

Literature Report 4

Chain Walking as a Strategy for Iridium-Catalyzed Migratory Amidation of Alkenyl Alcohols to Access α -Amino Ketones

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Checker: Yu-Qing Bai

Hwang, Y.; Baek, S. B.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* 2022, 144, 4277

2022.07.25

CV of Prof. Sukbok Chang



Research:

- ❑ C-H activation strategies especially for C-C, C-N and C-O bond formations
 - ❑ Methane functionalization
 - ❑ Catalytic selective defunctionalization
-

Education & Professional Experience:

- ❑ **1985** B.S. Chemistry, Korea University
 - ❑ **1987** M.S. Organic Chemistry, KAIST (Advisor: Prof. Sunggak Kim)
 - ❑ **1996** Ph.D. Organic Chemistry, Harvard University (Advisor: Prof. Eric. N. Jacobsen)
 - ❑ **1996-1998** Postdoc., Caltech (Advisor: Prof. Robert H. Grubbs)
 - ❑ **1998-2002** Assistant Professor, Ewha Womans University
 - ❑ **2002-Present** Professor, KAIST
 - ❑ **2018-Present** Appointed as Distinguished Professor at KAIST
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Previous Strategies toward α -Amino Ketones

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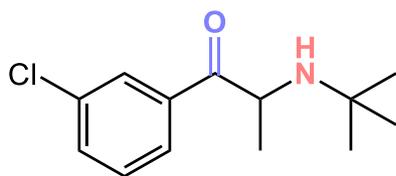
Chain Walking as a Strategy to Access α -Amino Ketones

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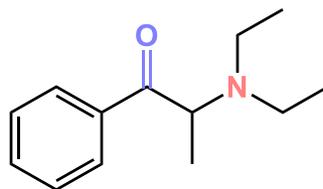
Summary

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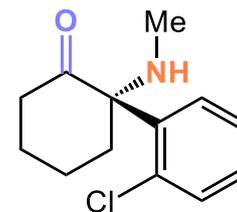
Representative examples of α -amino ketones



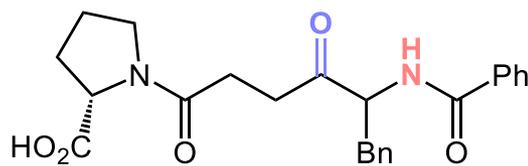
Bupropion
antidepressant



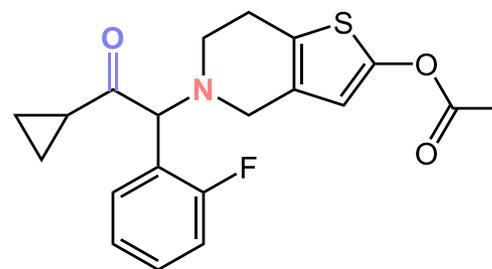
Amfepramone
appetite suppressant



(S)-Ketamine
analgesia & anesthesia

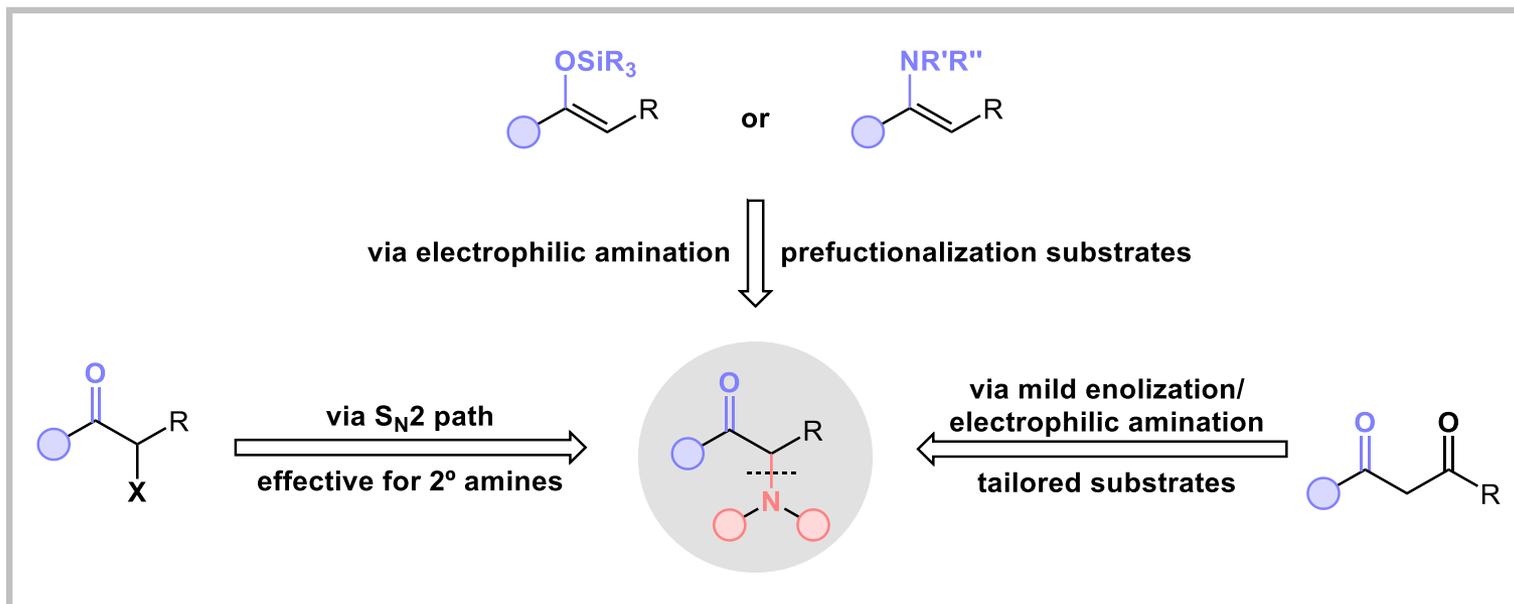
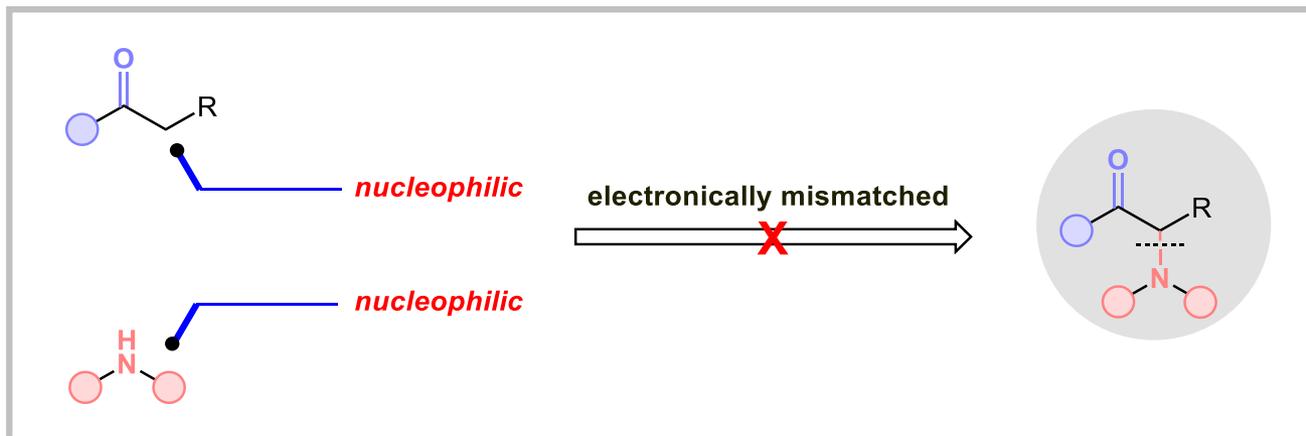


Keto-ACE
antihypertensive



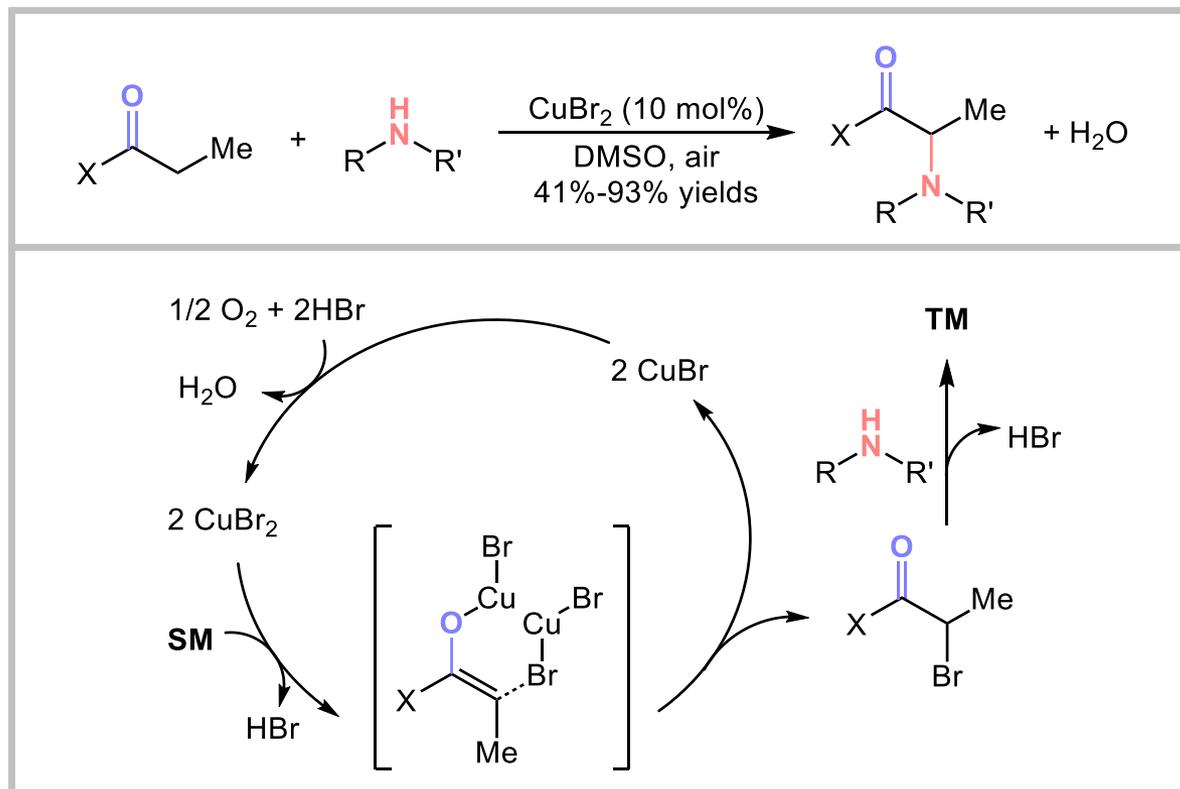
Effient
antiplatelet

Introduction



Previous Strategies toward α -Amino Ketones

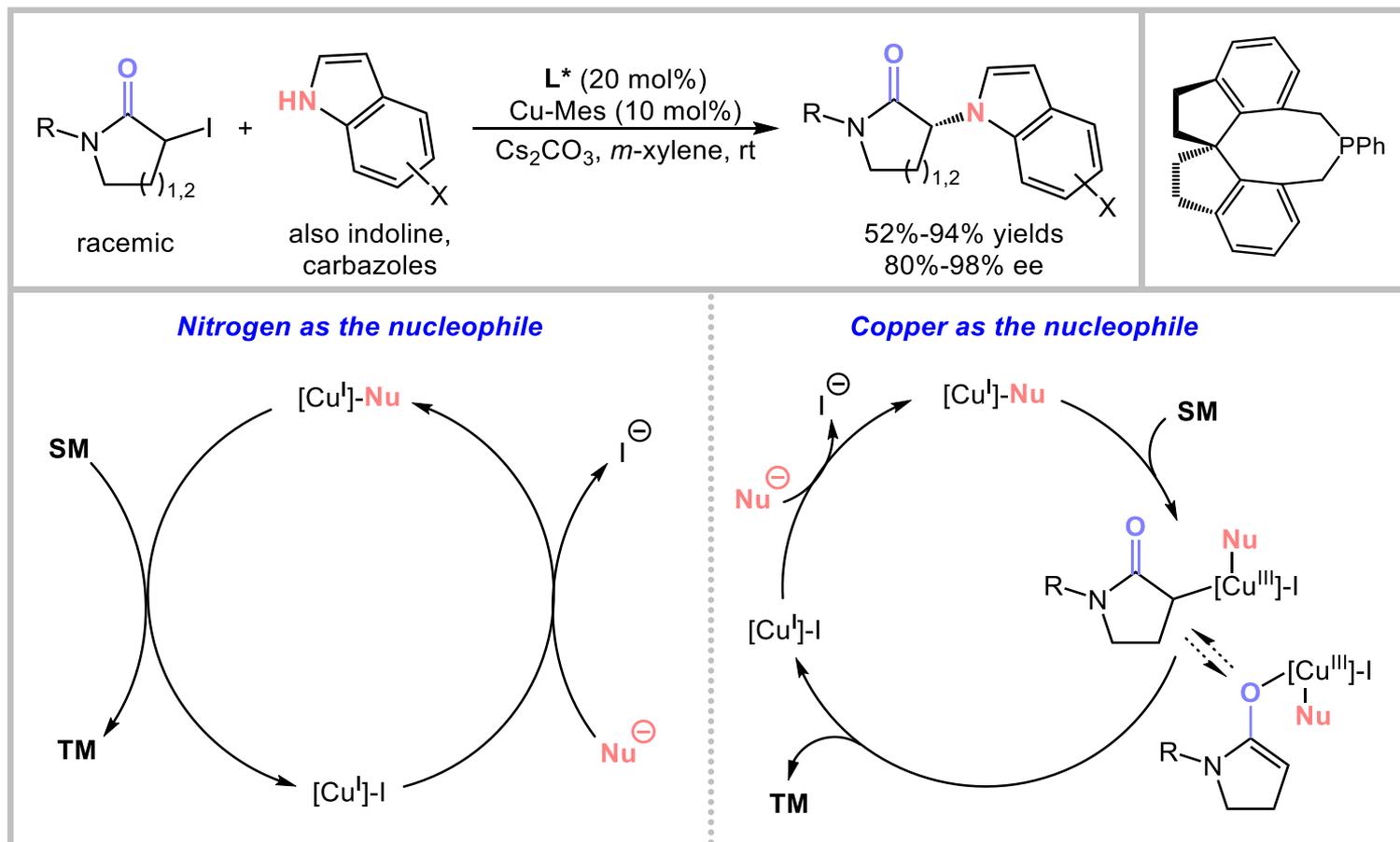
Amination of α -halogenated carbonyls via S_N2 pathway



Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074

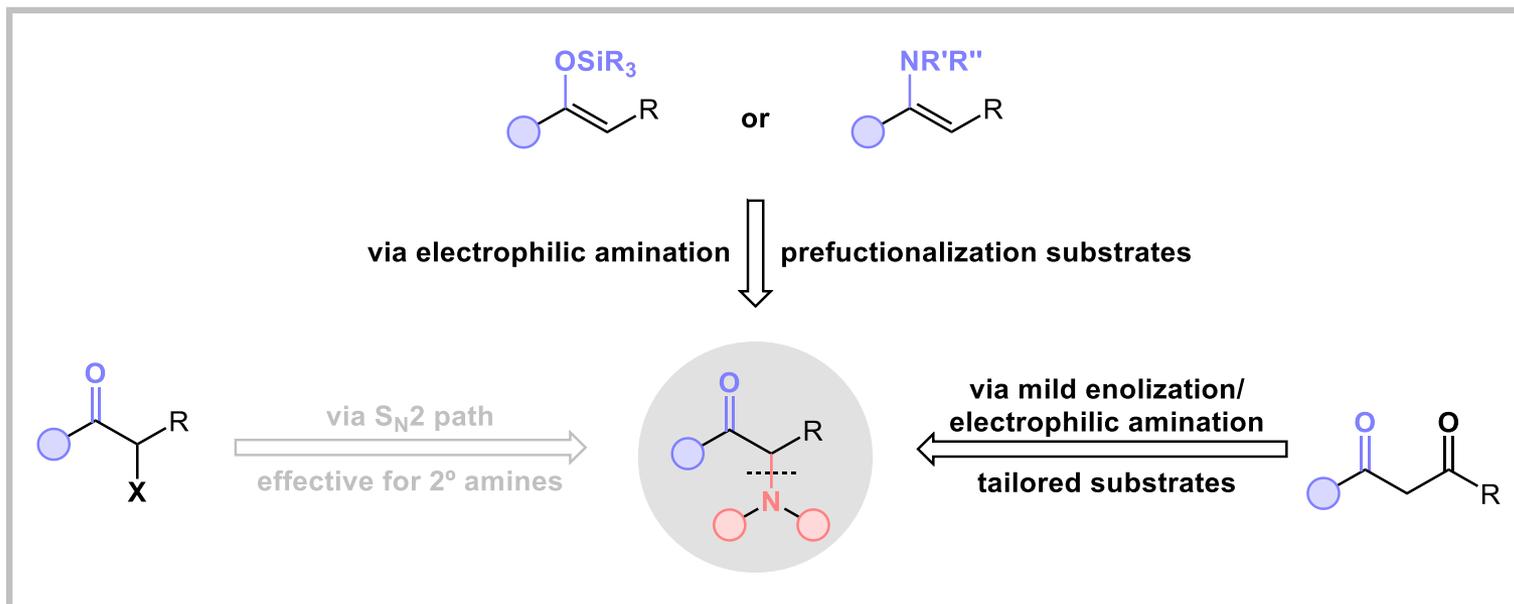
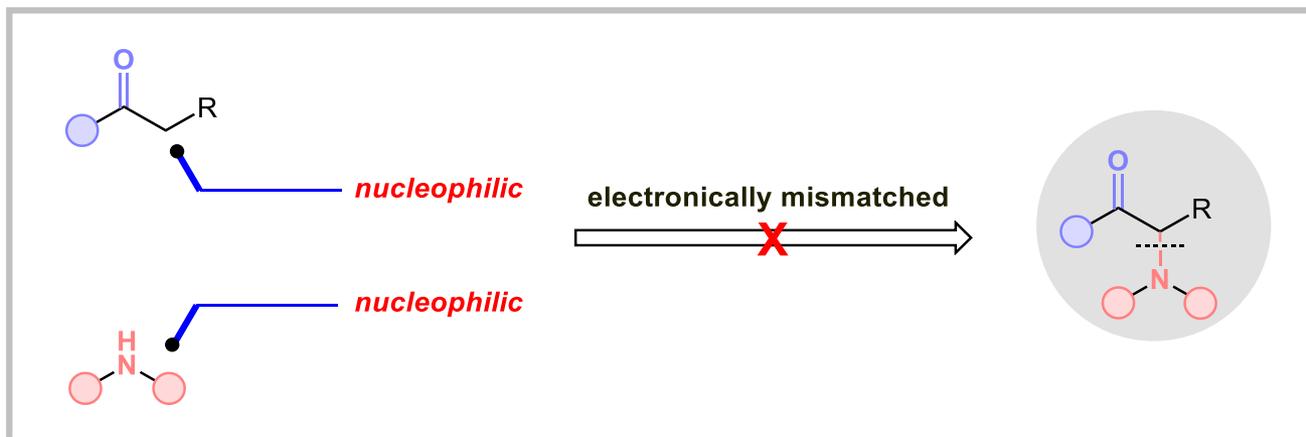
Previous Strategies toward α -Amino Ketones

Amination of α -halogenated carbonyls via S_N2 pathway

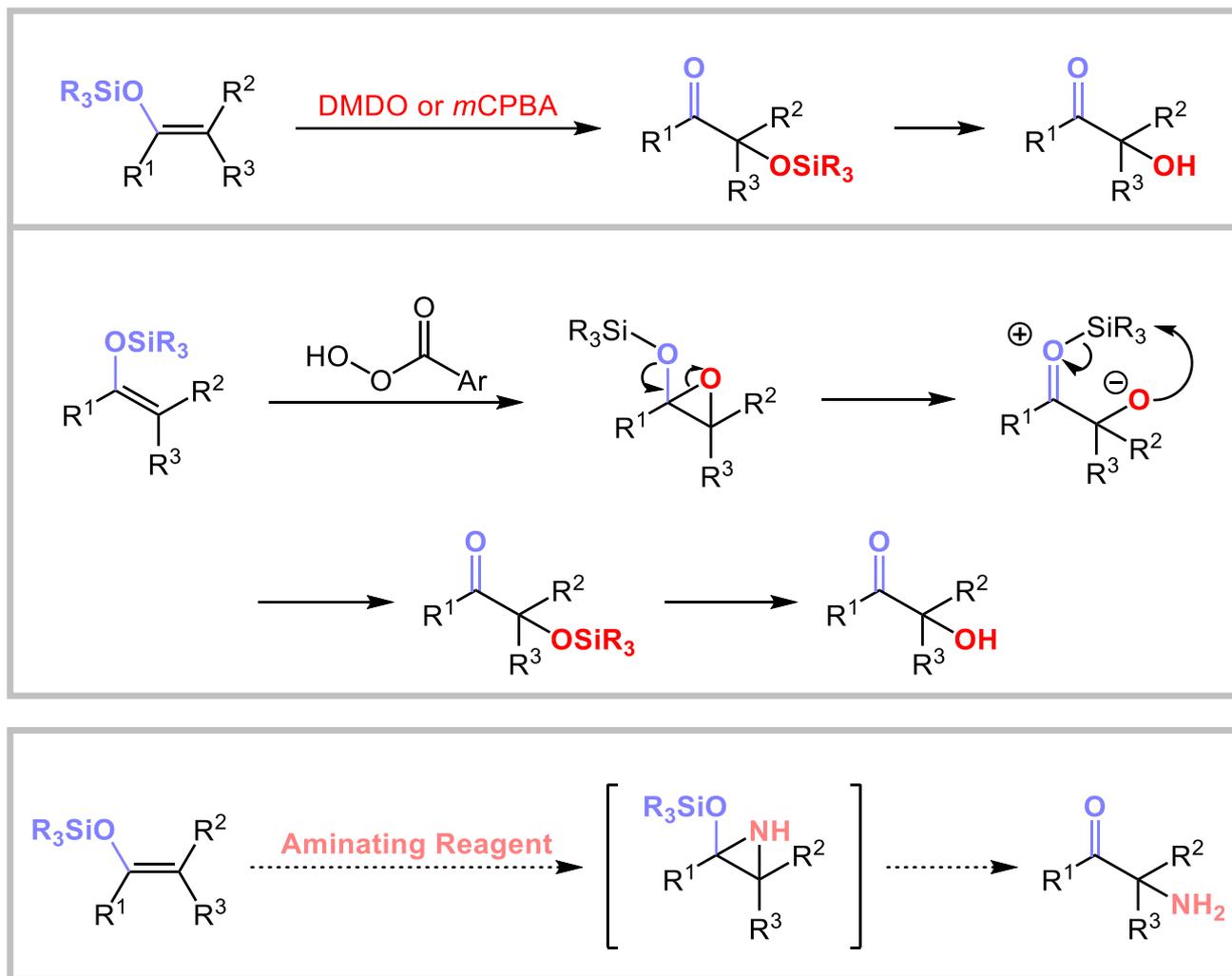


Bartoszewicz, A.; Matier, C. D.; Fu, G. C. *J. Am. Chem. Soc.* **2019**, *141*, 14864

Introduction



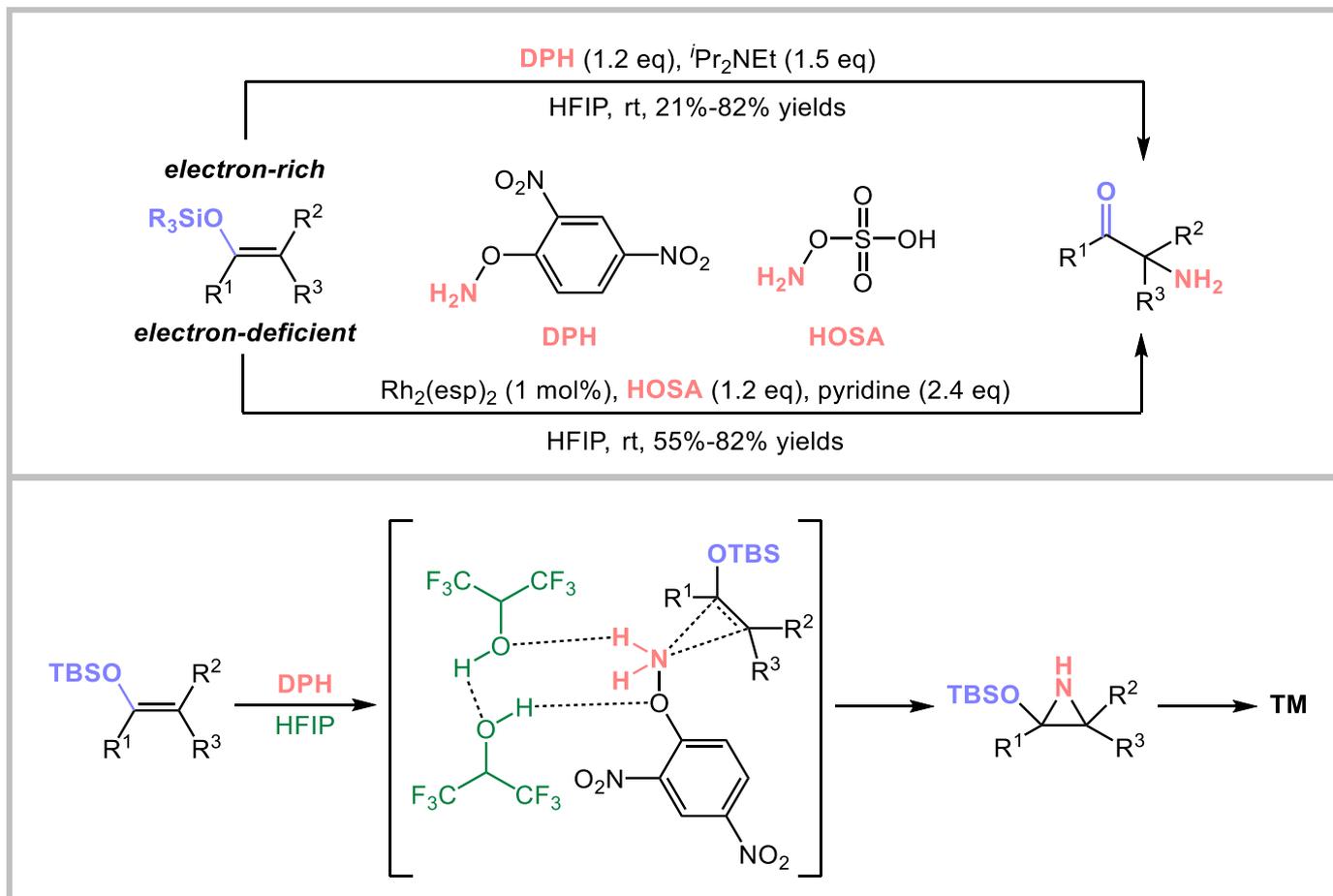
Rubottom Oxidation



Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 15, 4319.

Previous Strategies toward α -Amino Ketones

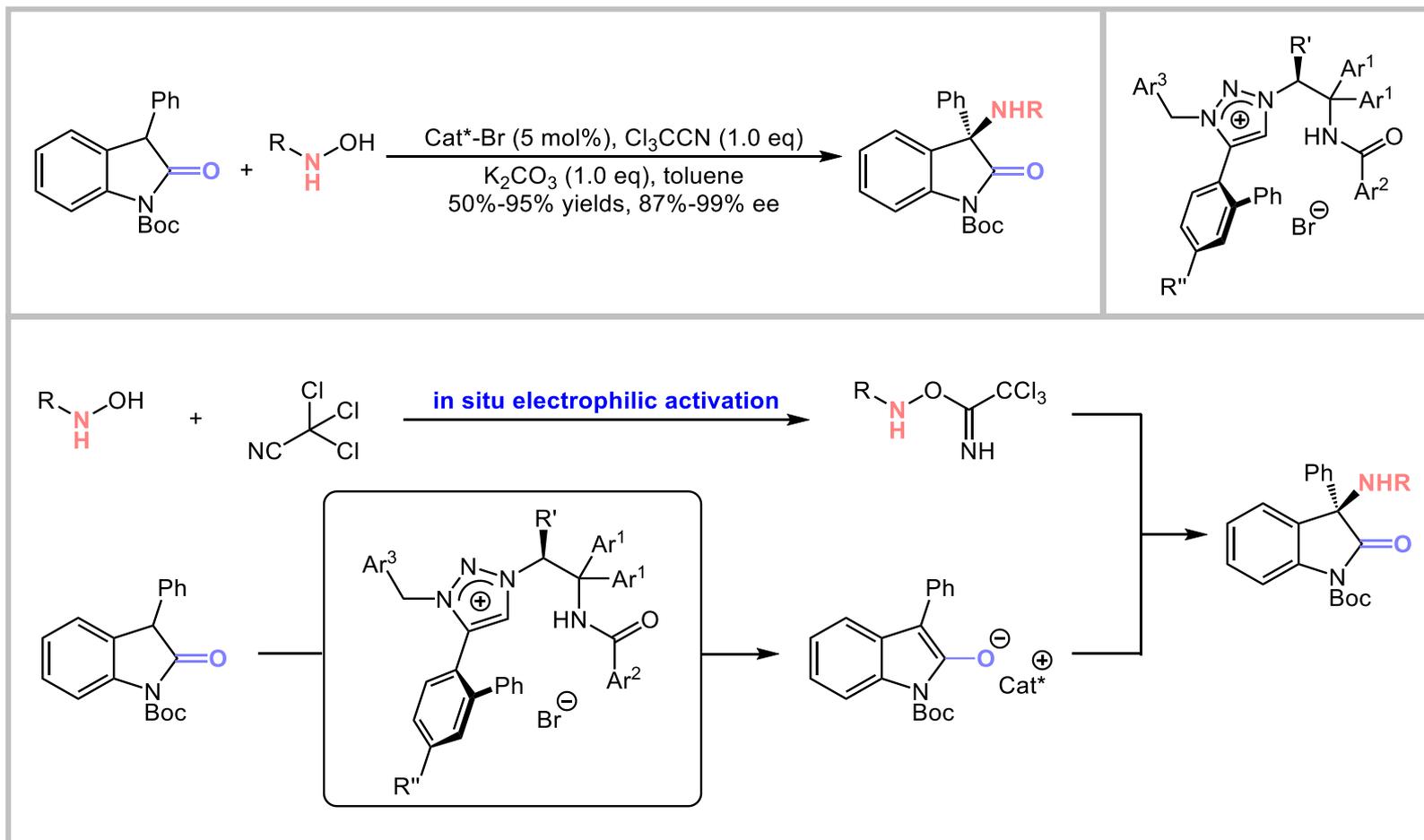
Construct α -amino carbonyls through electrophilic amination



Zhou, Z.; Cheng, Q.-Q.; Kürti, L. *J. Am. Chem. Soc.* **2019**, *141*, 2242

Previous Strategies toward α -Amino Ketones

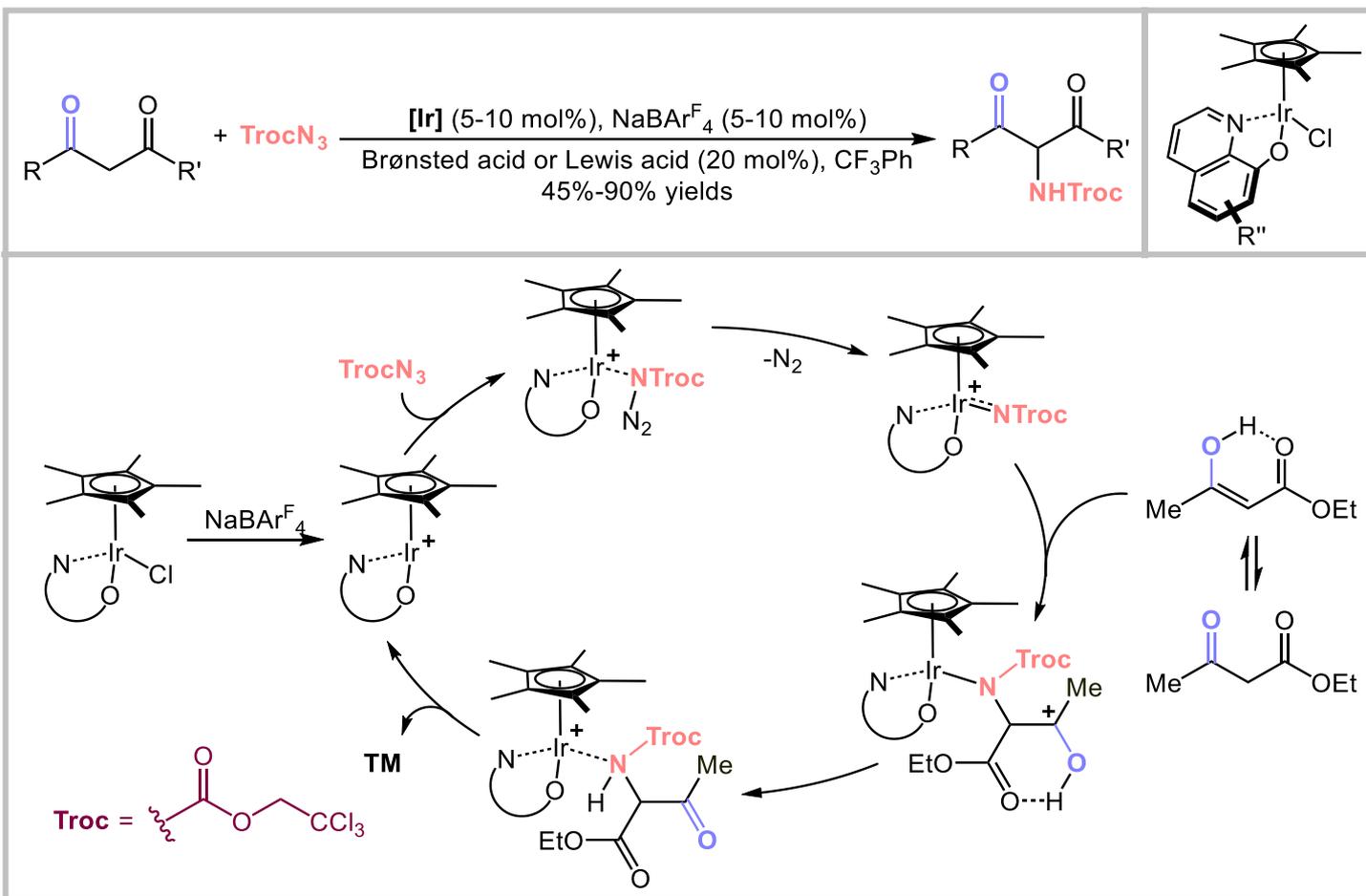
Construct α -amino carbonyls through electrophilic amination



Ohmatsu, K.; Ando, Y.; Nakashima, T.; Ooi, T. *Chem* **2016**, 1, 802

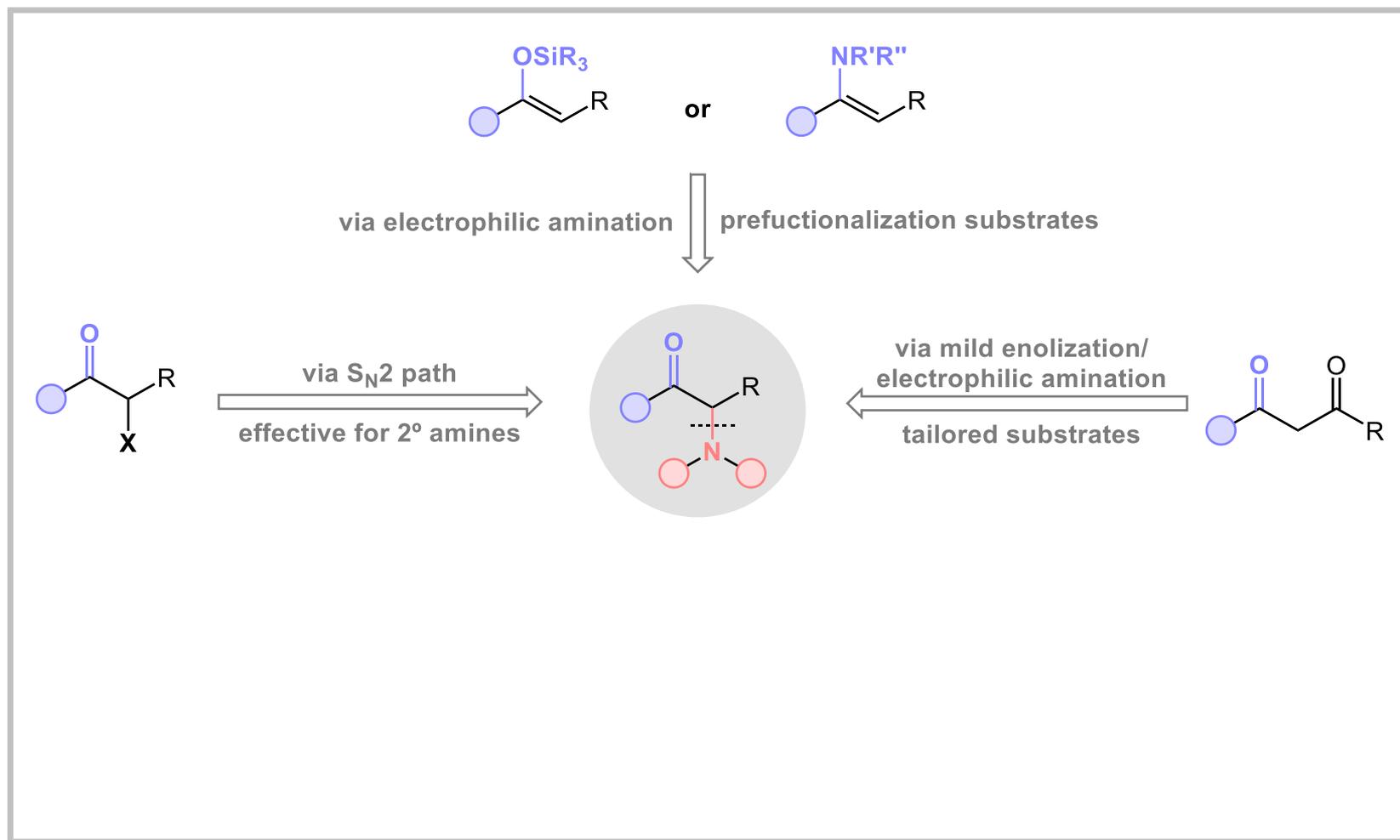
Previous Strategies toward α -Amino Ketones

Construct α -amino carbonyls through electrophilic amination



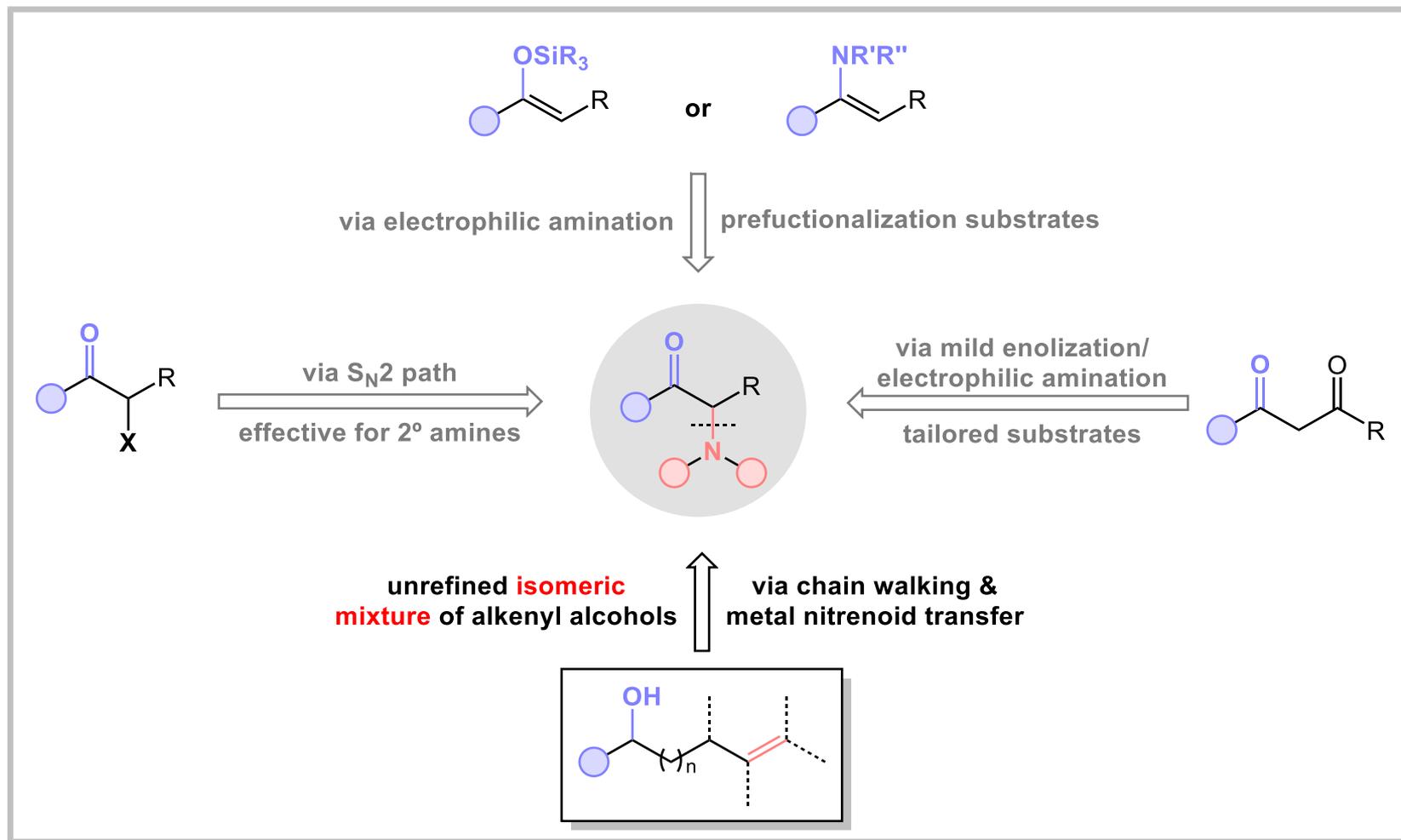
Lee, M.; Jung, H.; Kim, D.; Park, J.-W.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142*, 11999

Chain Walking as a Strategy to Access α -Amino Ketones



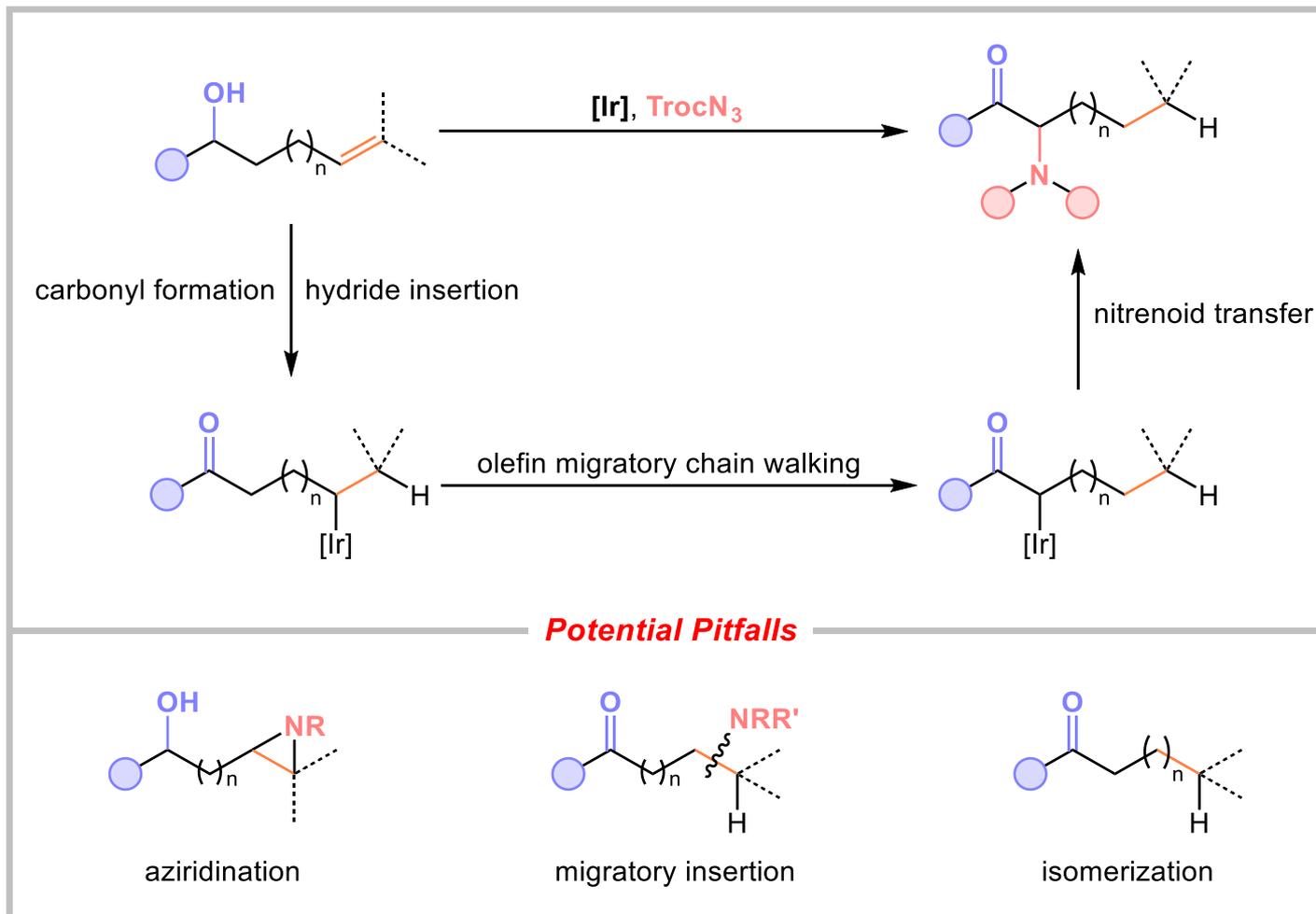
Hwang, Y.; Baek, S. B.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 4277

Chain Walking as a Strategy to Access α -Amino Ketones

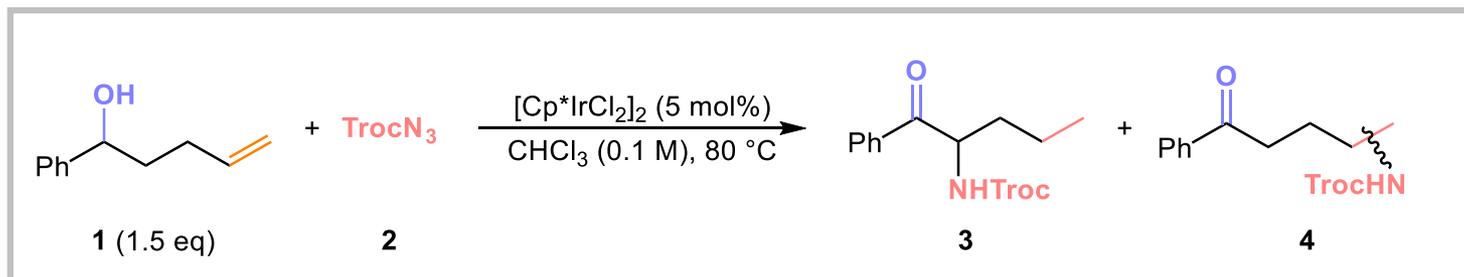


Hwang, Y.; Baek, S. B.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 4277

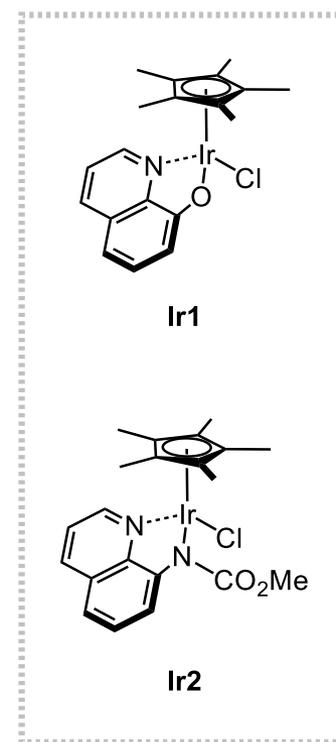
Chain Walking as a Strategy to Access α -Amino Ketones



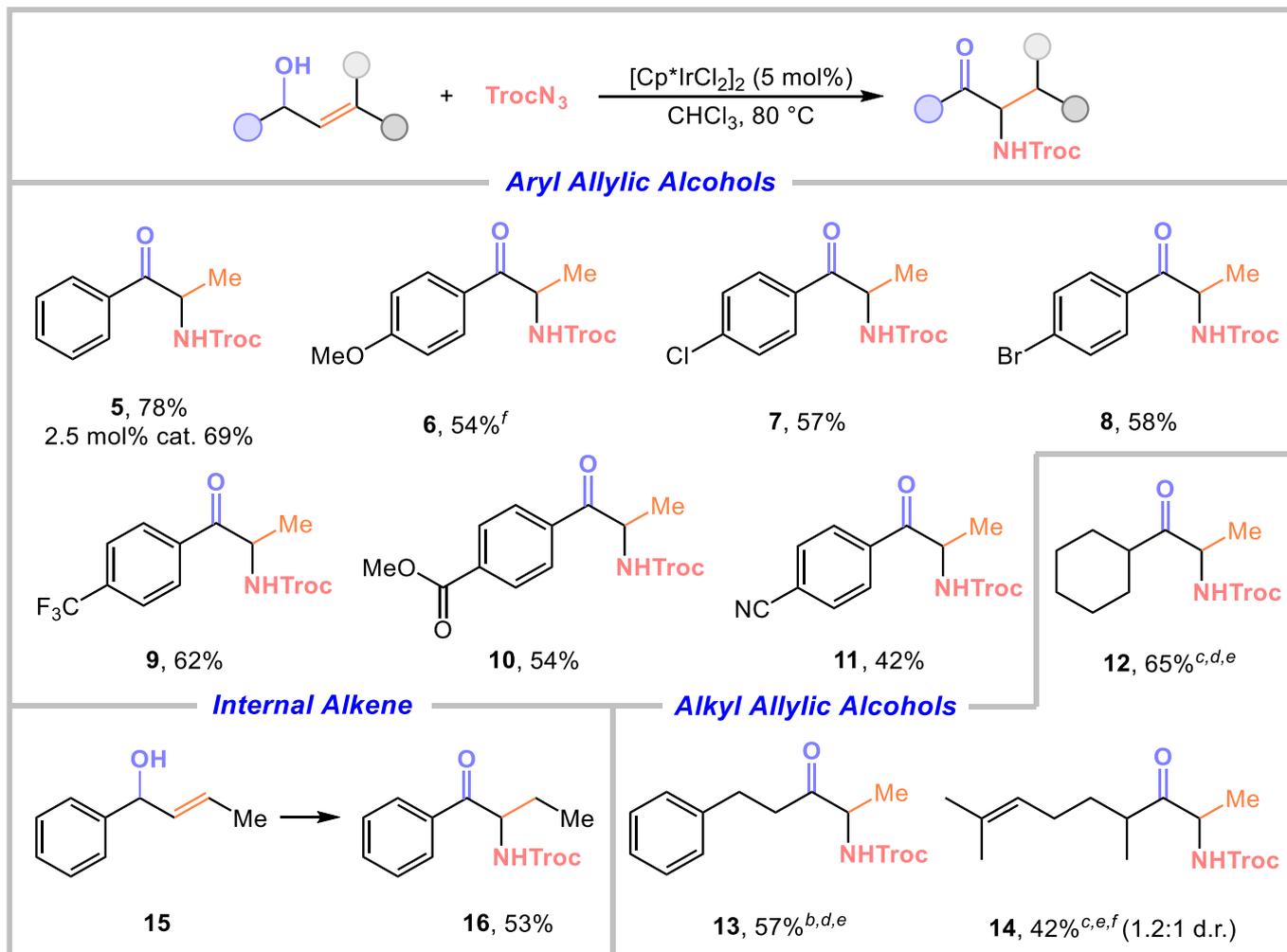
Optimization of the Migratory Amidation



Entry	Changes from the standard conditions	Yield of 3/4 (%)
1	none	63/<2
2	[Cp*RhCl ₂] ₂ as catalyst	<2/<2
3	[Cp*CoCl ₂] ₂ as catalyst	<2/<2
4	[(<i>p</i> -cymene)RuCl ₂] ₂ as catalyst	<2/<2
5	Ir1 as catalyst	8/<2
6	Ir2 as catalyst	6/<2
7	w/o [Cp*IrCl ₂] ₂	<2/<2
8	HFIP as solvent	<2/<2
9	DCE as solvent	53/<2
10	0.1 M to 0.5 M	41/<2
11	2.5 mol% of [Cp*IrCl ₂] ₂	52/<2
12	1.1 equiv of 1	60/<2

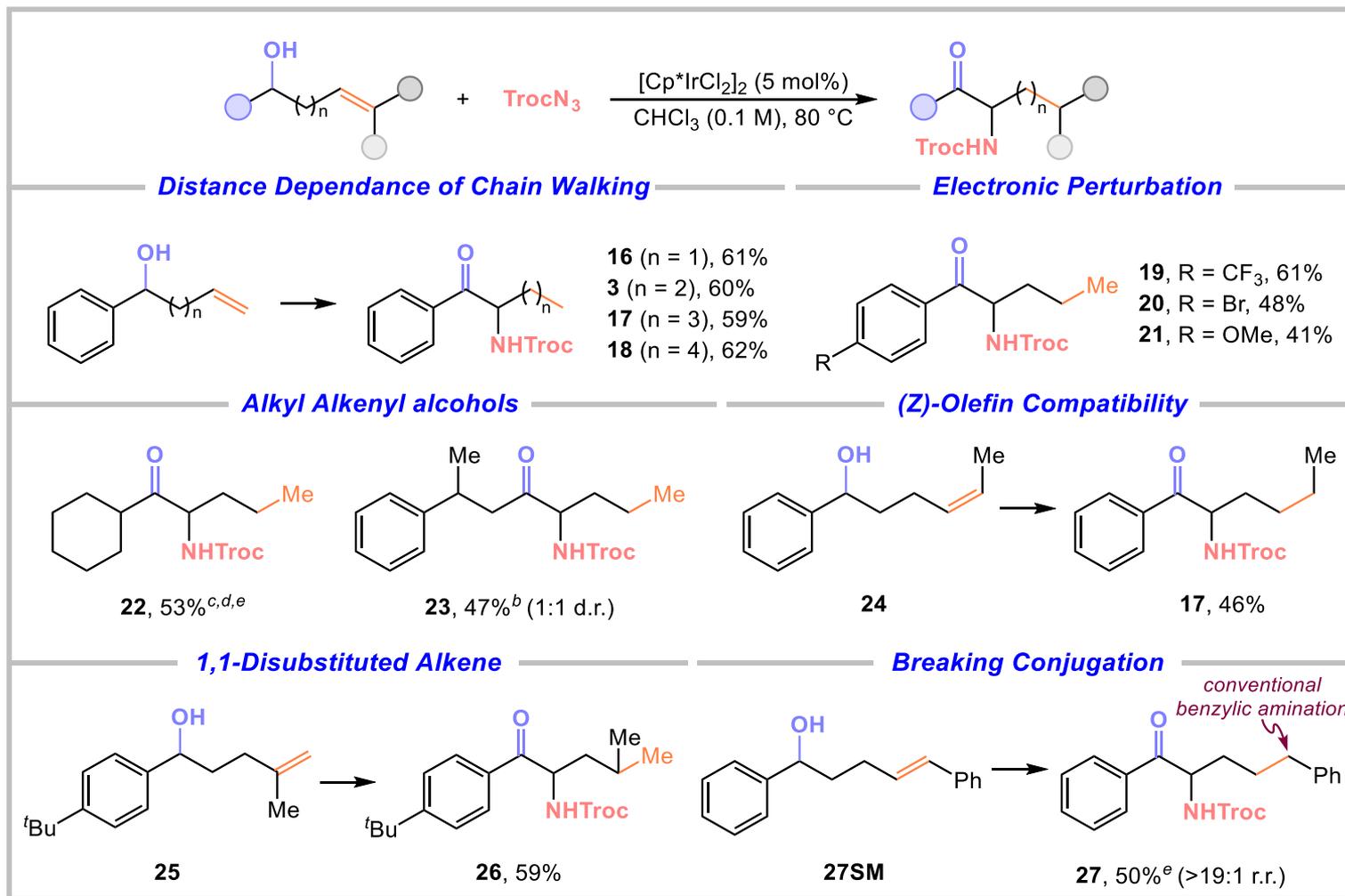


Substrate Scope of Allylic Alcohols



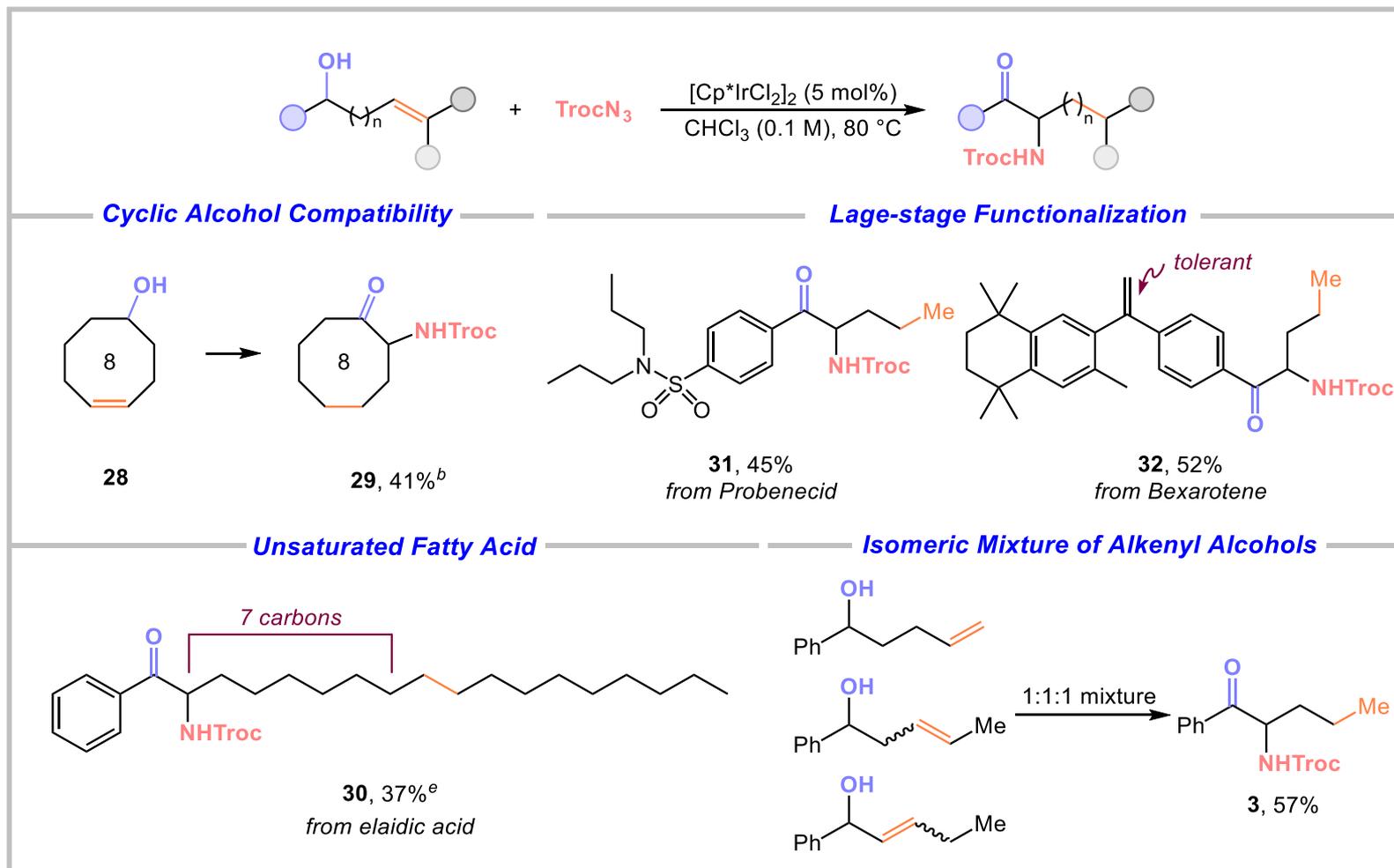
^b 1,2-DCE (0.2 M) solvent was used. ^c 1,2-DCE (0.05 M) was used. ^d Diethyl ketone (1 eq) was added. ^e 2.5 eq of alcohol was used. ^f 7.5 mol % of catalyst was used.

Substrate Scope of Alkenyl Alcohols



^b CHCl₃ (0.17 M) solvent was used. ^c 1,2-DCE (0.05 M) was used. ^d 2.5 eq of alcohol was used. ^e 7.5 mol % of catalyst was used.

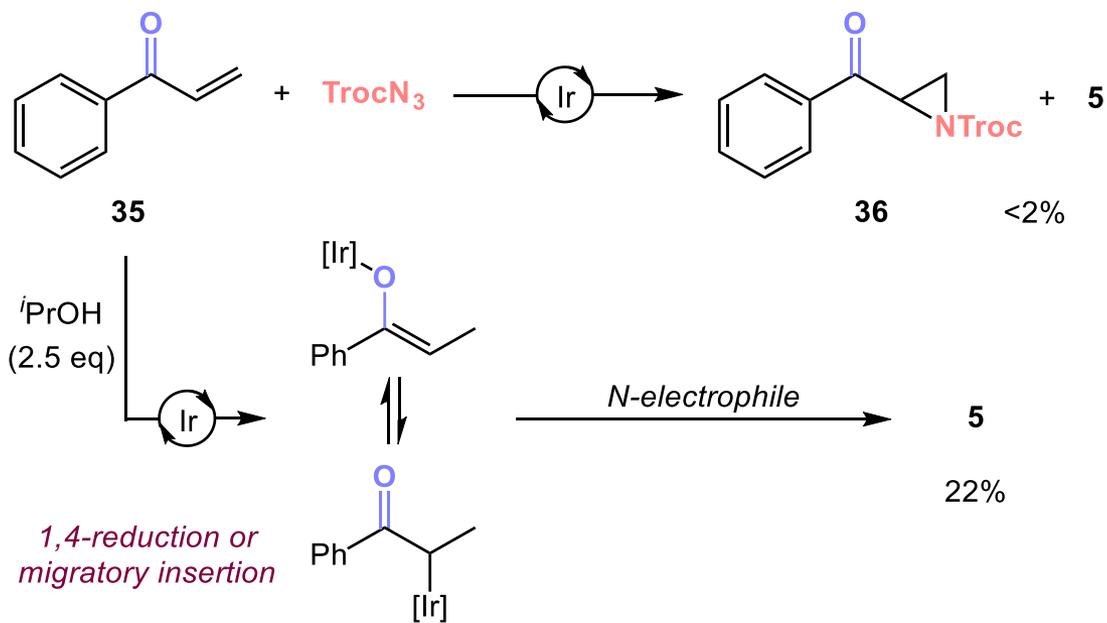
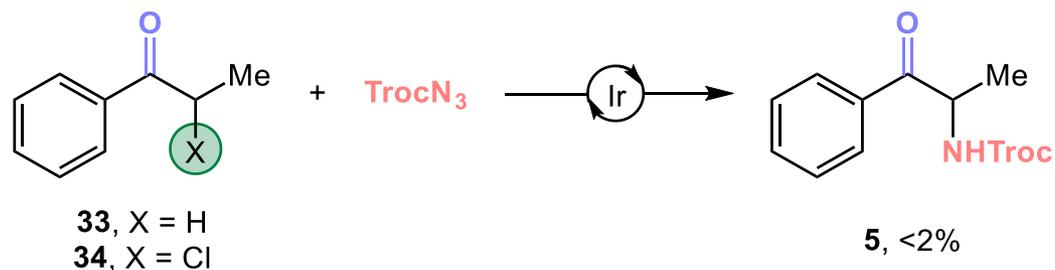
Synthetic Applications



^b CHCl₃ (0.17 M) solvent was used. ^c 1,2-DCE (0.05 M) was used. ^d 2.5 eq of alcohol was used. ^e 7.5 mol % of catalyst was used.

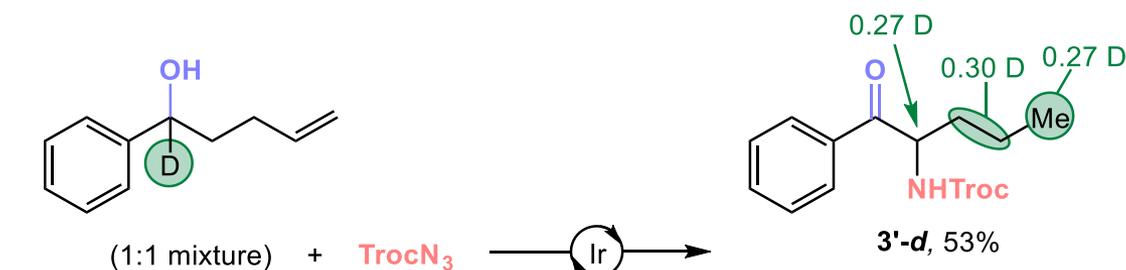
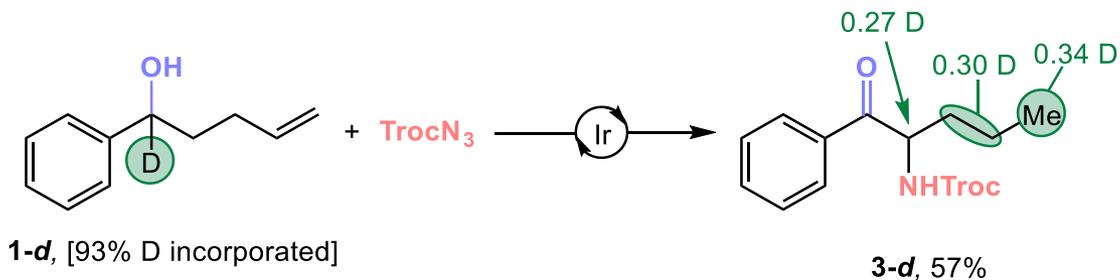
Experimental Mechanistic Studies

Control Experiments

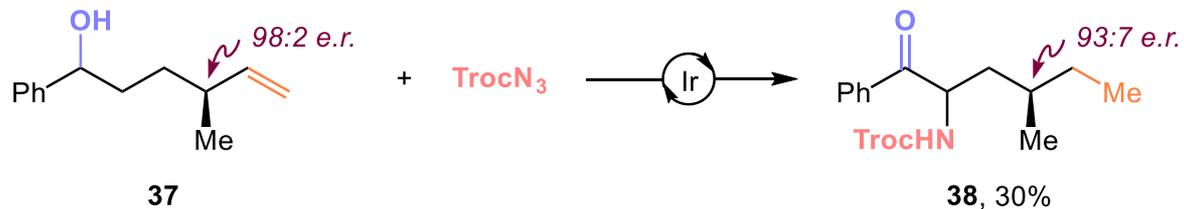


Experimental Mechanistic Studies

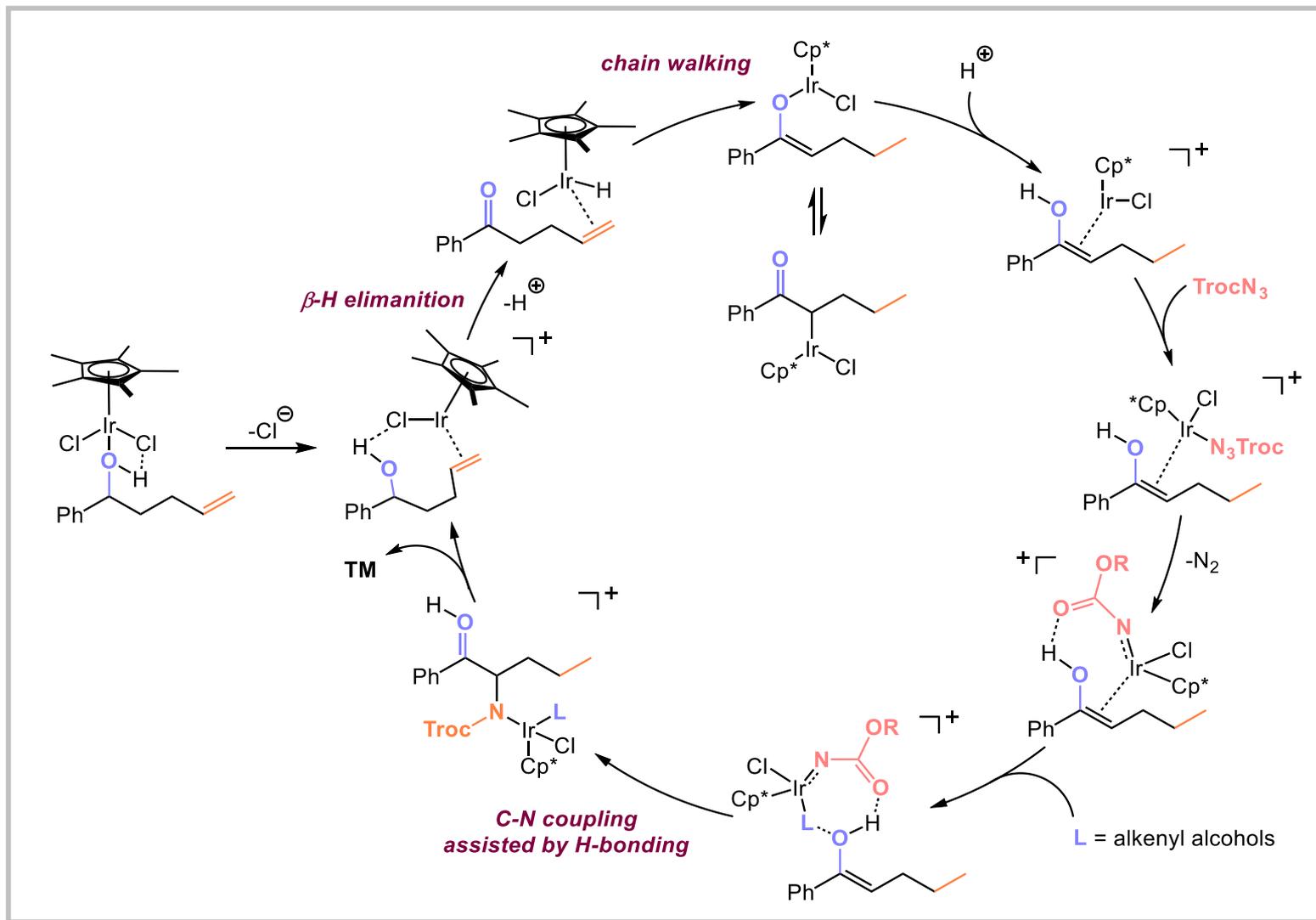
D-Labeling Studies



Preservation of Stereogenic Center



Proposed Mechanism



Summary



Regioselective amidation



Readily available starting materials



Merge of redox-relay *chain walking* and *Ir-nitrenoid transfer*



Unrefined *isomeric mixture* of alkenyl alcohols

Writing Strategies

□ The First Paragraph

The importance of **α -amino ketones**
in medicines and natural products



Previous methods to access
 α -amino ketones



The necessity to develop
new catalytic system

The First Paragraph

Carbonyl compounds bearing α -amino substitution are a ubiquitous structural motif in a myriad of medicines, agrochemicals, and natural products. Thus, the invention of catalytic methods to build this high-valued bifunctional scaffold from readily accessible starting materials in a rapid, straightforward, and convenient manner has been of great interest for synthetic chemists. The vast majority of current strategies often rely on laborious approaches to construct the C–N bonds from carbonyl synthons. One classical route is the amination of α -halogenated carbonyls via a S_N2 -type pathway; however, this method requires prefunctionalized carbonyl starting materials. Furthermore, this approach is most efficient with secondary amines and cannot be extended to other synthetically versatile nucleophiles such as amides and carbamates, thus limiting the scope of accessible products.

The First Paragraph

On the other hand, a polarity reversal of reacting components has expanded the repertoire of retrosynthetic strategies in the carbonyl α -aminations. Indeed, the catalytic activity in this electrophilic amination has been improved to introduce various N-electrophiles, such as azodicarboxylates, nitroso, or sulfonyliminoiodinane reagents. However, to achieve a satisfactory level of umpolung reactivity, a stoichiometric amount of pregenerated silyl enol ethers is generally utilized, although in situ enolization procedures are also available under acidic conditions albeit with limited scope and low functional group compatibility. In this context, the development of a multifaceted catalytic system that can readily utilize abundant feedstock starting materials with high functional group compatibility would be highly appealing.

Writing Strategies

□ The Last Paragraph

Summary of the work



Advantages of the current
catalytic system



Outlook of this work

The Last Paragraph

In summary, we have developed an efficient protocol to harness two mechanistically distinctive processes of Ir-catalyzed redox-relay chain walking and nitrenoid transfer in sequence. The developed catalytic platform granted access to olefin migratory amidation of readily available alkenyl alcohol substrates, with excellent regioselectivity by suppressing nonamidative side pathways. It allows a new route to various α -amino ketones from both aliphatic and aromatic allylic alcohols. Moreover, a remote functionalization has been achieved on the basis of olefin migration over up to seven methylene linkers. The synthetic utility of the developed method was further demonstrated by achieving regioconvergent migratory amidation of inconsequential isomeric olefin mixtures.

The Last Paragraph

The combined experimental and theoretical investigations suggested a dual role of the Ir catalyst in generating both the key Ir-nitrenoids and the enolate intermediate, thereby achieving rather elusive redox-relay amidation. The current method is anticipated to pave the way to access a diverse range of α -amino carbonyl compounds, which are highly sought after in the synthetic and medicinal chemistry communities.

Representative Examples

- ✓ In particular, the use of alkenyl alcohols was expected to **streamline** (精简) synthetic routes **in that** (由于, 引导原因状语从句) they are readily available carbonyl synthons as well as an internal hydride source, thus **obviating** (obviate, 避免) the need of a large quantity of external hydride sources (e.g., hydrosilanes) for the required redox event.
- ✓ This approach incorporates a chain walking through multiple methylene linkers, and it displays exceptional regioselectivity that is **unattainable** (难以达到的) by the conventional alkene hydroamidation methods.
- ✓ At the beginning, several **issues were considered to address** (需要解决的问题) in order to **effectuate** (实现) the hypothetical cascade processes in the desired direction.

Acknowledgement

Thanks for your attentions!