EPFL

LSPN

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

New C(sp^3)-H Alkynylation Methodologies:
Beyond Classical Activated Positions

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June 6th, 2019

EPFL

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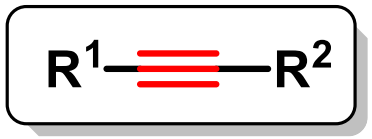
LABORATOIRE DE SYNTHESE ET PRODUITS NATURELS

Contents

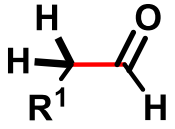
Introduction

Alkynes

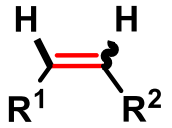


Why are they so relevant?

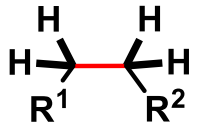
-Synthetic intermediates



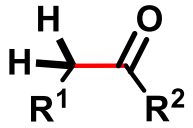
aldehydes



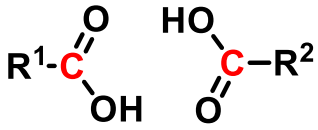
alkenes



alkanes

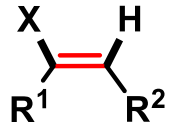


ketones



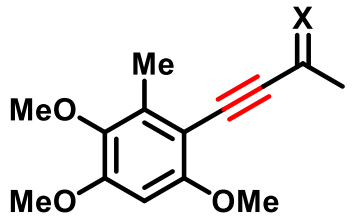
carboxylic acids

triazoles

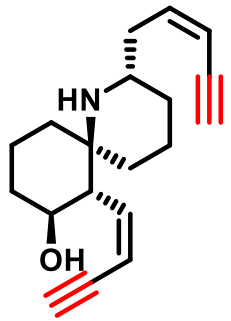


addition products

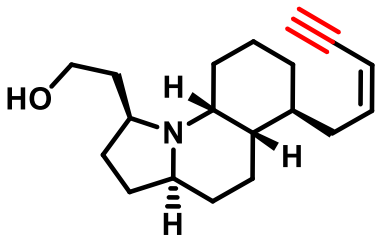
-Natural products



Antrocamphin A, X = CH_2
Antrocamphin B, X = O
anti-inflammatory

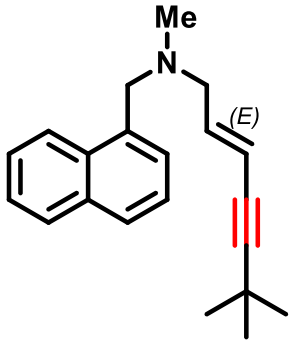


Histrionicotoxin
frog poison

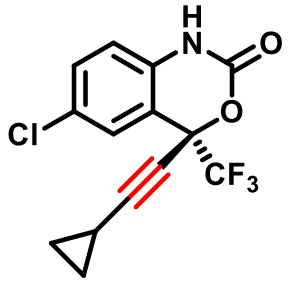


Gephyrotoxin
frog poison

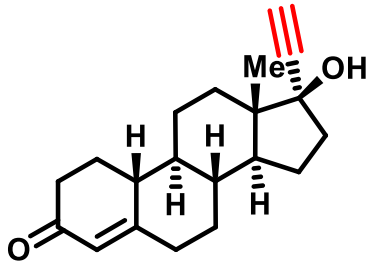
-Pharmaceuticals and agrochemicals



Terbinafine
fungicide



Efavirenz
antiretroviral



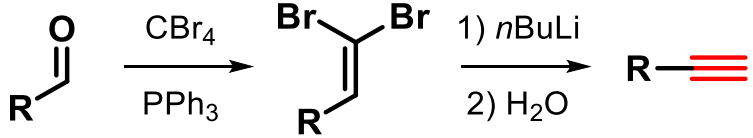
Norethisterone
birth control pills

F. Diederich, P. J. Stang, R. R. Tykwinski, *Acetylene Chemistry: Chemistry, Biology and Material Science*, Wiley-VCH, **2005**.
V. P. Ananikov, *et al. Molecules* **2018**, *23*, 2442.

Synthesis of alkynes

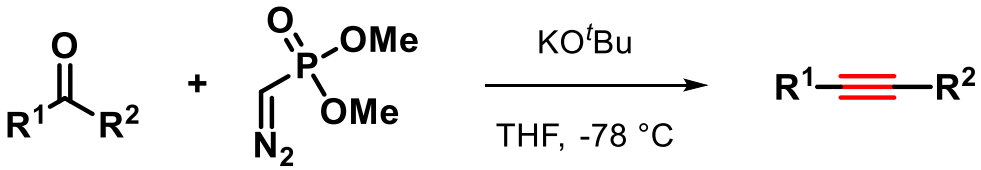
First approach

Corey-Fuchs



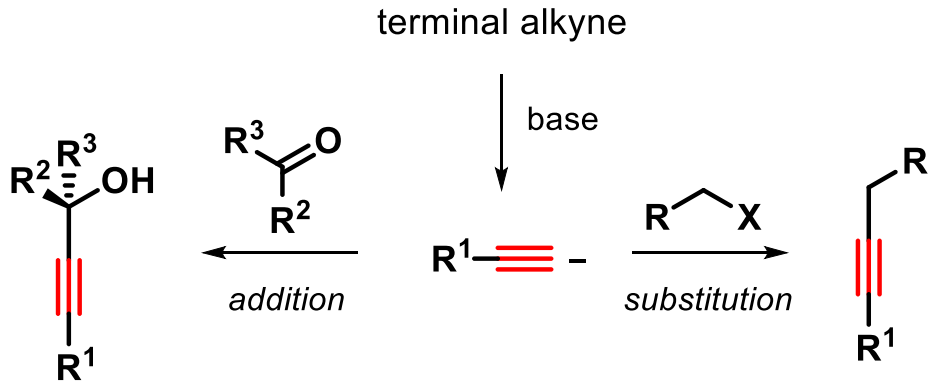
E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769.

Seyferth-Gilbert

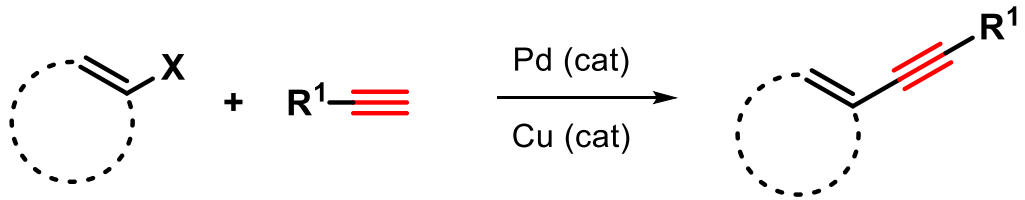


D. Seyferth, *et al. J. Org. Chem.*, **1971**, *36*, 1379.

Second approach

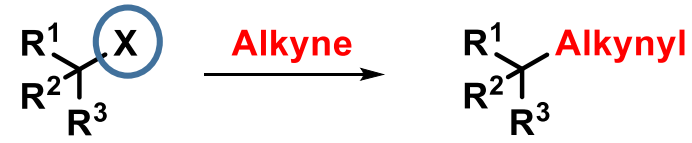


B. M. Trost, *et al. Adv. Synth. Catal.* **2009**, *351*, 963.



R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874.
V. Gevorgyan, *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 2096.

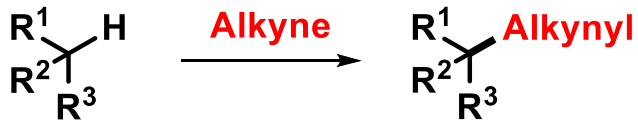
Alkynylation of C(sp^3) bonds



C(sp^3)-X

Prefuctionalization is required…

Ideal scenario

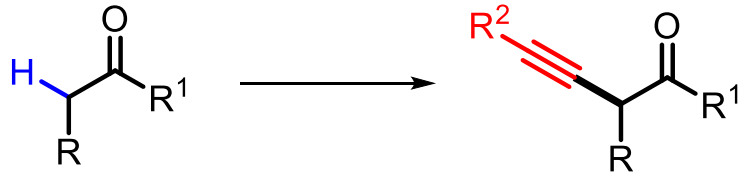


C(sp^3)-H

1. Alkynylation on activated C(sp^3)-H bonds

-Acidic proton

Carbonyl compounds → Electrophilic alkynylation

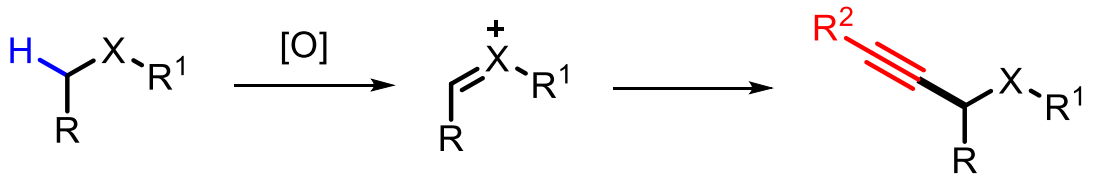


C(sp^3)-H

J. Waser, *et al. Chem. Soc. Rev.* **2012**, *41*, 4165
J. Waser, *et al. Chem. Eur. J.* **2010**, *16*, 9557

-Easily oxidizable positions

Allylic, benzylic, α to heteroatoms → Cross-dehydrogenative coupling

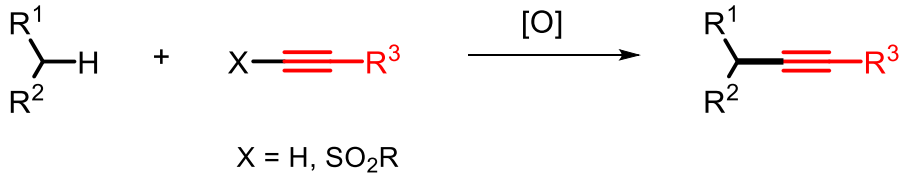


C(sp^3)-H

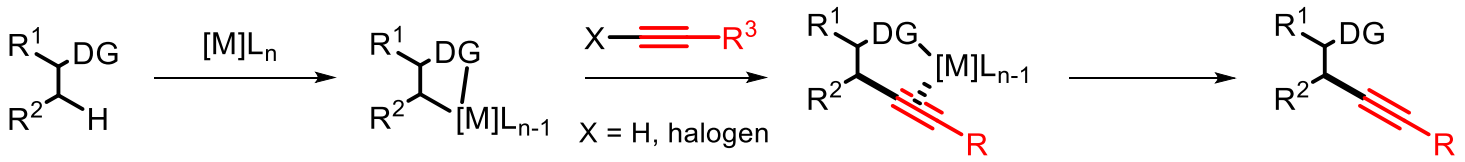
C.-J. Li, *et al. Angew Chem. Int. Ed.* **2014**, *53*, 74

2. Unactivated C(sp^3)-H bonds

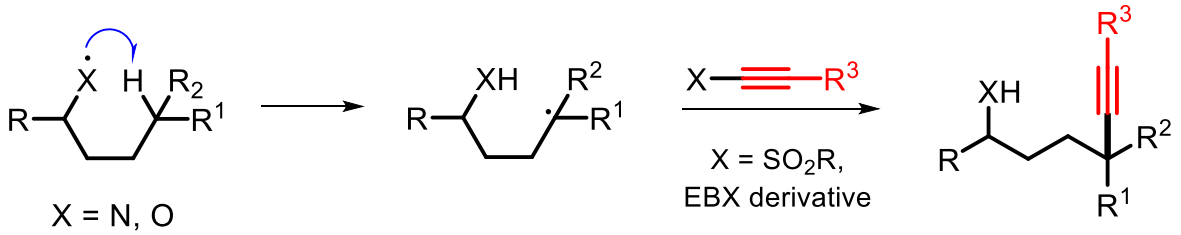
-Direct alkynylation



-Alkynylation mediated by C-H activation



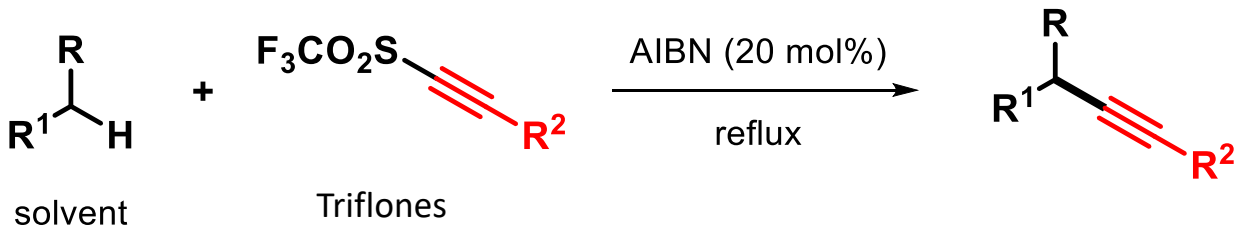
-Distal alkynylation mediated by 1,5-HAT



New C(sp^3)-H Alkynylation Reactions

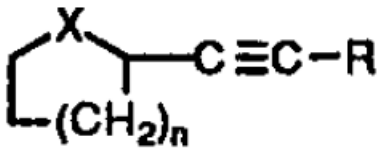
Direct Alkynylation of C(sp^3)-H Bonds

Seminal work

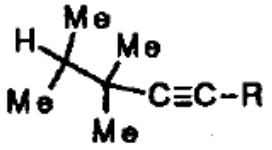


solvent

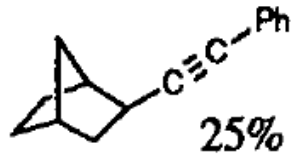
Triflones



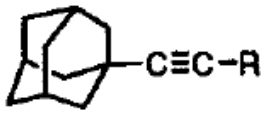
X=CH$_2$, n=1, R=Ph	63%
X=CH$_2$, n=2, R=Ph	83%
X=CH$_2$, n=2, R=n-C$_6$H$_{13}$	62%
X=CH$_2$, n=3, R=Ph	64%



R=Ph 78%
R=n-C$_6$H$_{13}$ 49%



25%



R=Ph 60%
R=n-C$_6$H$_{13}$ 40%*

Advantages:

-Moderate to good yields

-Saturated heterocycles, Et_2O and DCE were also alkynylated

-Triflones are easily synthesized

-Metal-free protocol

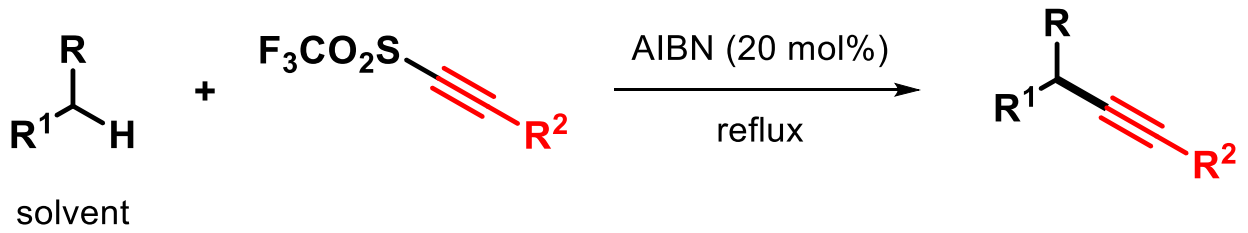
-Aromatic and aliphatic alkynes

Disadvantages:

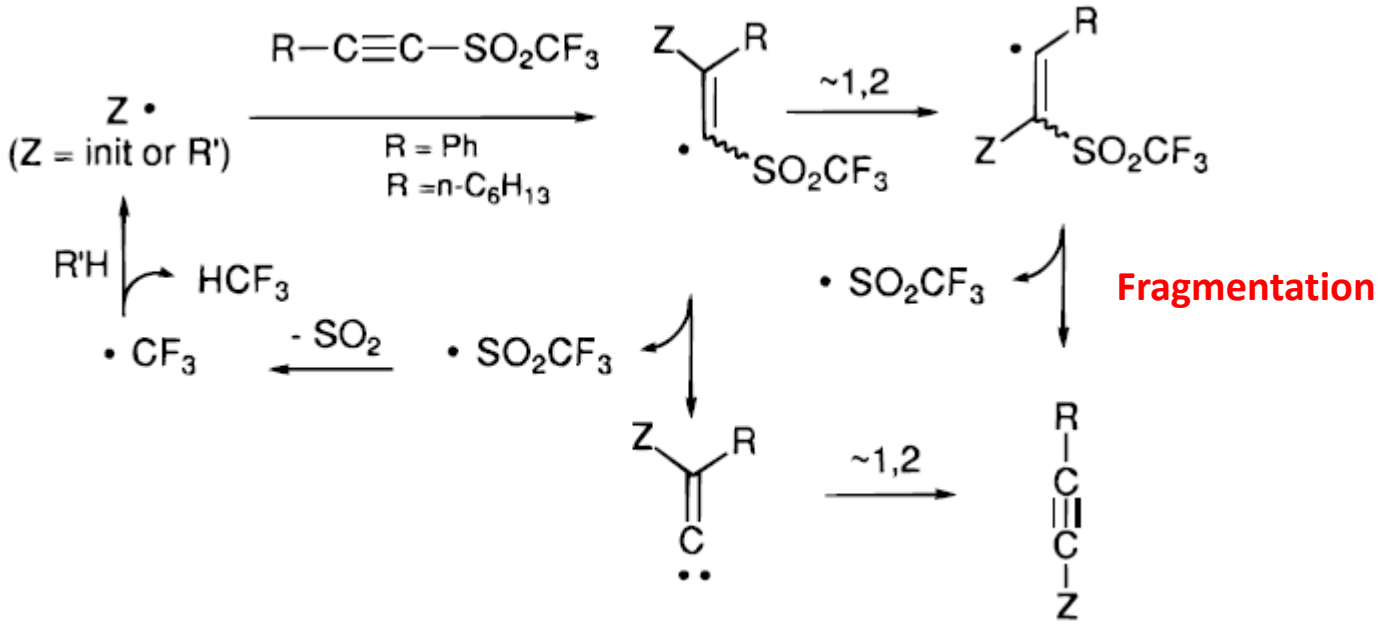
-Few examples

-Large excess of the alkane

P.-L. Fuchs, *et al. J. Am. Chem. Soc.* **1996**, *118*, 4486.

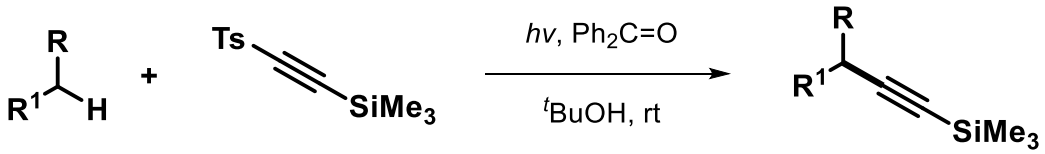


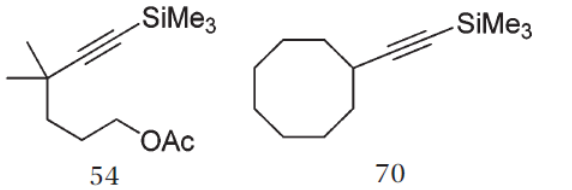
Mechanism

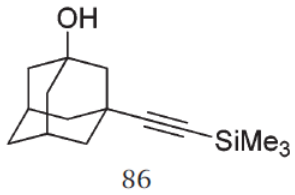


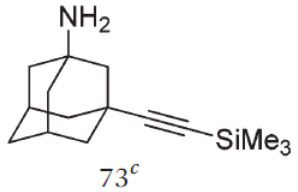
Fritch-Buttenberg-Weichell rearrangement

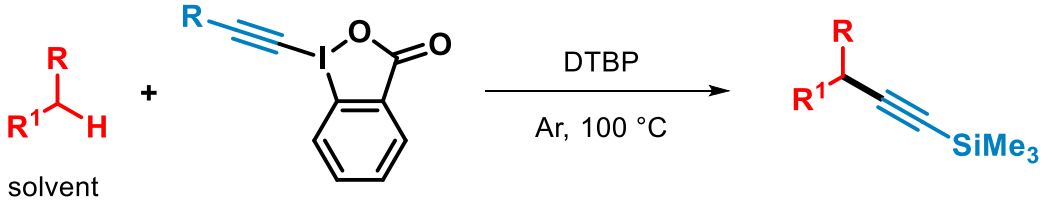
P.-L. Fuchs, *et al. J. Am. Chem. Soc.* **1996**, *118*, 4486.

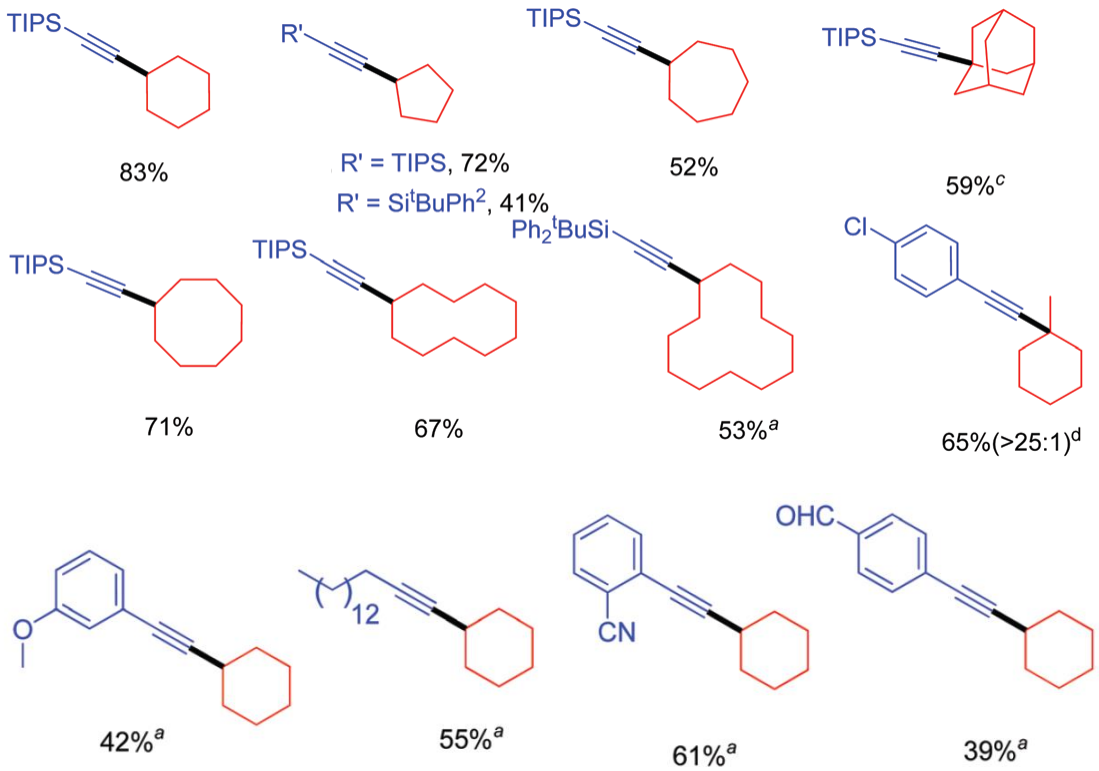












Advantages:

-Good to high yields

-Metal-free protocols

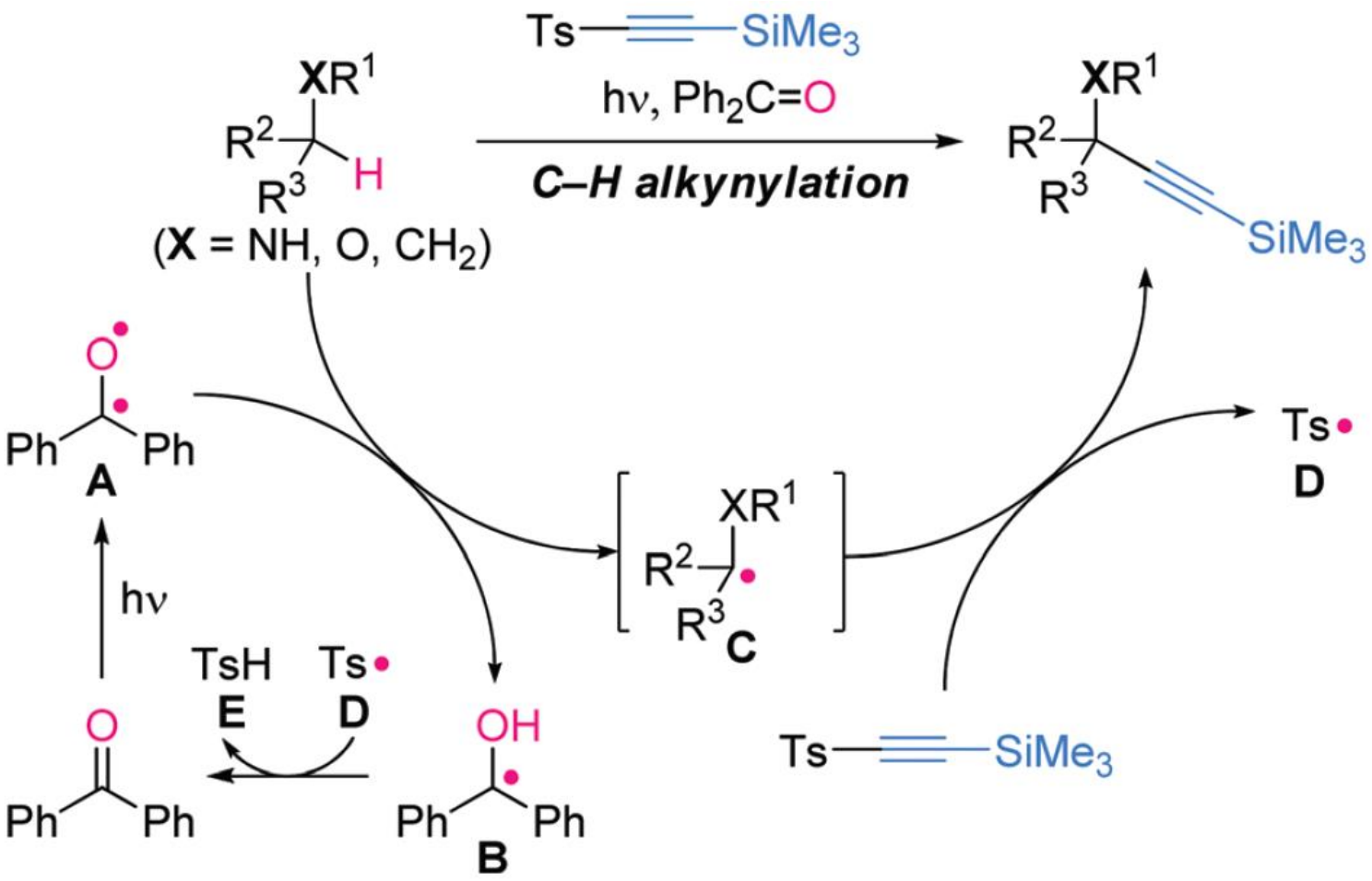
-Predictable regioselectivity

Disadvantages:

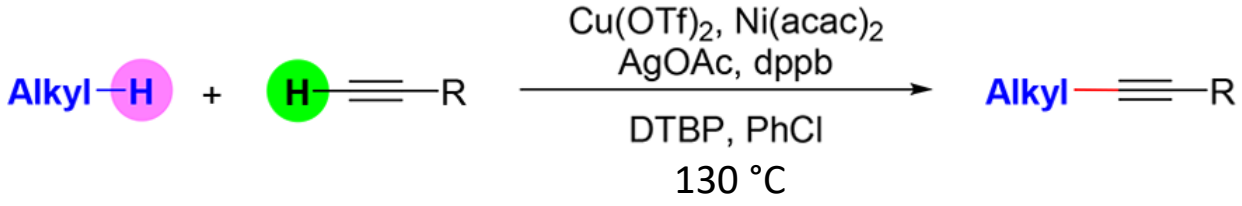
-Large excess of the alkanes

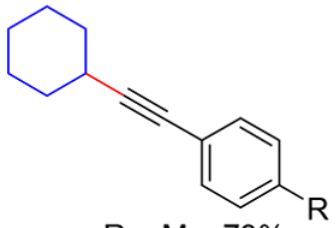
Photochemical reaction: M. Inoue, *et al. Org. Biomol. Chem.* **2013**, *11,* 164.
Hypervalent iodine: H.-J. Xu, *et al. Green Chem.* **2016**, *18*, 4185.

Mechanism

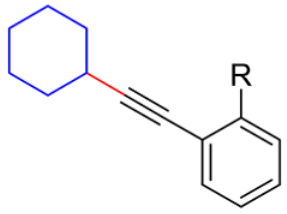


M. Inoue, *et al. Org. Biomol. Chem.* **2013**, *11,* 164.

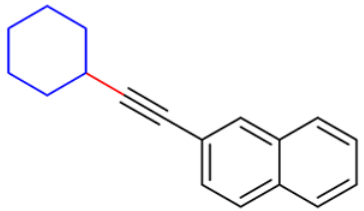




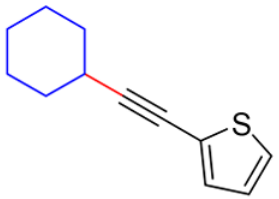
R = Me, 73%
R = OMe, 91%
R = $^{n}C_5H_{11}$, 83%
R = F, 61%
R = Cl, 78%
R = Br, 65%
R = Ac, 50%
R = COOMe, 65%



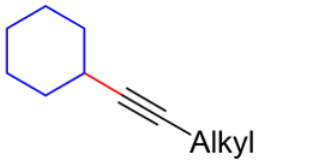
R = Me, 76%
R = Cl, 71%



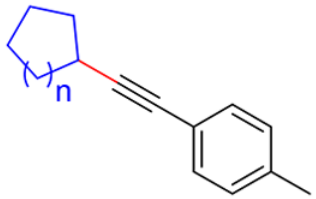
66%



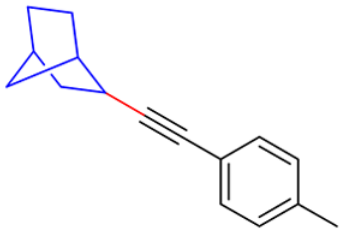
69%



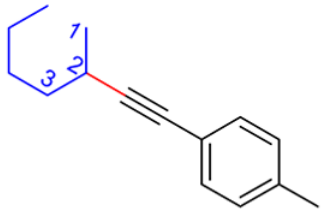
Alkyl = $^{n}C_5H_{11}$, 63%
Alkyl = Cy, 86%



n = 1, 52%
n = 3, 44%



49%



47%
[C(1):C(2):C(3) = 3:6:2]

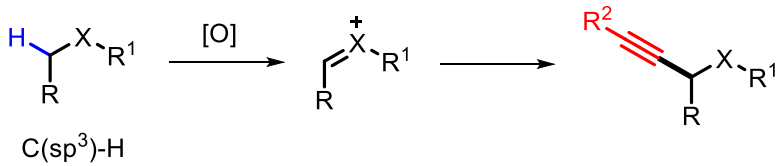
Advantages:

-Good chemical yields
-Terminal alkynes were used
-Catalyst are not expensive

Disadvantages:

-Regioselectivity issues in linear alkanes
-Large excess of alkane

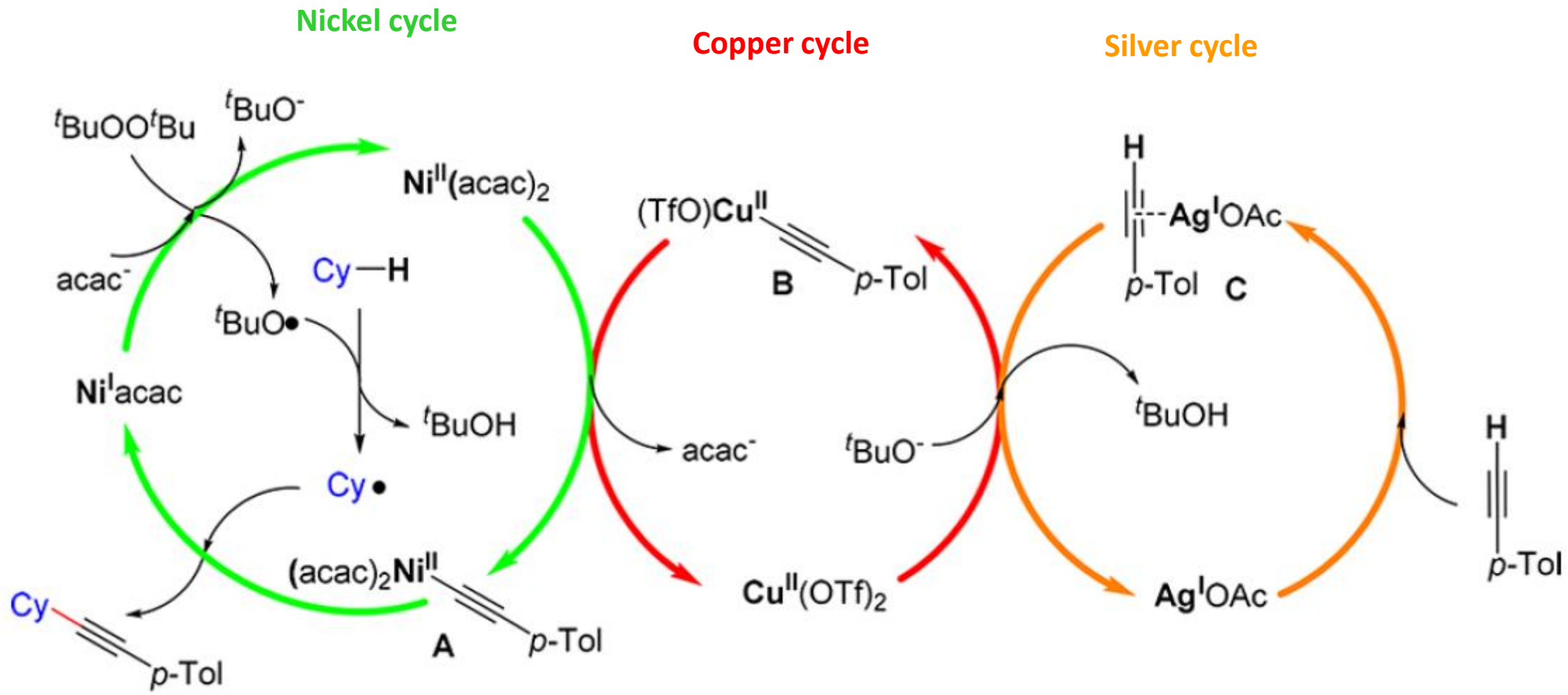
Alternative to CDC



C(sp^3)-H

Aiwen Lei, *et al. Nat. Commun.* **2016**, *7*, 11676.
Aiwen Lei, *et al. J. Am. Chem. Soc.* **2018**, *140*, 6006.

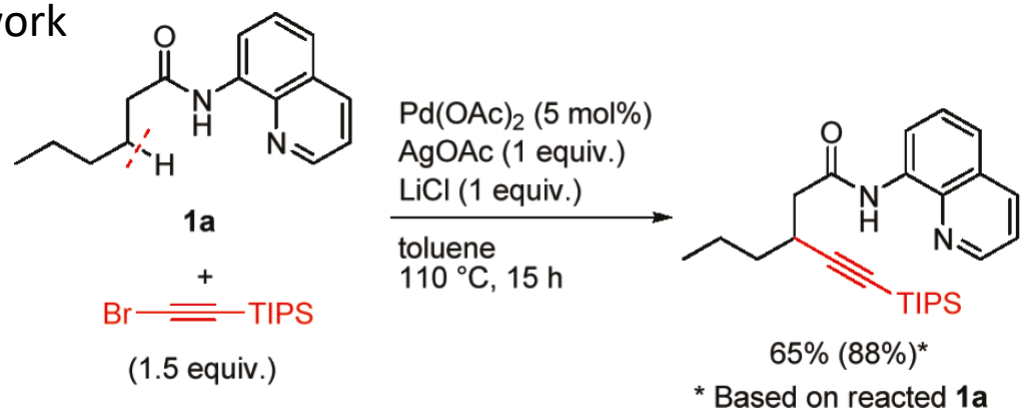
Mechanism



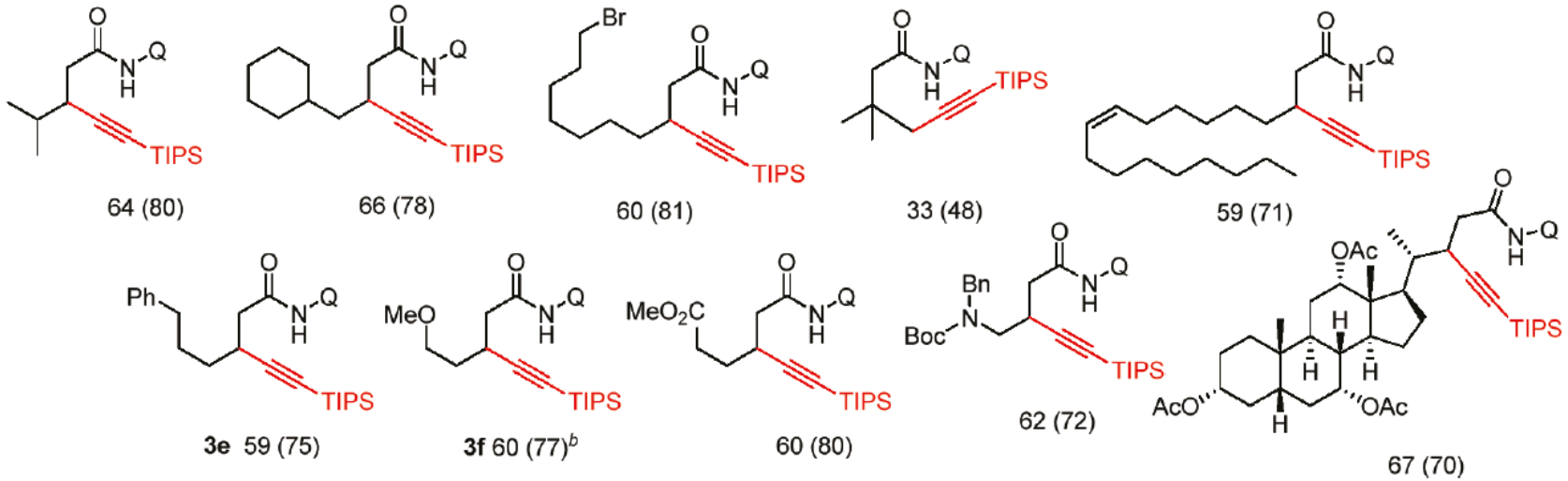
Aiwen Lei, *et al. Nat. Commun.* **2016**, *7*, 11676.
Aiwen Lei, *et al. J. Am. Chem. Soc.* **2018**, *140*, 6006.

Alkynylation through C(sp³)-H Activation

Seminal work

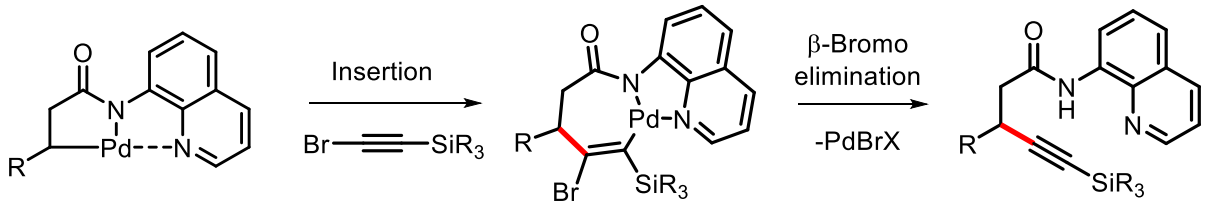


Advantages:
-Tolerant to several functionalities
-γ-Position was also alkynylated
-Quinoline scaffold is easily detachable

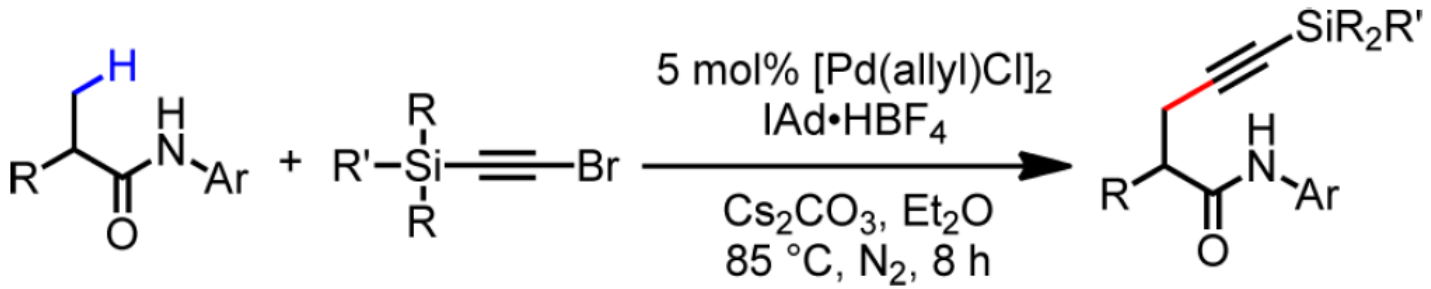


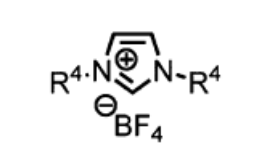
Limitations:
-Mostly on secondary carbons
-No full conversion

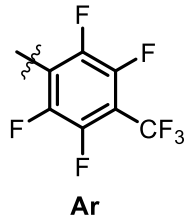
Mechanism

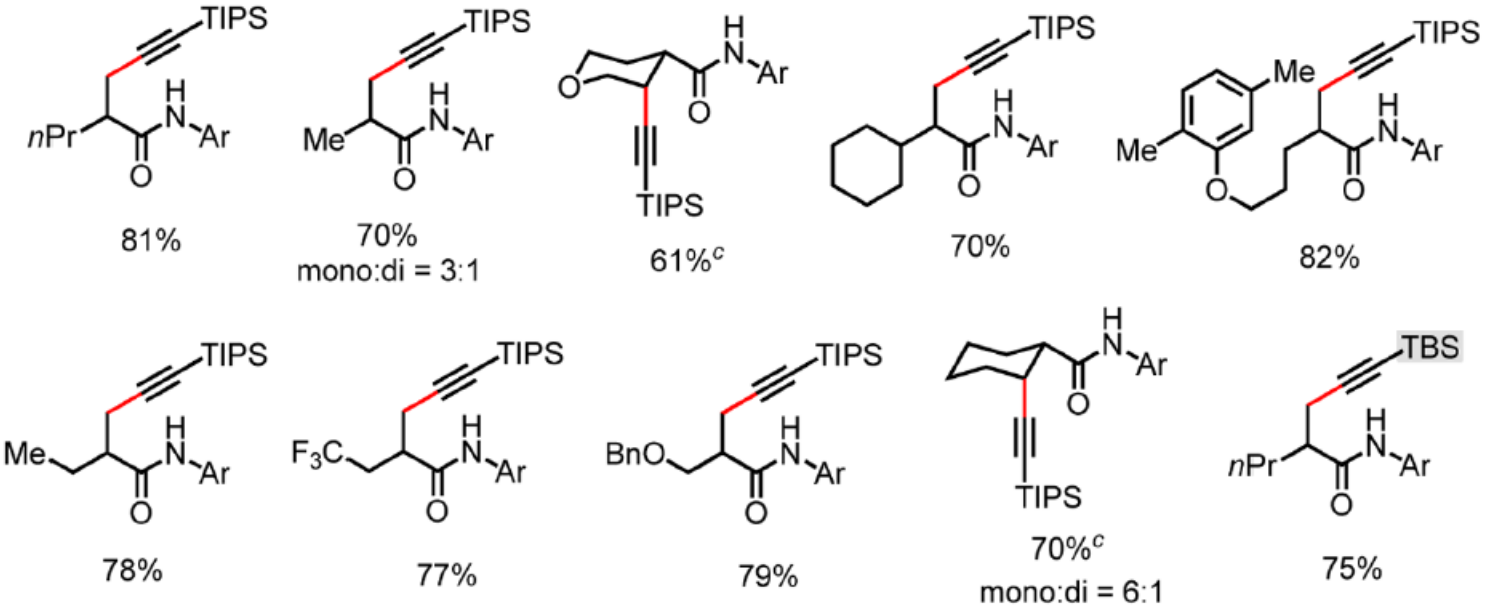


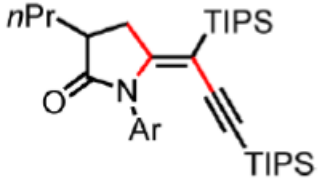
N. Chatani, *et al. J. Am. Chem. Soc.* **2011**, *133*, 12984.







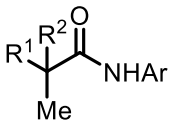




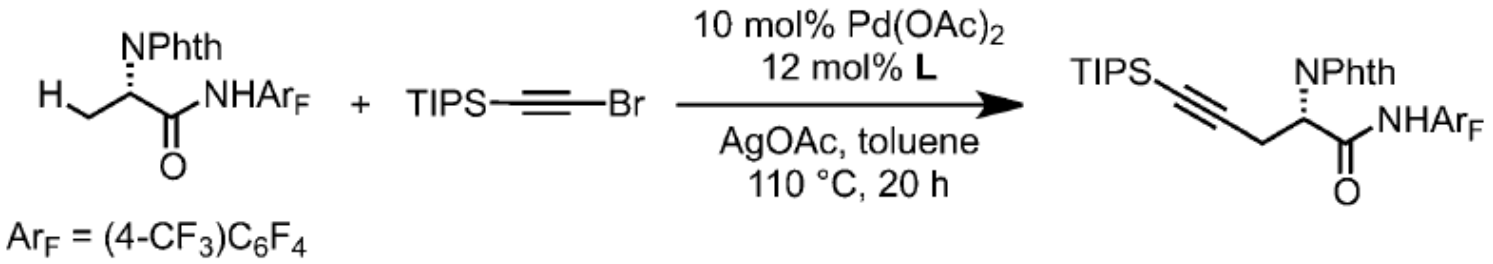
Side product detected during optimization

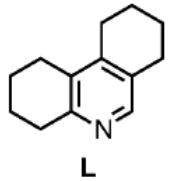
Advantages:
-Broad scope and good yields (primary over secondary carbons)
-Oxidant is not required

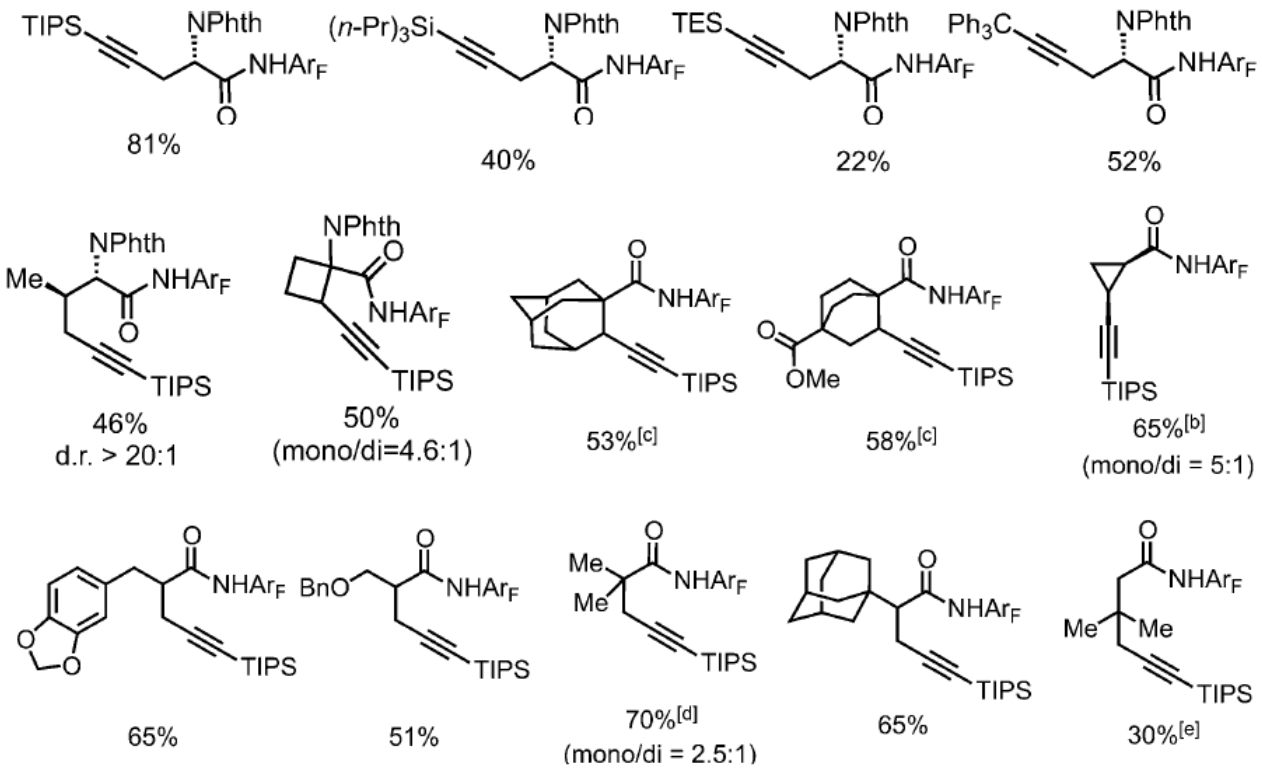
Limitations:
-Amides possessing a quaternary carbon at C-2 gave poor yields



J.-Q. Yu, *et al. J. Am. Chem. Soc.* **2013**, *135*, 3387.







Advantages:

-Broader scope and good yields (primary and secondary carbons)

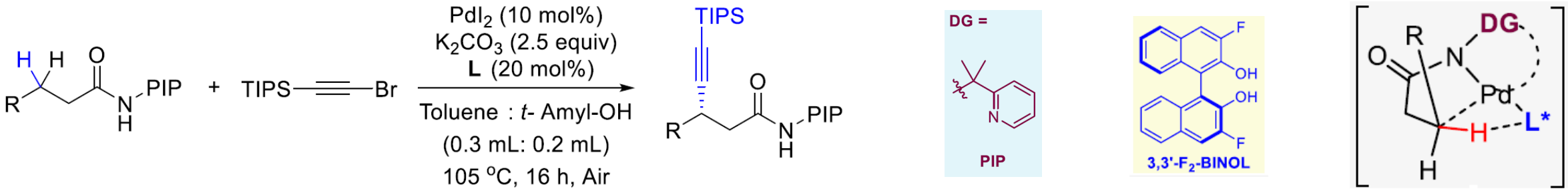
-Amides possessing a quaternary carbon at C-2

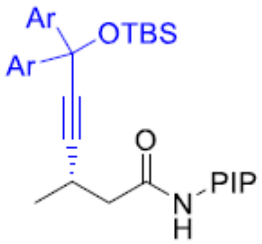
-Alkynylation at C-3 position is feasible

Limitations:

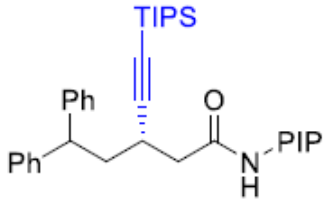
-Reaction conditions are not the same for each substrate

J.-Q. Yu, *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 1873.

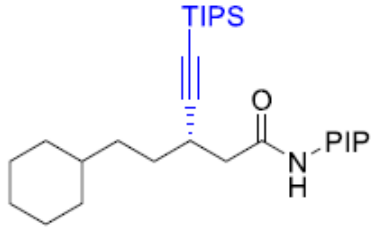




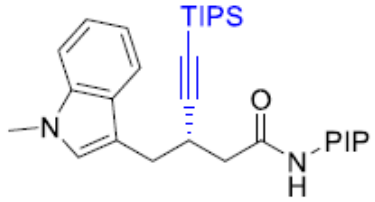
Ar = Ph, 64% yield, 94% ee
Ar = *p*-MeC_6H_4, 55% yield, 90% ee
Ar = *p*-ClC_6H_4, 61% yield, 95% ee



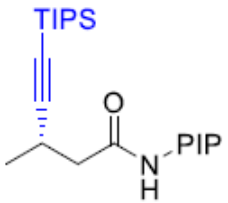
81% yield, 90% ee



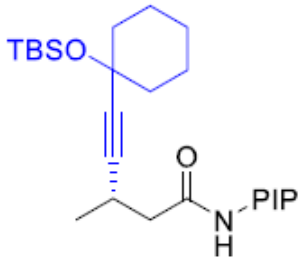
73% yield, 93% ee



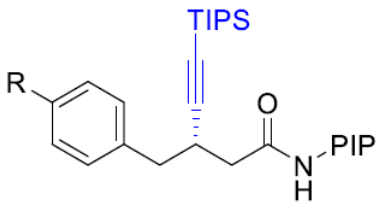
43% yield, 93% ee



70% yield, 96% ee



66% yield, 88% ee



3n, R=H, 78% yield, 96% ee
3o, R=Cl, 84% yield, 94% ee
3p, R=Br, 80% yield, 95% ee
3q, R=Me, 76% yield, 95% ee
3r, R=NO_2, 58% yield, 96% ee
3s, R=F, 84% yield, 96% ee

Remarks:

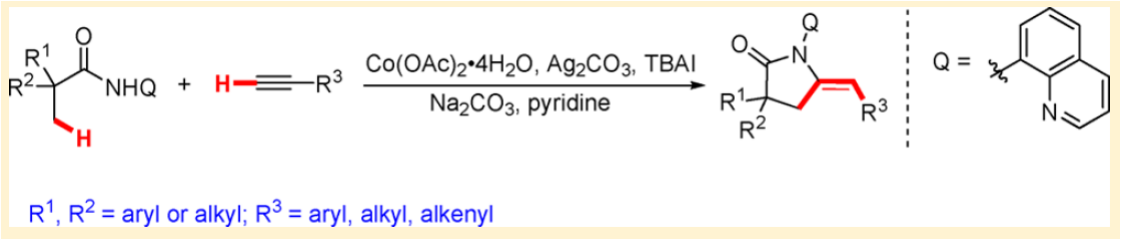
-First enantioselective C(sp^3)-H alkynylation

-BINOL was crucial in for both the reactivity and enantioselectivity

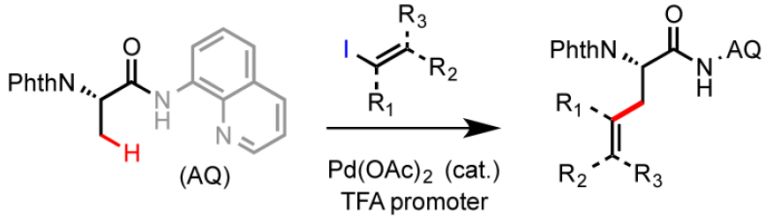
B.-F. Shi, *et al. J. Am. Chem. Soc.* **2019**, *141*, 4558.

Other remarkable works on this field:

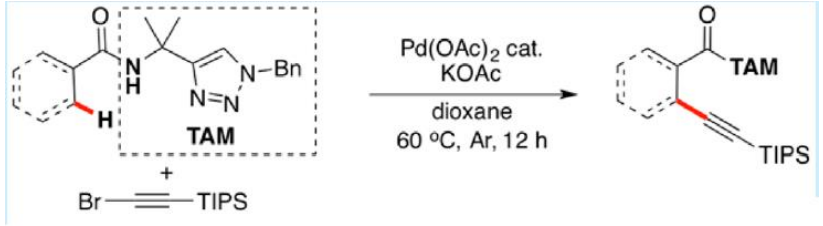
1. Y. Zhang, *et al. J. Am. Chem. Soc.* **2015**, *137*, 12990



2. G. Chen, *et al. Org. Lett.* **2014**, *16*, 6260

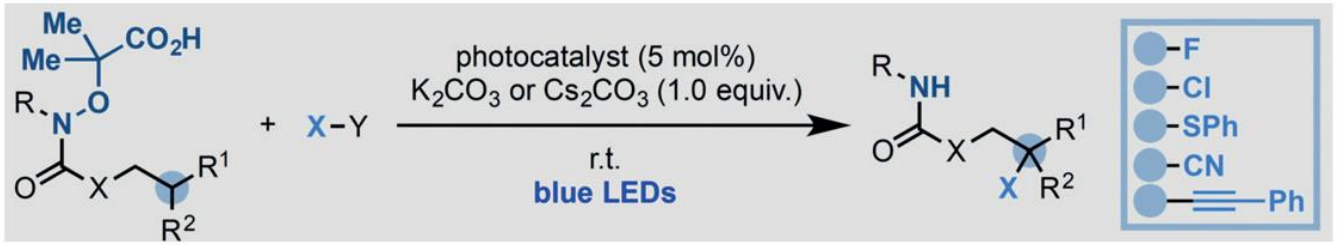


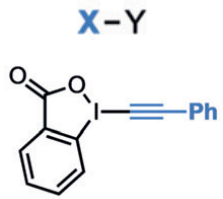
3. X. Shi, *et al. Org. Lett.* **2016**, *18*, 2970

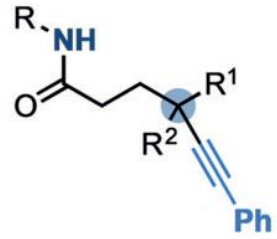


Seminal work

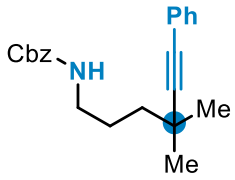
Distal Alkynylation Based on 1,5-HAT



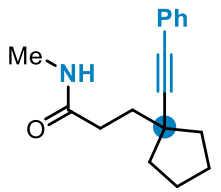




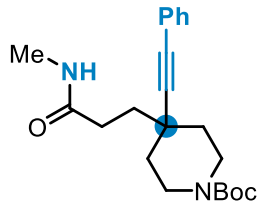
R	R^1	R^2	Yield (%)
Me	Me	Me	80
Me	Me	H	65
Me	Ph	H	–
Bn	Me	Me	30
H	Me	Me	28



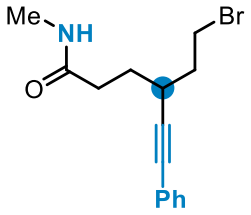
52%



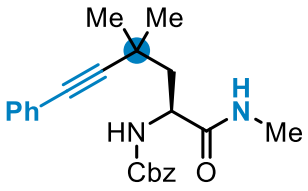
76%



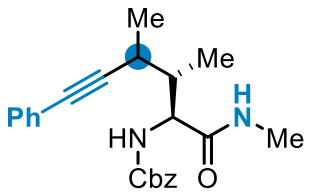
79%



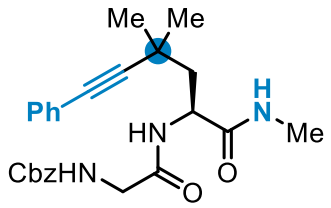
58%



47%



54%, 2:1 dr



65%

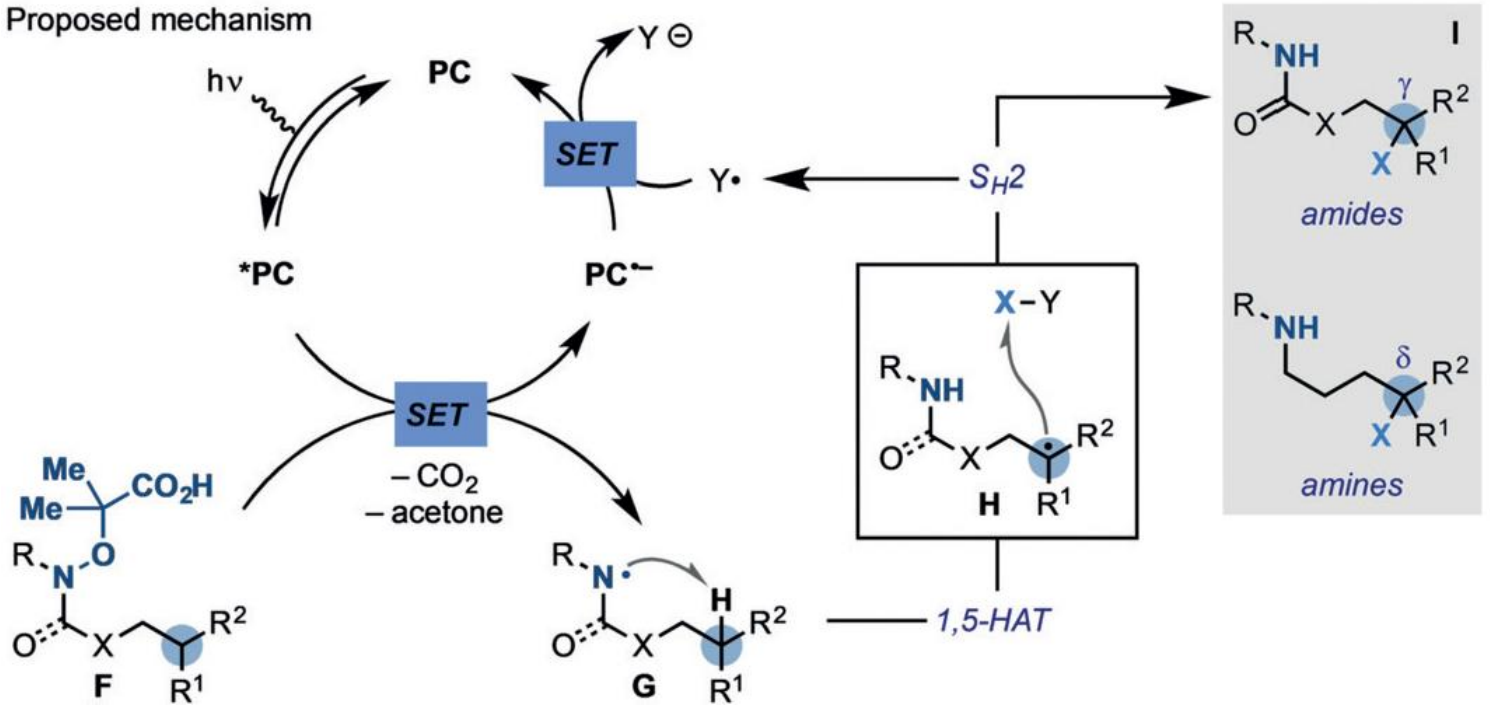
Advantages:

-Carbamoyl and amidyl radicals performed well
-Broad FG tolerance
-Functionalization of secondary and tertiary positions
-Good yields

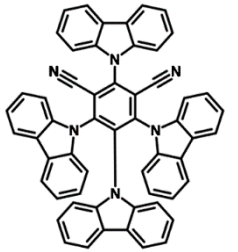
Limitations:

-Functionalization in a benzylic position failed
-Only phenyl acetylene moiety was installed

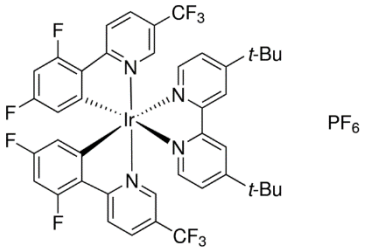
D. Leonori, *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12945.



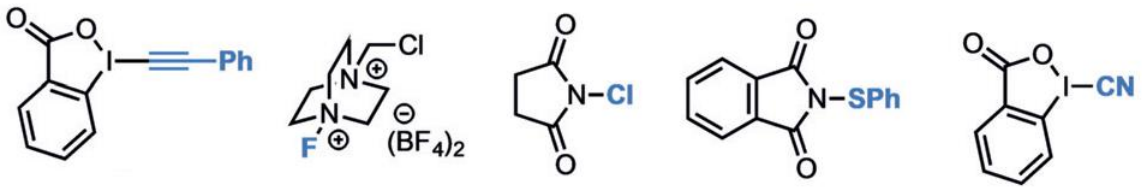
PCs



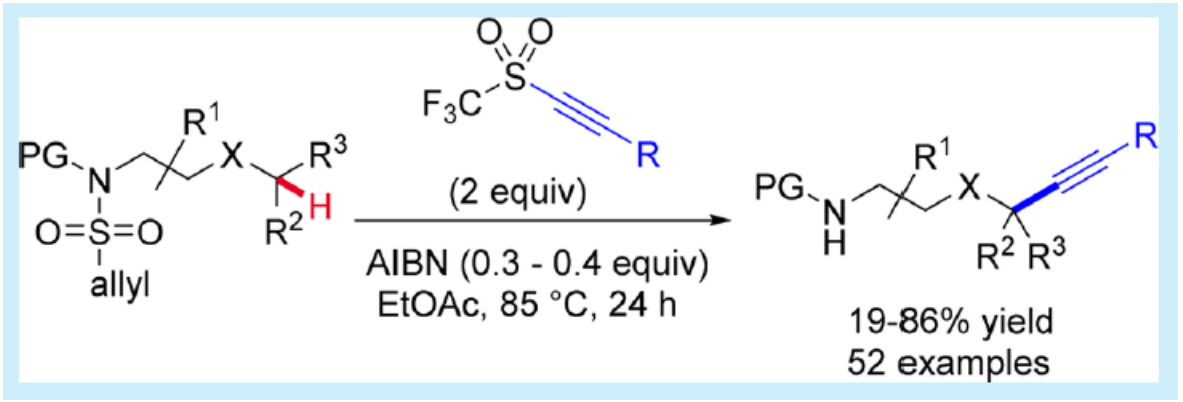
4CzIPN



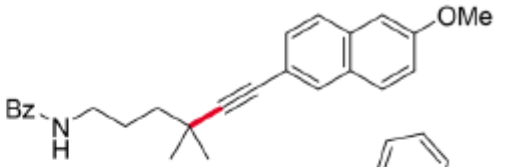
X–Y



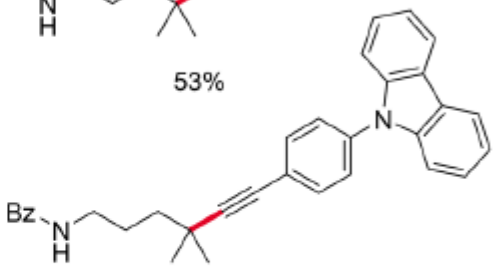
D. Leonori, *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12945.



78% (R = H)
72% (R = OMe)
70% (R = *t*-Bu)
74% (R = *n*-Hex)
85% (R = CF_3)
85% (R = F)
81% (R = Cl)
80% (R = Br)

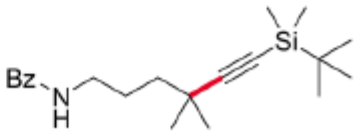


53%



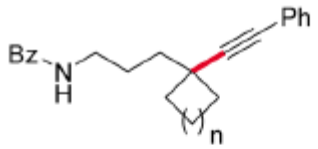
47%

36%

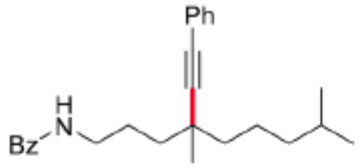


45%

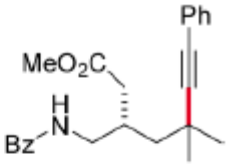
-Aromatic and aliphatic alkynes



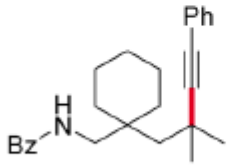
83% (n = 1)
72% (n = 2)
65% (n = 3)



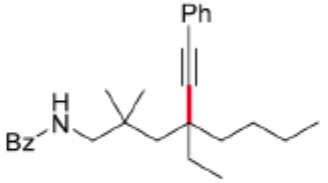
81%



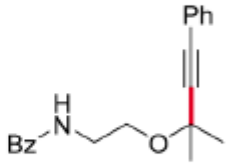
56%



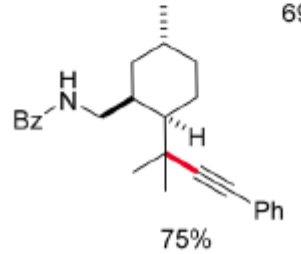
60%



66%



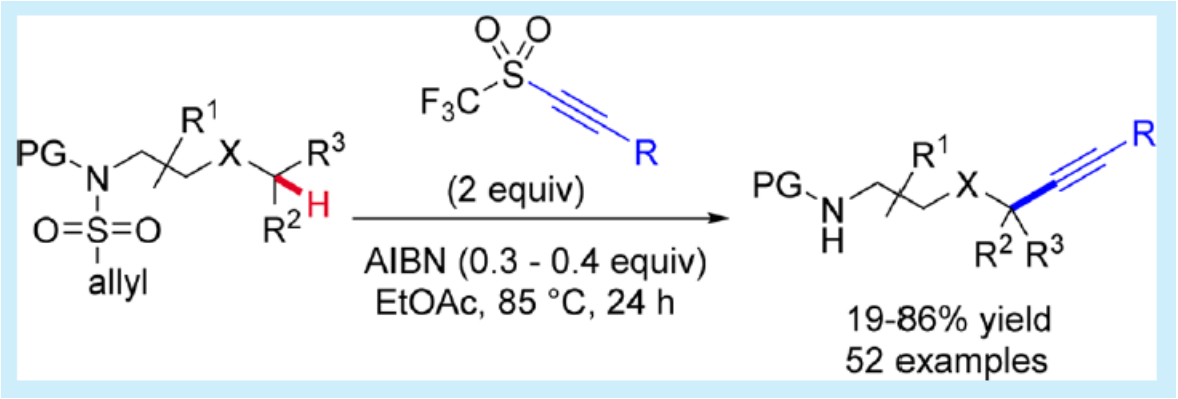
69%

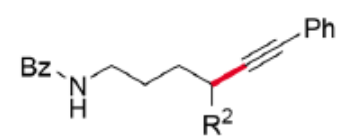


75%

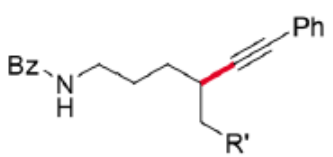
-Tertiary carbons

A. Studer, *et al. Org. Lett.* **2018**, *20*, 5817.

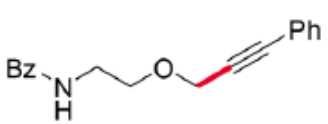




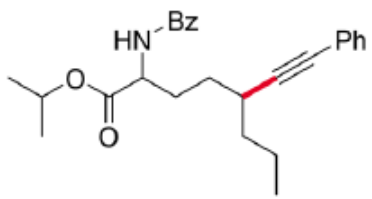
59% (R^2 = Me)
61% (R^2 = Et)
70% (R^2 = *n*-hexyl)
49% (R^2 = Ph)



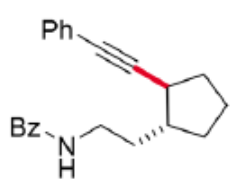
63% (R' = Cl)
70% (R' = OTBS, *rr* = 1:1.2)
56% (R' = CO_2Me)



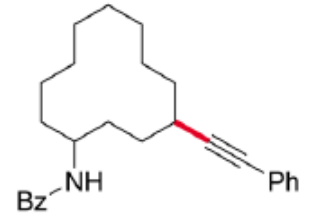
57%



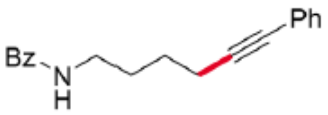
66% (*dr* = 1:1)



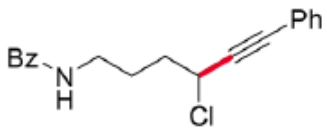
60% (*dr* = 7:1)



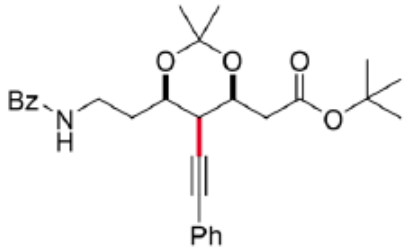
53% (*dr* = 1:1)



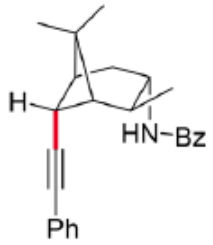
19%



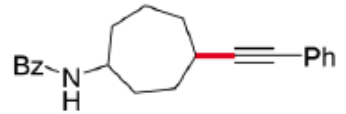
54%



39% (*dr* = 1.3:1)



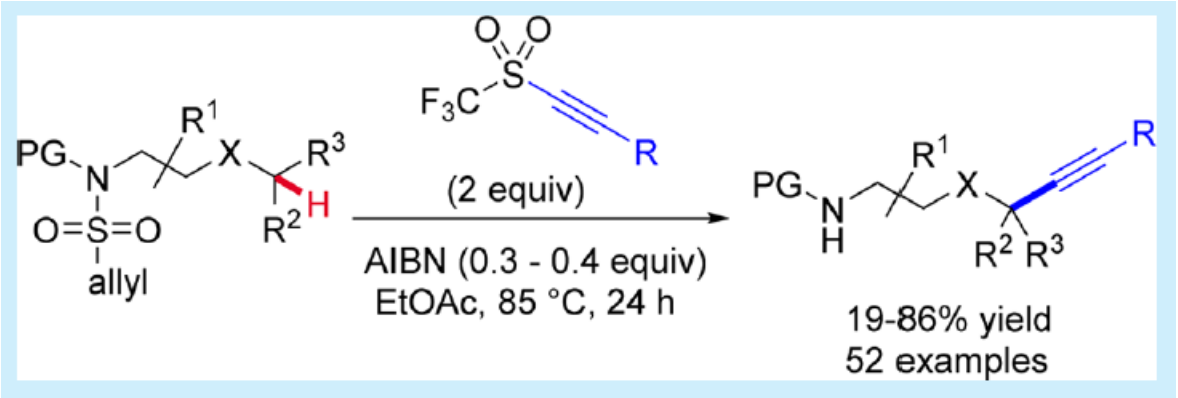
51% (*dr* > 98:2)



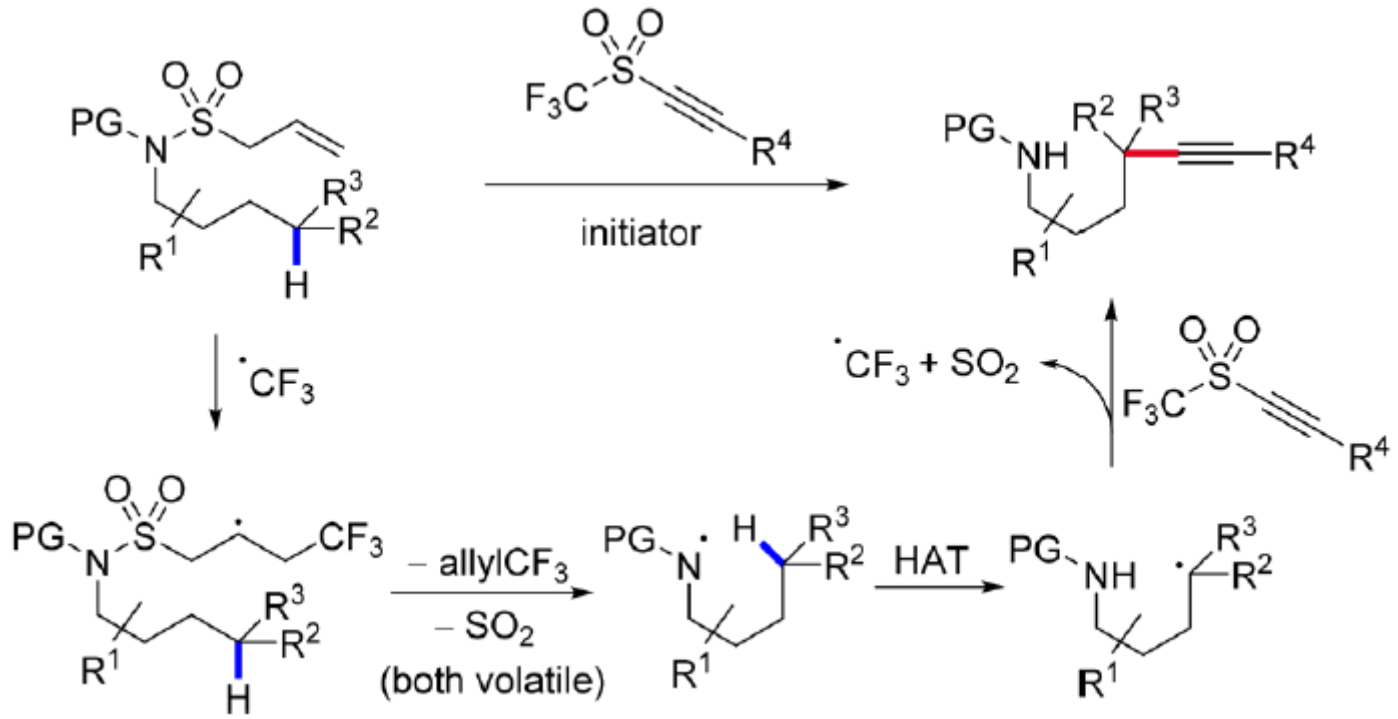
67% (*dr* = 1:1)

-Secondary and primary carbons

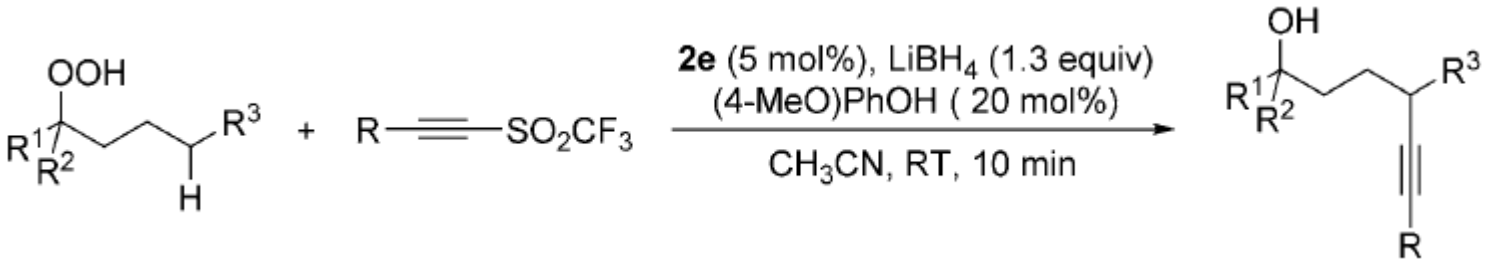
A. Studer, *et al. Org. Lett.* **2018**, *20*, 5817.

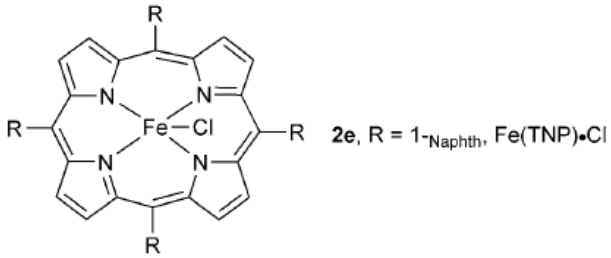


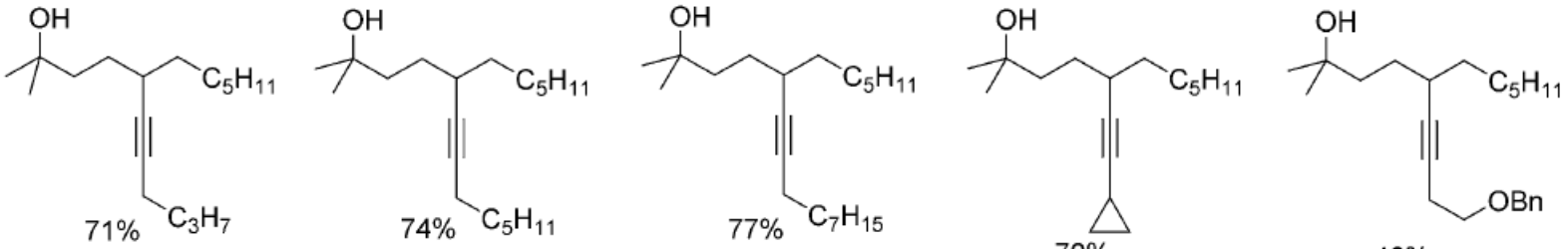
Mechanism

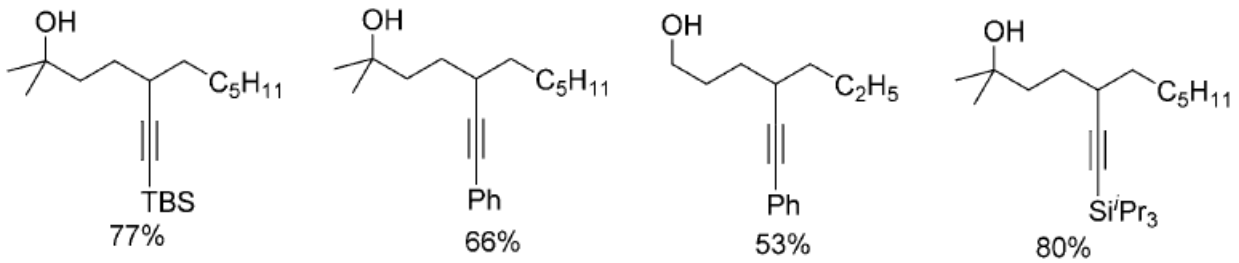


A. Studer, *et al. Org. Lett.* **2018**, *20*, 5817.









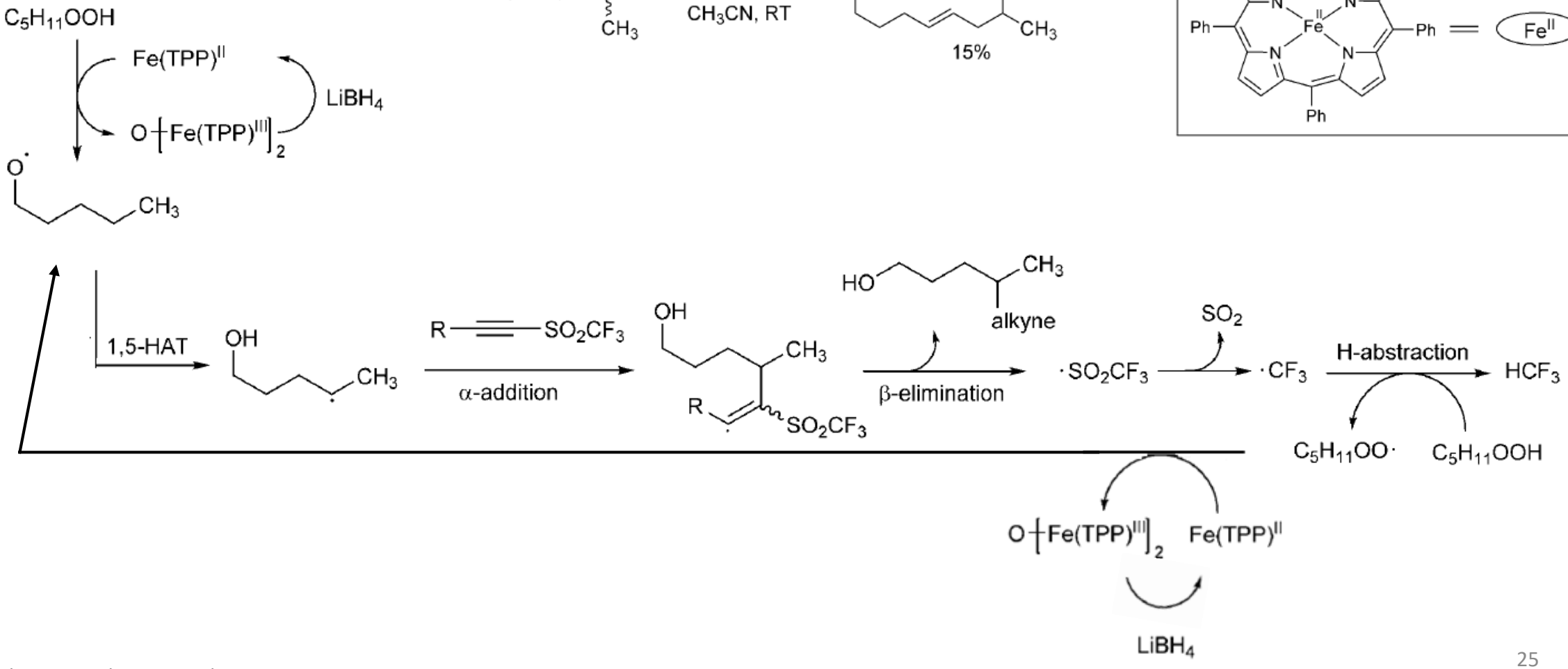
Other performed functionalizations:

Chlorination (TsCl)
Amination (DEAD)
Fluorination (NFSI)

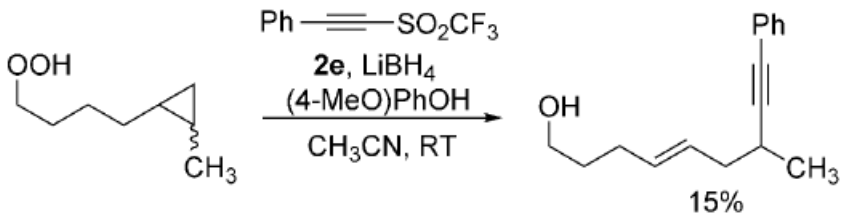
-Aliphatic or aromatic alkynes
-Primary and tertiary hydroperoxides

L. Liu, *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 11413.

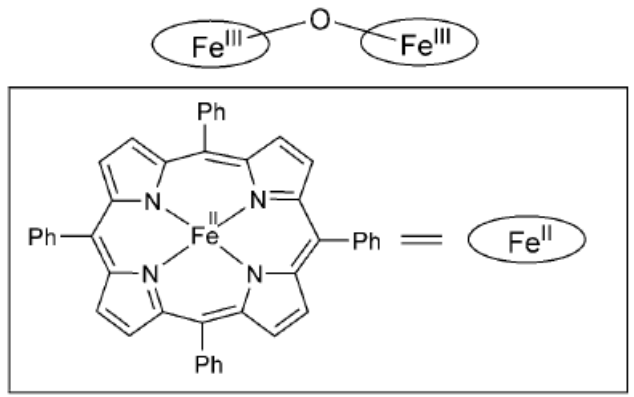
Mechanism



Clock experiment



Real catalytic specie



L. Liu, *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 11413.

Conclusions

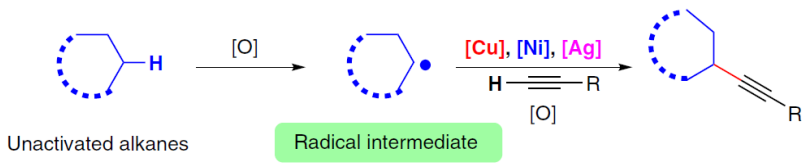
New C(sp^3)-H/alkynylation reactions on unactivated positions

- -Direct alkynylation
- -Mediated by C-H activation
- -Mediated by 1,5-HAT

→ Supplementary to other well-established procedures

-Good chemical yields

-Terminal alkynes can be used



-High enantioselectivities are feasible