMe, 78%, 94% ee
3ai, X = Ph, 92%, 93% ee



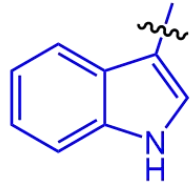
Ar =



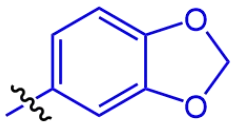
3aj, 95%, 91% ee



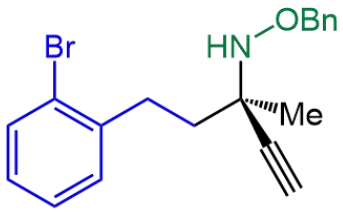
3ak, 93%, 95% ee



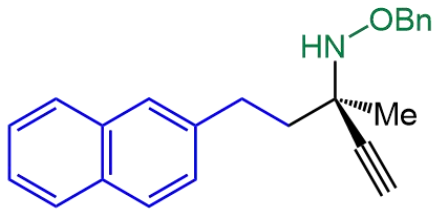
3al, 88%, 94% ee



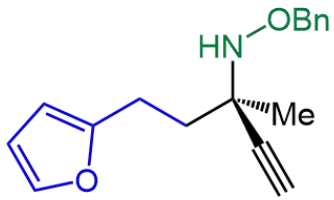
3am, 90%, 94% ee



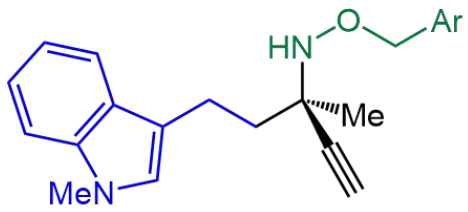
7a, 75%, 92% ee



7b, 85%, 75% ee

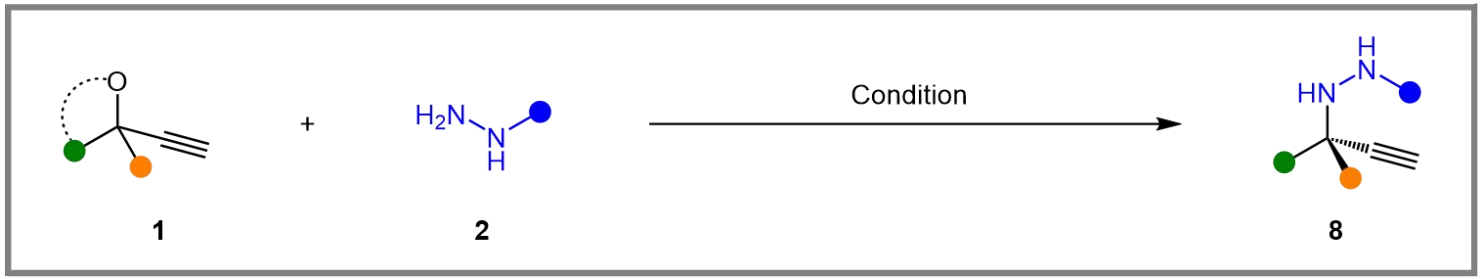


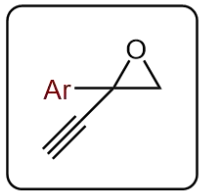
7c, 80%, 83% ee

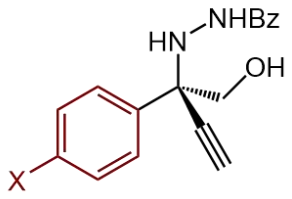


7d, Ar = Ph
78%, 94% ee
7e, Ar = 4-FC_6H_4
67%, 94% ee
7f, Ar = 4-$OMeC_6H_4$
61%, 93% ee

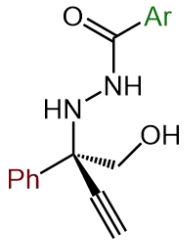
Substrate Scope





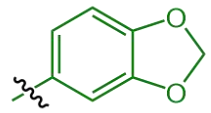


8a, X = H,
76%, 93% ee
8b, X = Cl,
80%, 92% ee

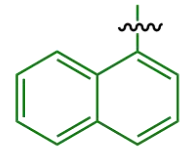


8c, Ar = 4-MeC_6H_4,
78%, 90% ee
8d, Ar = 4-BrC_6H_4
75%, 89% ee

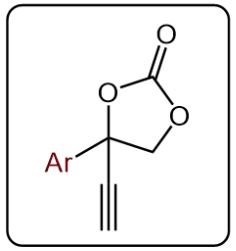
Ar =

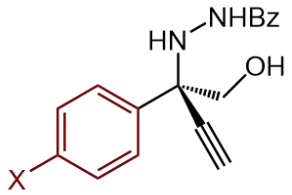


8e, 72%, 90% ee

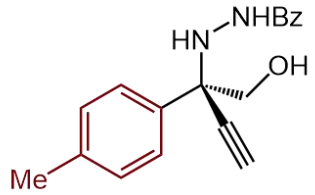


8f, 70%, 86% ee

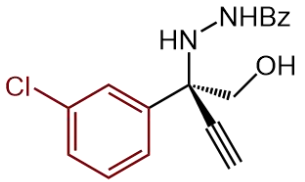




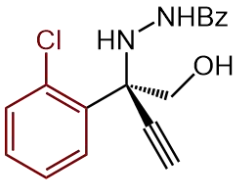
8a, X = H,
88%, 98% ee
8b, X = Cl,
90%, 97% ee



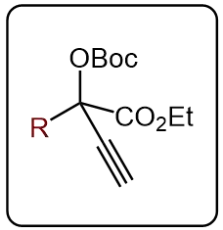
8g, X = Me, 84%, 98% ee

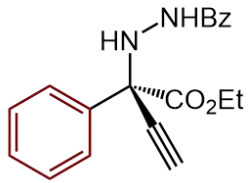


8h, 83%, 92% ee

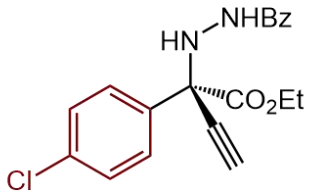


8i, 77%, 97% ee

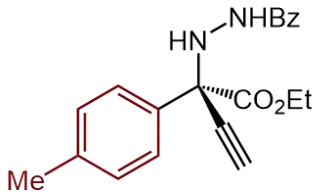




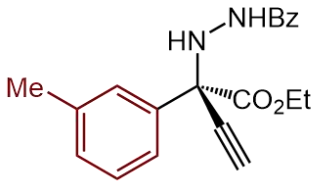
8j, 82%, 90% ee



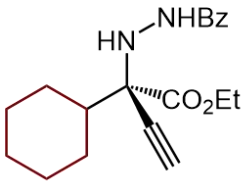
8k, 84%, 84% ee



8l, 78%, 90% ee

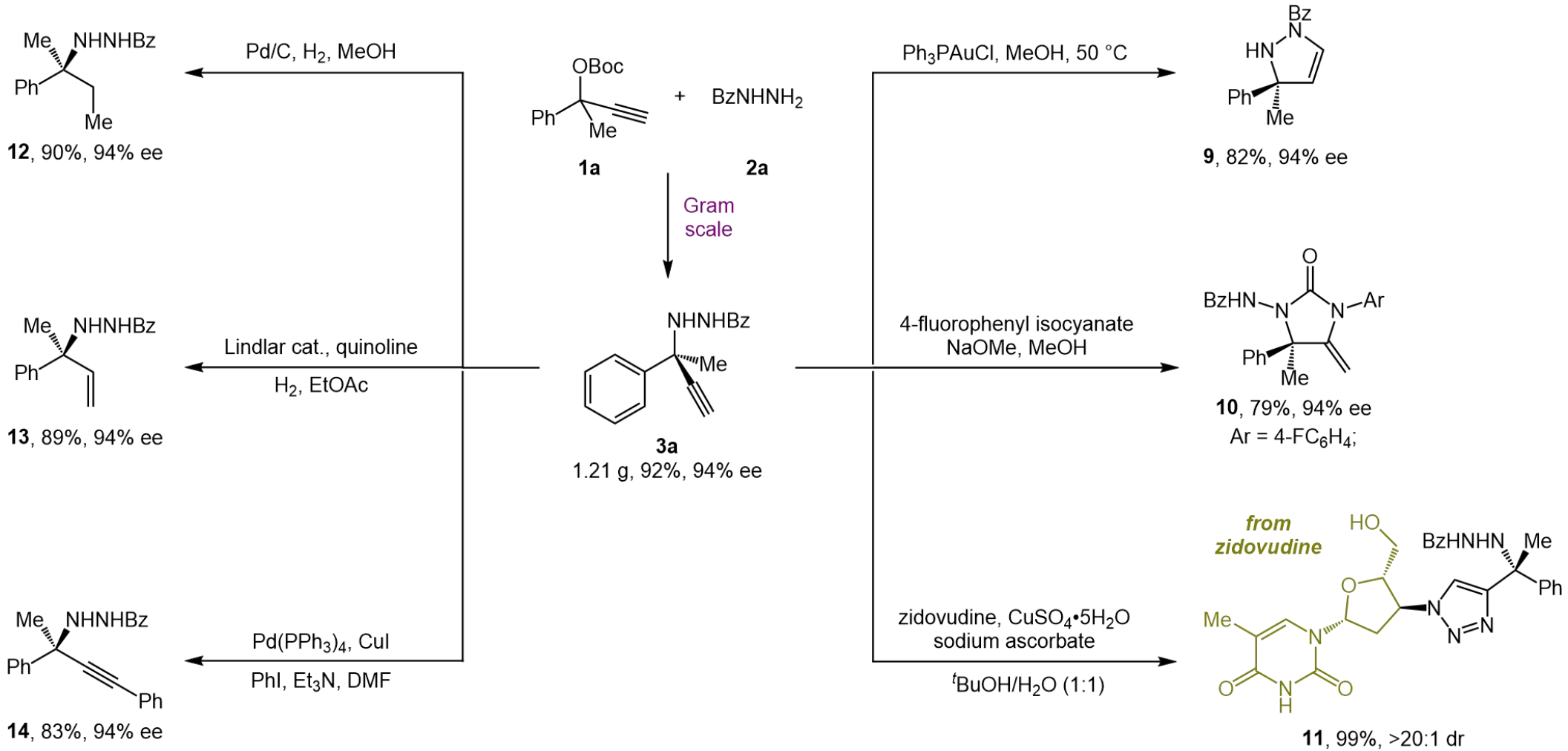


8m, 85%, 82% ee

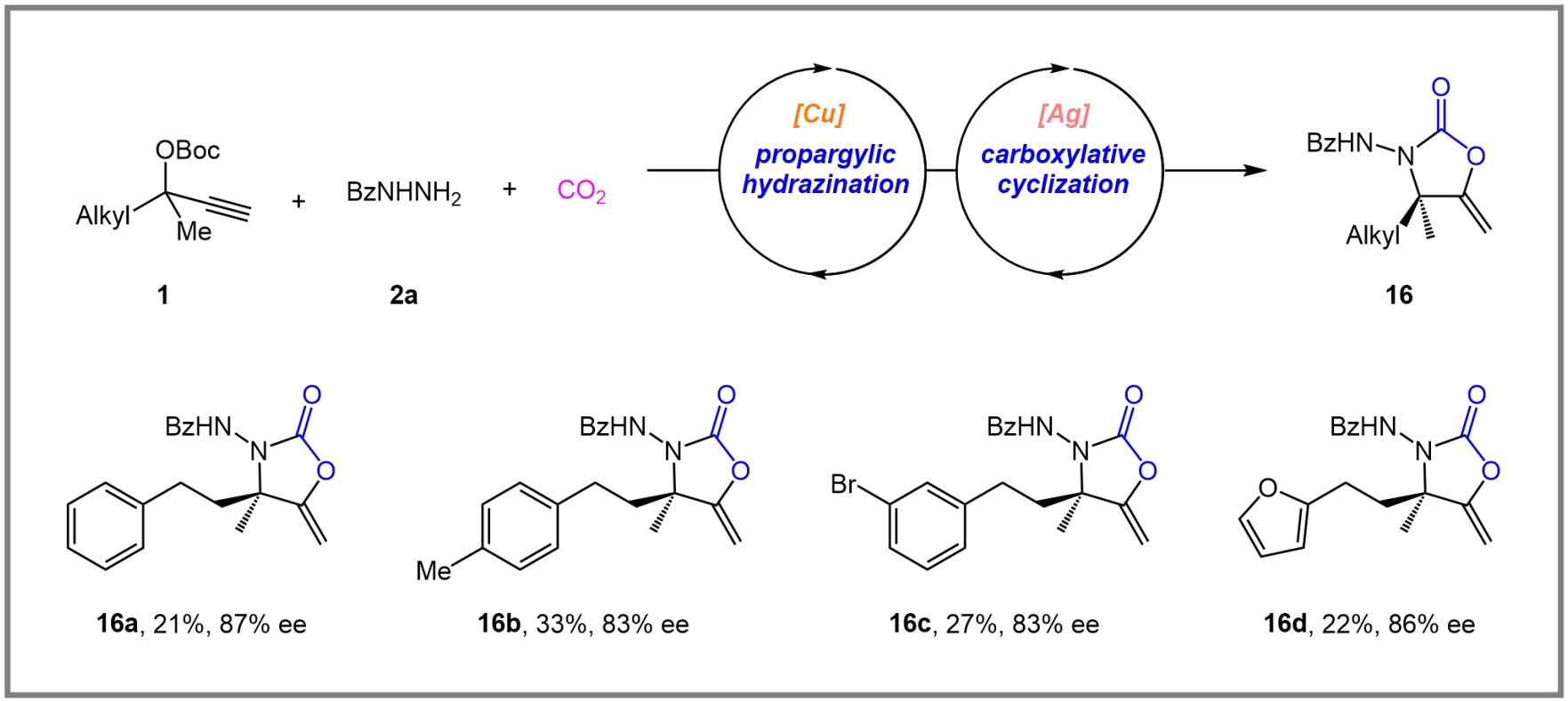


8n, 46%, 66% ee

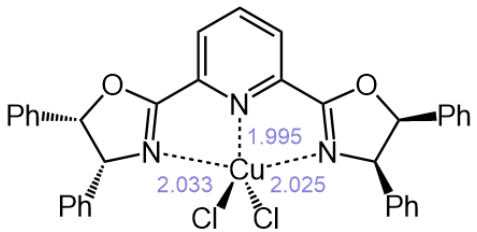
Transformations



Transformations

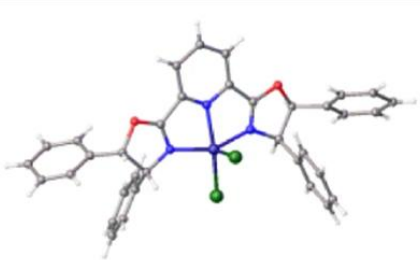


Mechanistic Studies



$CuCl_2/L_1$

≡



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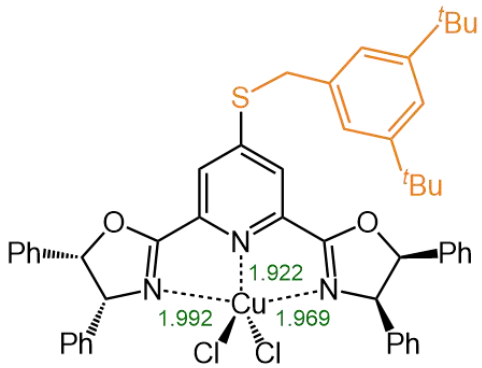
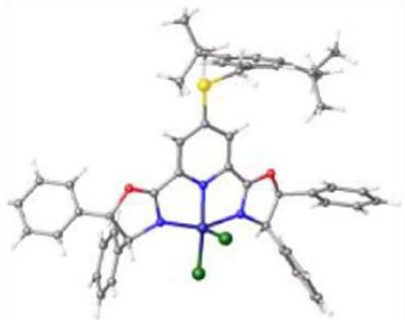


$CuCl_2/L_9$

≡



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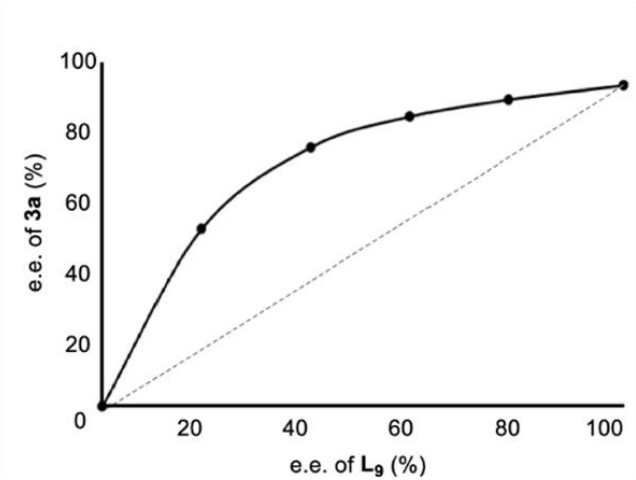
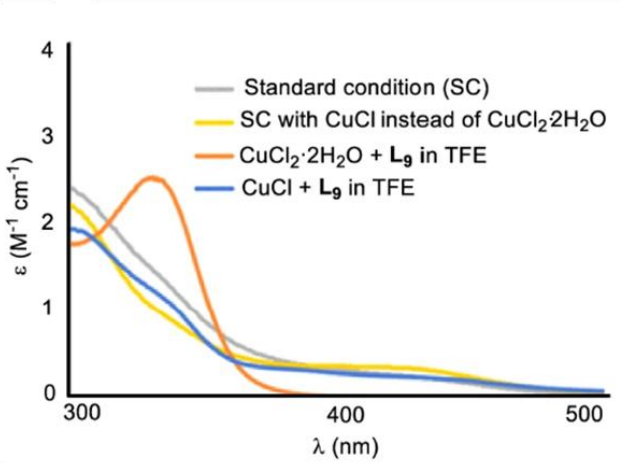
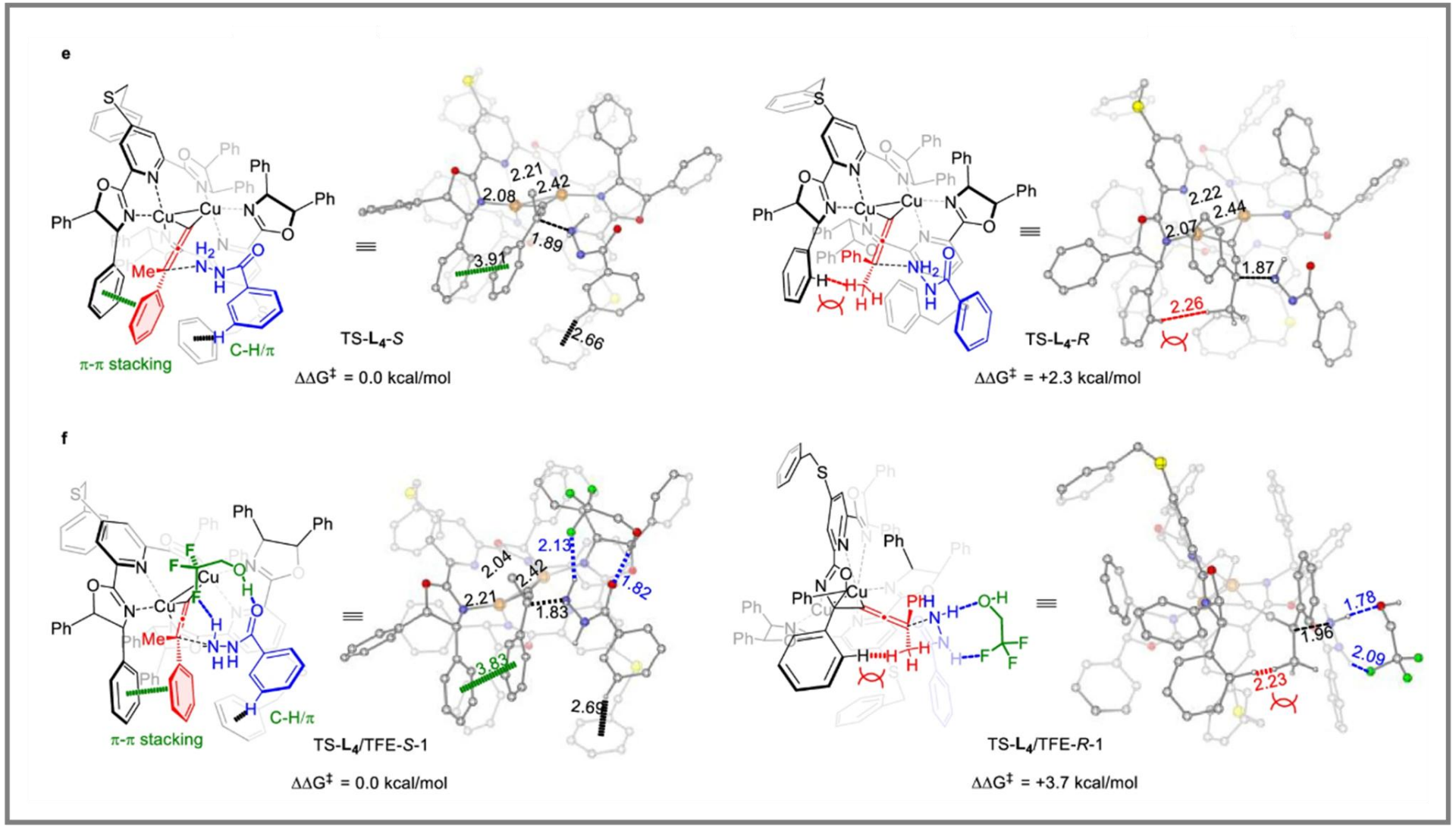


Entry	$CuCl_2/L_9$	Yield of **3a** (%)	ee of **3a**
1	1/1.5	91	94
2	1/1.2	94	94
3	1/1.0	93	93
4	1.2/1	95	75
5	1.5/1	95	44

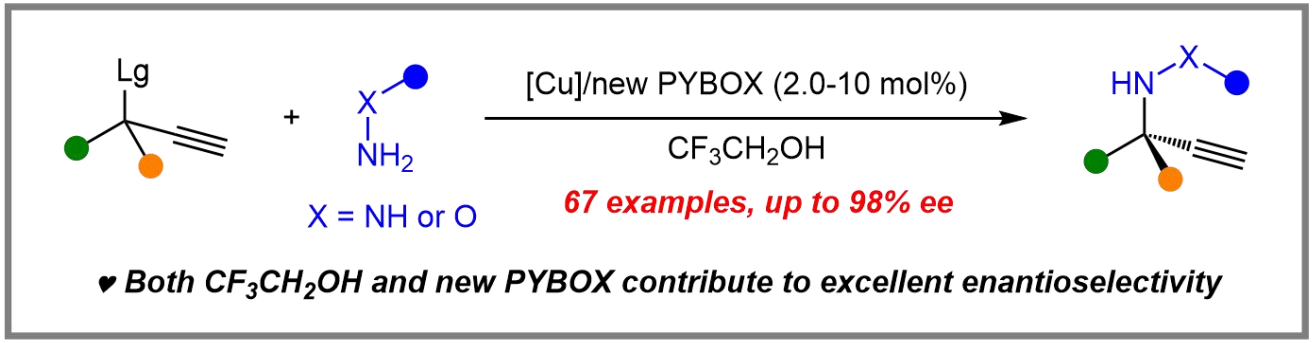


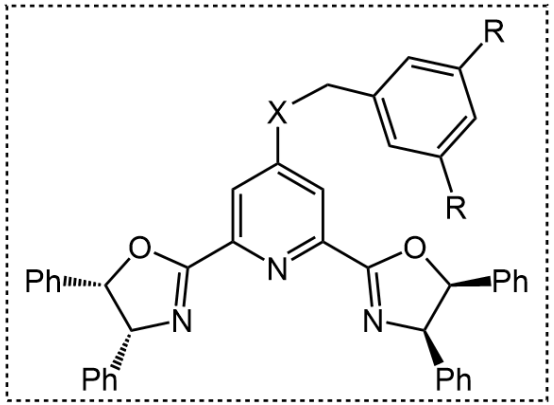
Mechanistic Studies



Summary

Asymmetric Propargylic Hydrazination to α-tertiary Ethynylhydrazines





- A Cu-catalyzed method was developed to access *α*-tertiary ethynylhydrazines with high enantioselectivity;
- Sterically bulky PYBOX ligands and TFE solvent together ensured high yield and stereocontrol;
- The products serve as versatile intermediates for constructing diverse bioactive hydrazine derivatives.

The First Paragraph

写作思路

α-叔胂类化合物的重要性

↓

目前合成该类化合物的策略

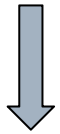
↓

提出本文的构建策略

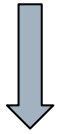
The Last Paragraph

写作思路

总结本文的研究成果



强调关键创新点



展望本工作在药物合成等方面的应用

Representative Examples

- The sterically confined pyridinebisoxzolines (PYBOX), featuring a bulky benzylthio shielding group also contribute to the excellent enantioselectivity. (sterically confined : 空间上受限的)
- The resulting hydrazine-based H-bond adduct might have beneficial steric effects that would enhance enantiofacial discrimination. (discrimination: 辨别，区别)
- These are multifunctional building blocks that are used to access chiral *α*-tertiary hydroxylamines, which are prominent structural motifs in pharmaceutically active compounds that are difficult to synthesize. (prominent: 重要的，著名的，杰出的)