Literature Report VI

Radical-Mediated Difunctionalization of Unactivated Alkenes *via* Docking-Migration Mode

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Checker: Yi-Xuan Ding
Date: 2020-10-26

Zhu, C. *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 8195.

CV of Prof. Chen Zhu

Education and Employment:

☐ **1999–2003** B.S., Xiamen University

☐ **2003–2008** Ph.D., Shanghai Institute of Organic Chemistry

☐ **2008–2009** Postdoc., Gakushuin University

☐ **2009–2013** Postdoc., The University of Texas Southwestern Medical Center

☐ **2013–Now** Professor, Soochow University

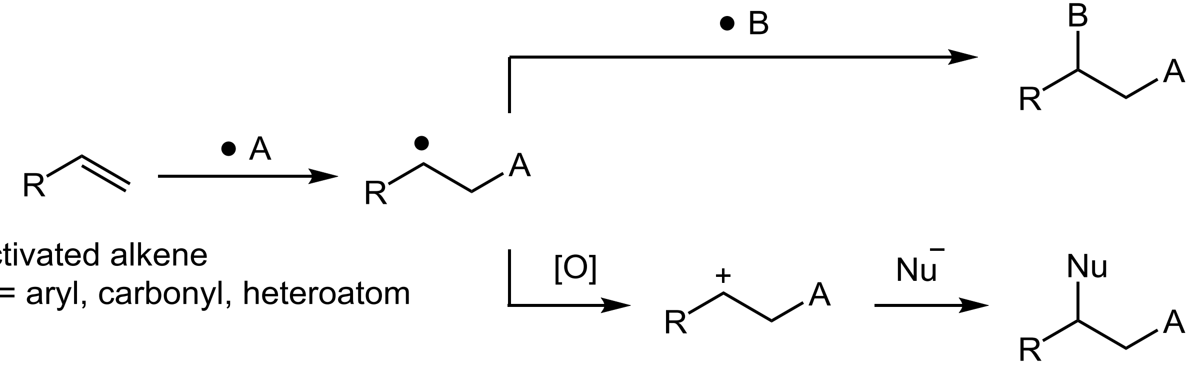
Research Interests:

➢ Radical chemistry, rearrangement reactions, ring-opening reactions, functional group migration, C-C activation, C-H activation.

Contents

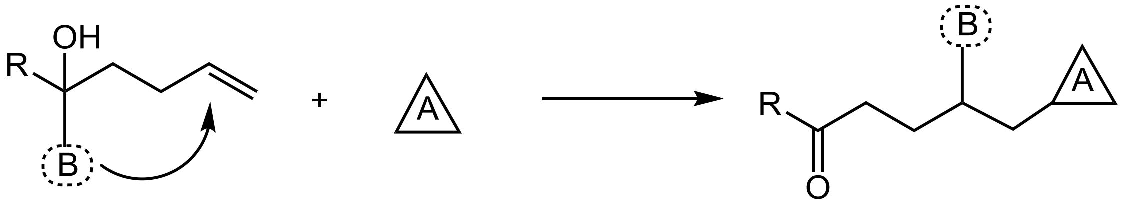
Introduction

General protocols:



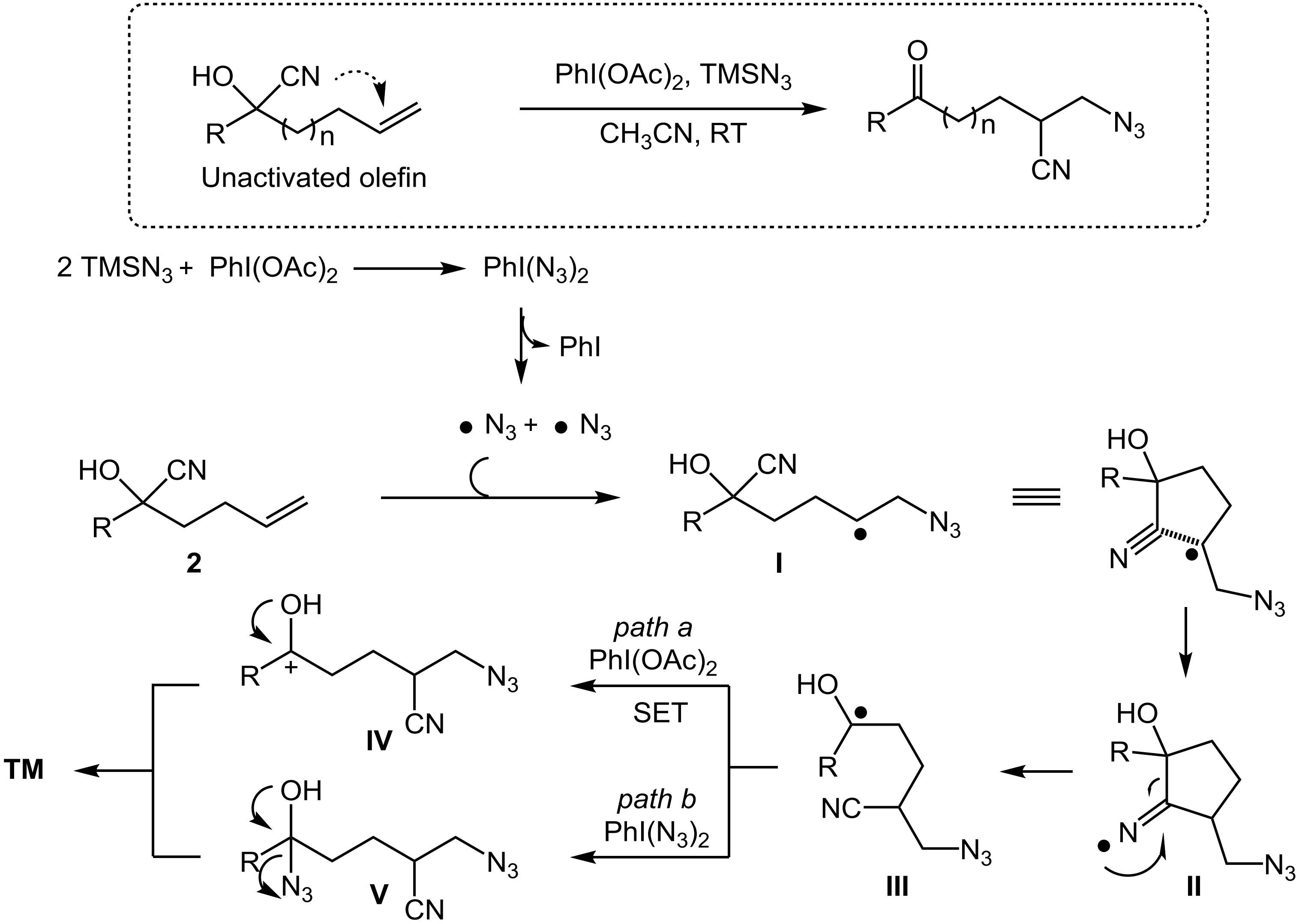
Activated alkene
R = aryl, carbonyl, heteroatom

Intramolecular migration mode:



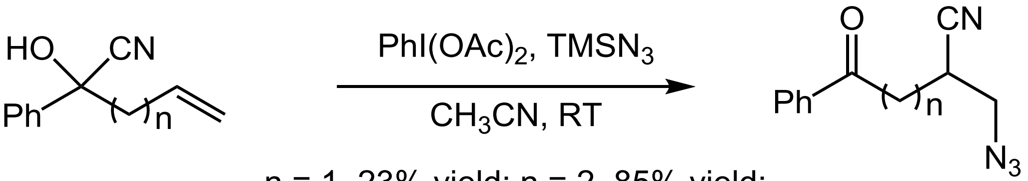
Unactivated alkene

Introduction-cyano migration



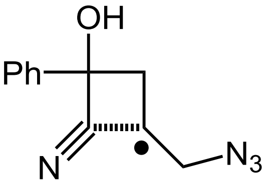
Zhu, C. *et al. Angew. Chem. Int. Ed.* **2016**, *55,* 10821.

Introduction-cyano migration

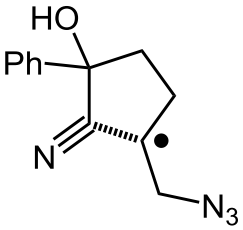


n = 1, 23% yield; n = 2, 85% yield;
n = 3, 66% yield; n = 4, <5% yield.

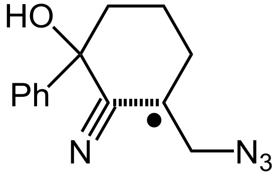
Migration transition-state



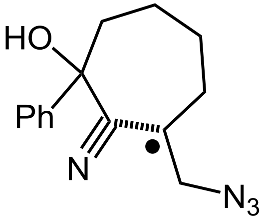
Four-membered
ring
Disfavored



Five-membered
ring
Favored



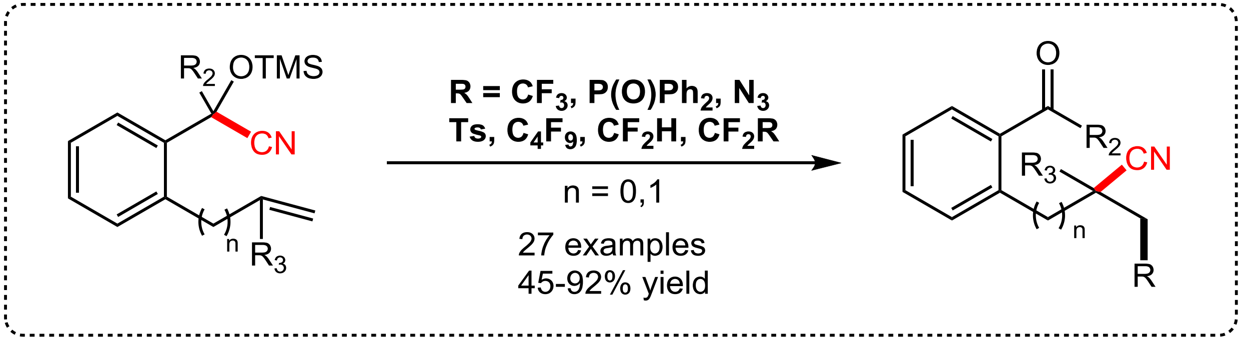
Six-membered
ring
Favored



Seven-membered
ring
Disfavored

Zhu, C. *et al. Angew. Chem. Int. Ed.* **2016**, *55,* 10821.

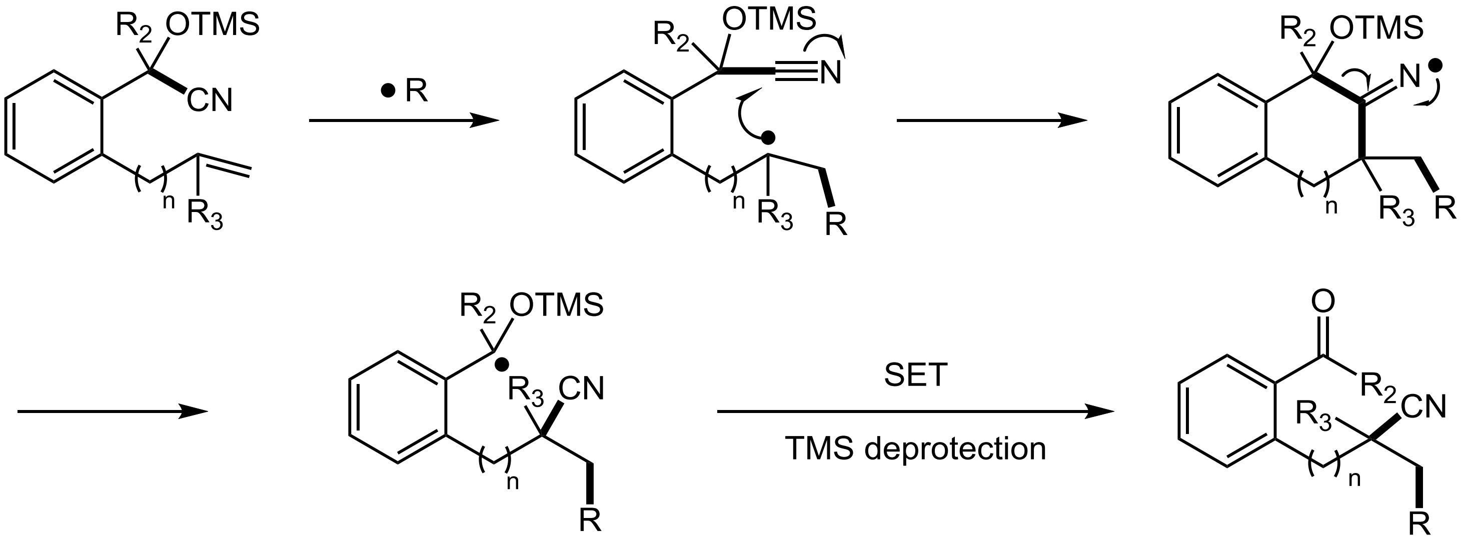
Introduction-cyano migration



R = CF_3, $P(O)Ph_2$, N_3
Ts, C_4F_9, CF_2H, CF_2R

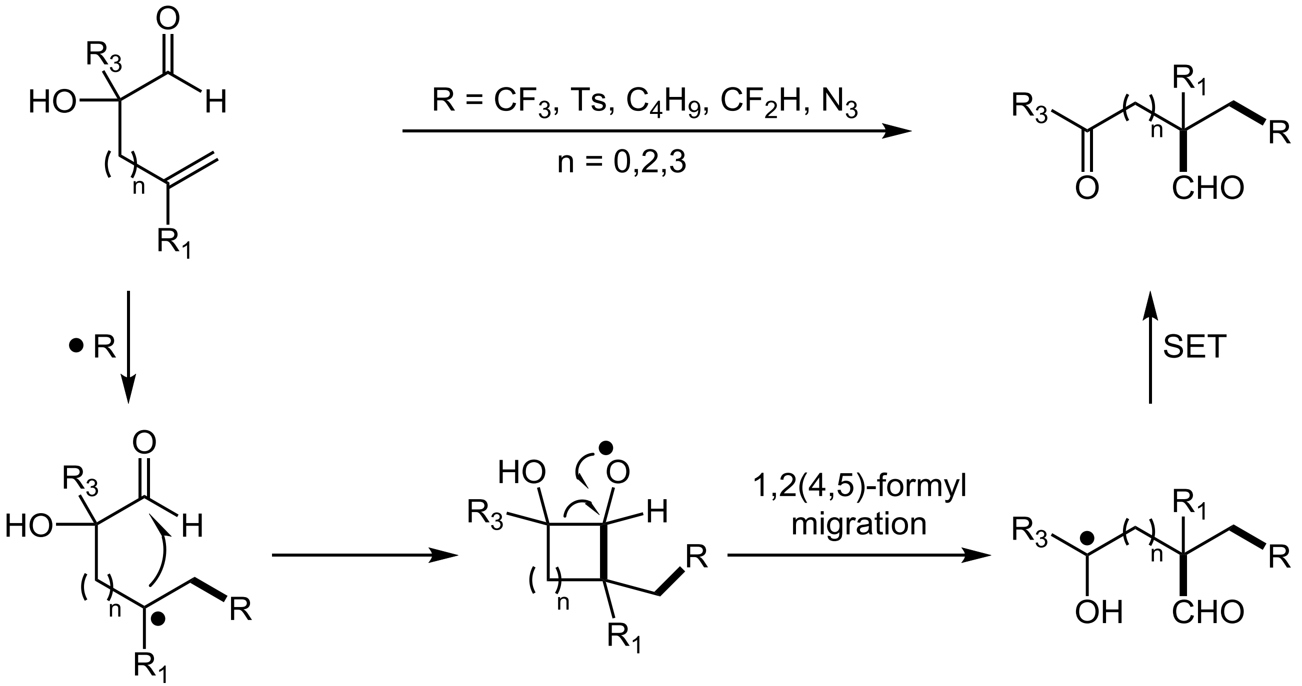
n = 0,1

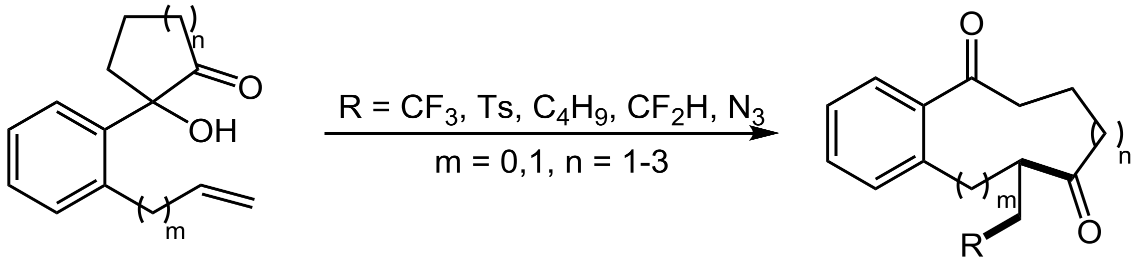
27 examples
45-92% yield



Liu, X.-Y. *et al. Org. Lett.* **2016**, *18,* 6026.

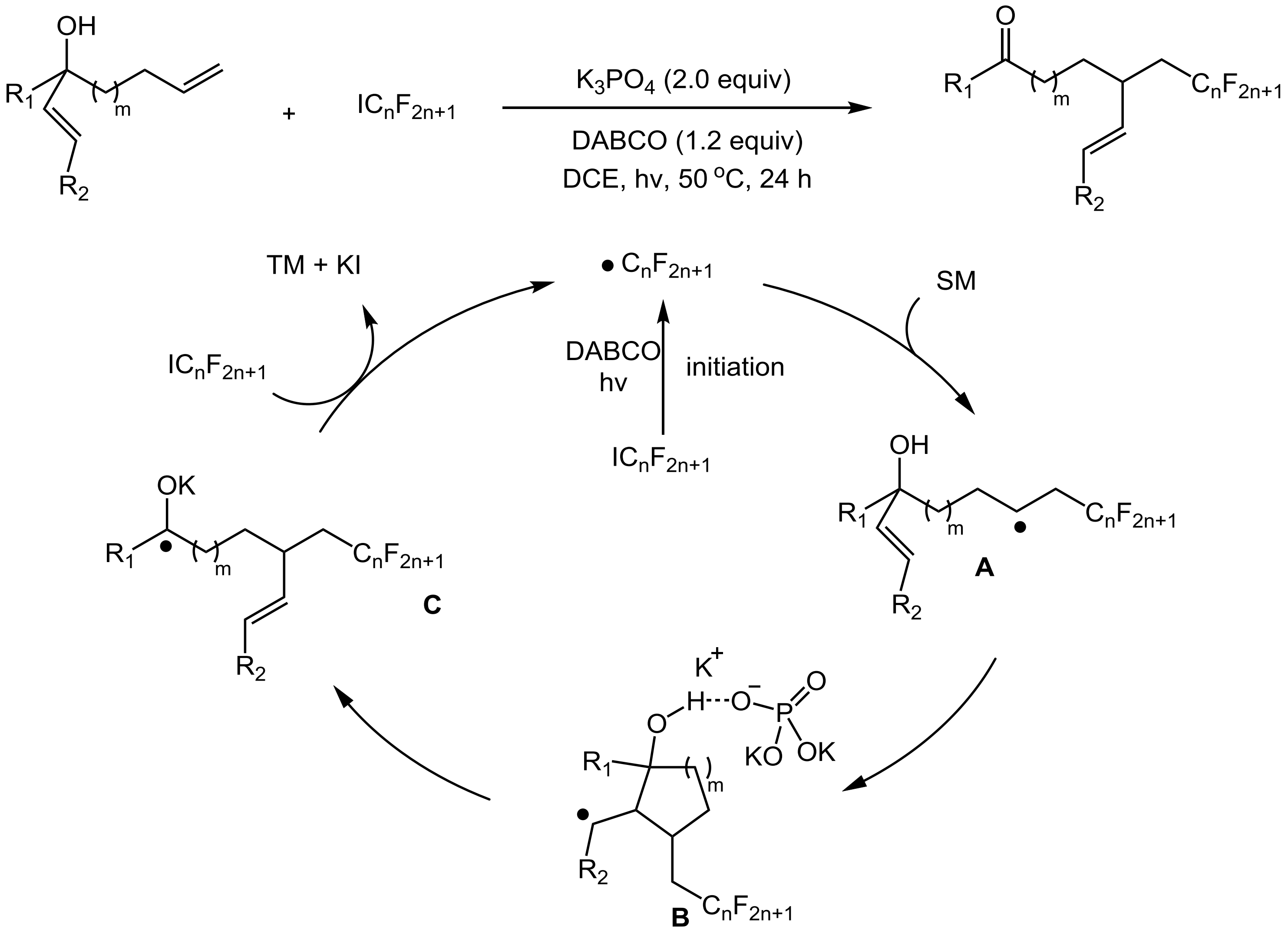
Introduction-formyl migration





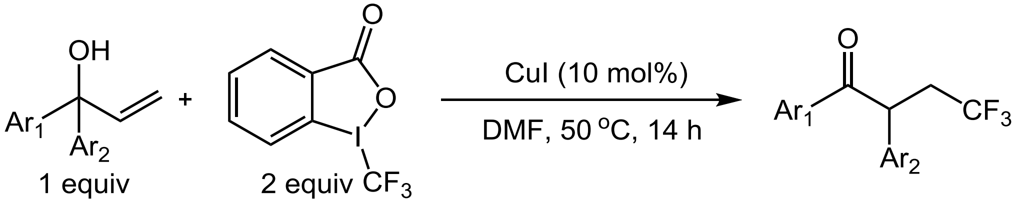
Liu, X.-Y. *et al. Angew. Chem. Int. Ed.* **2016**, *55,* 15100.

Introduction-vinyl migration



Studer, A. *et al. Angew. Chem. Int. Ed.* **2018**, *57,* 814.

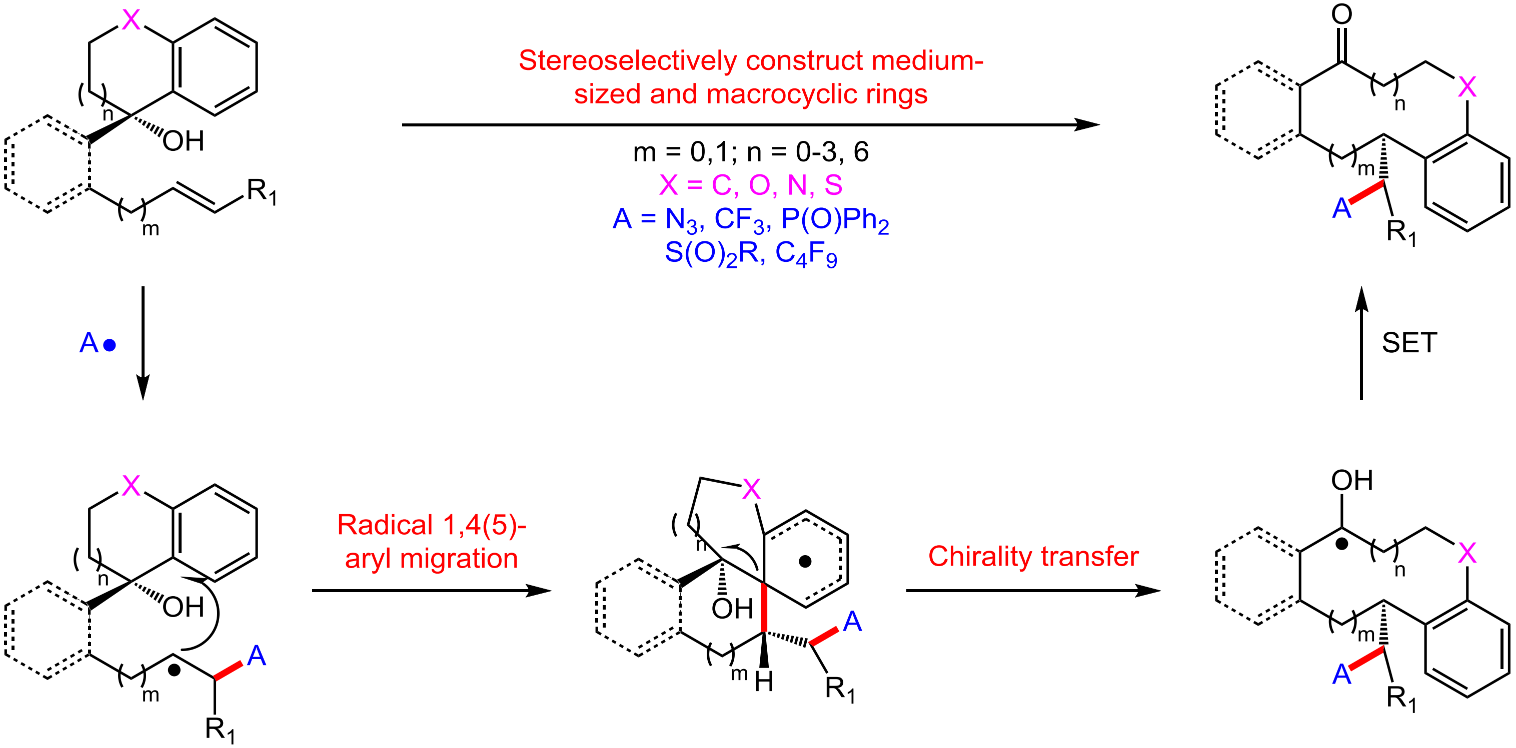
Introduction-aryl migration



CuI (10 mol%)

DMF, 50 °C, 14 h

Wu, X. *et al. Angew. Chem. Int. Ed.* **2013**, *52,* 6962.



Stereoselectively construct medium-sized and macrocyclic rings

m = 0,1; n = 0-3, 6

X = C, O, N, S

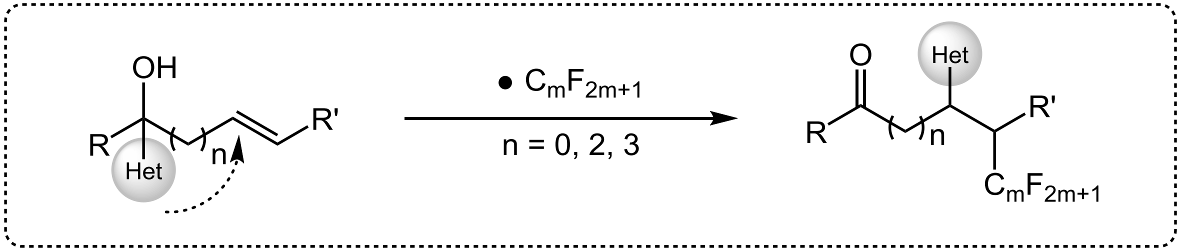
A = N_3, CF_3, P(O)Ph_2
S(O)$_2$R, C_4F_9

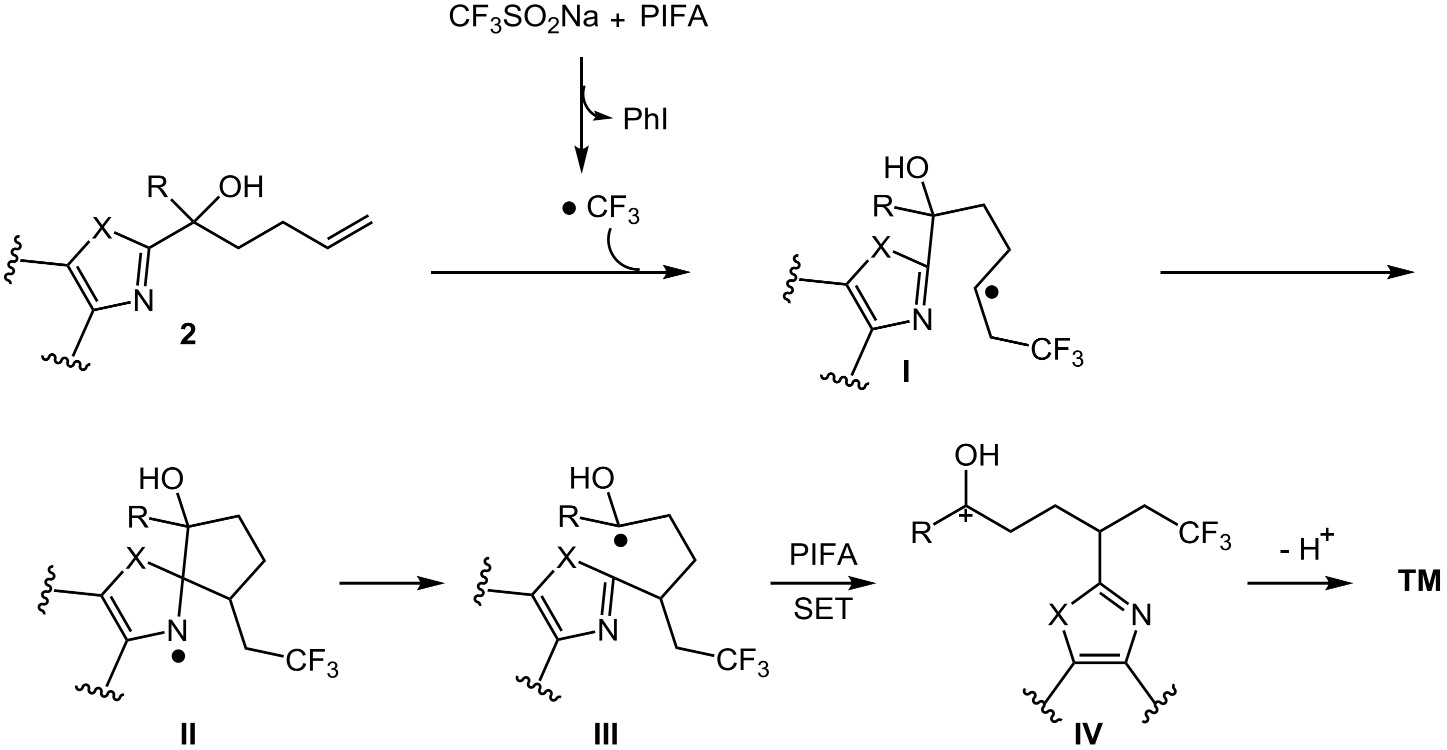
Radical 1,4(5)-aryl migration

Chirality transfer

Liu, X.-Y. *et al. Nat. Commun.* **2016**, *7,* 13852.

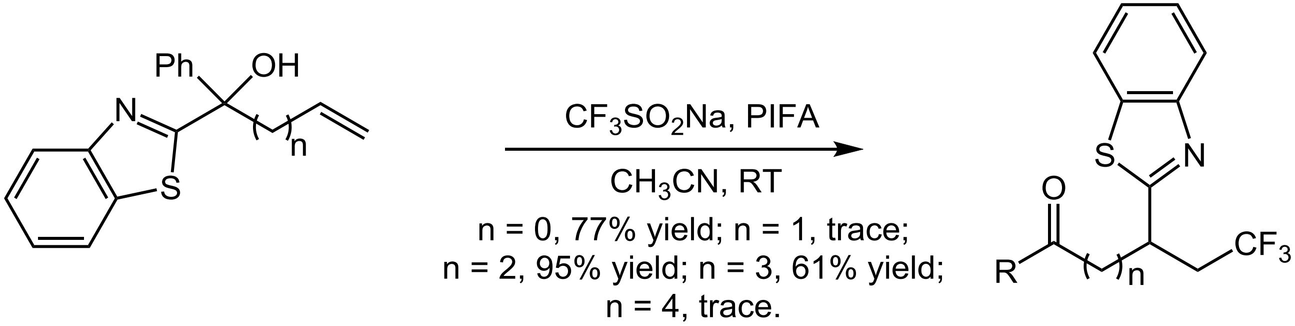
Introduction-heteroaryl migration





Zhu, C. *et al. J. Am. Chem. Soc.* **2017**, *139,* 1388.

Introduction-heteroaryl migration

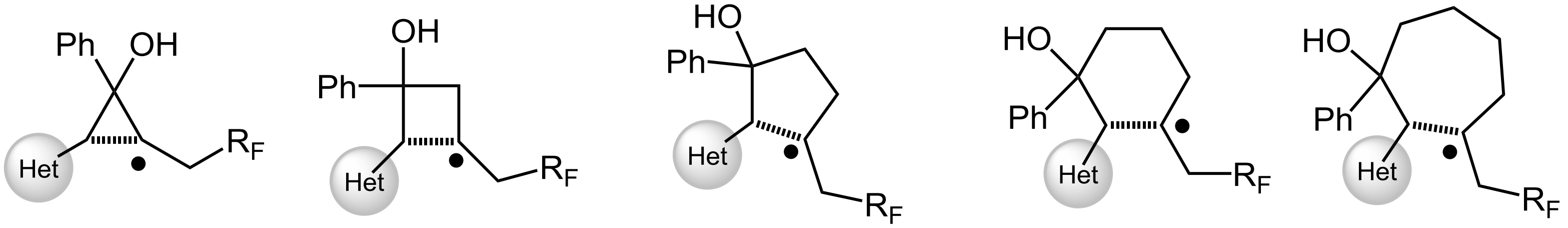


CF_3SO_2Na, PIFA

CH_3CN, RT

n = 0, 77% yield; n = 1, trace;
n = 2, 95% yield; n = 3, 61% yield;
n = 4, trace.

Heteroaryl migration transition-state



Three-membered ring
Favored

Four-membered ring
Disfavored

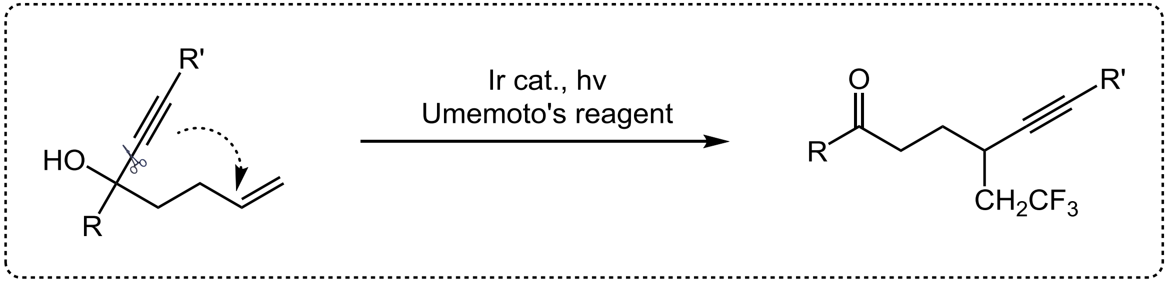
Five-membered ring
Favored

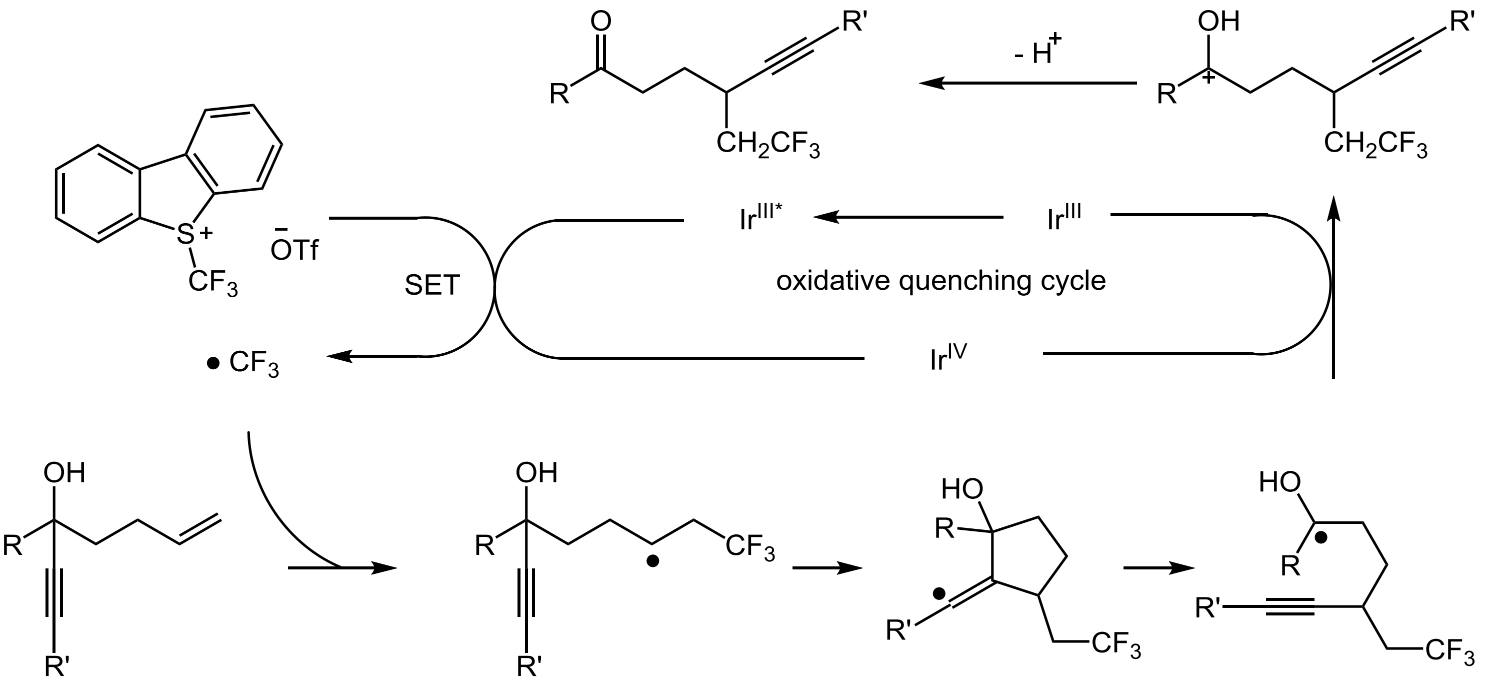
Six-membered ring
Favored

Seven-membered ring
Disfavored

Zhu, C. *et al. J. Am. Chem. Soc.* **2017**, *139,* 1388.

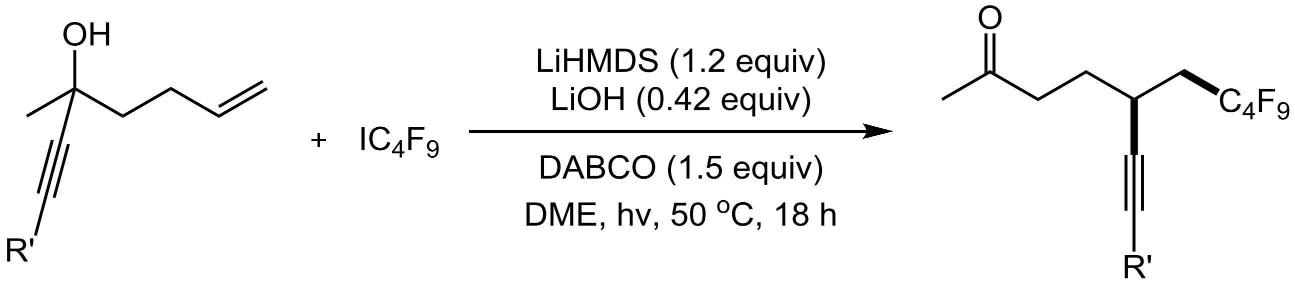
Introduction-alkynyl migration



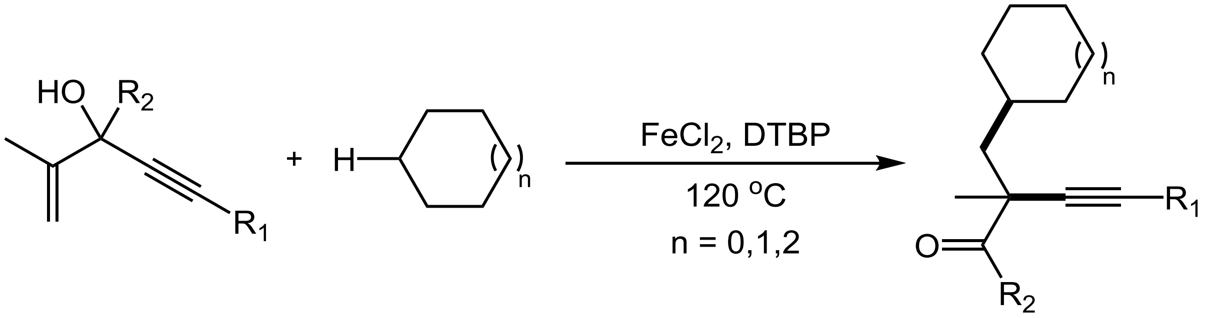


Zhu, C. *et al. Angew. Chem. Int. Ed.* **2017**, *56,* 4545.

Introduction-alkynyl migration



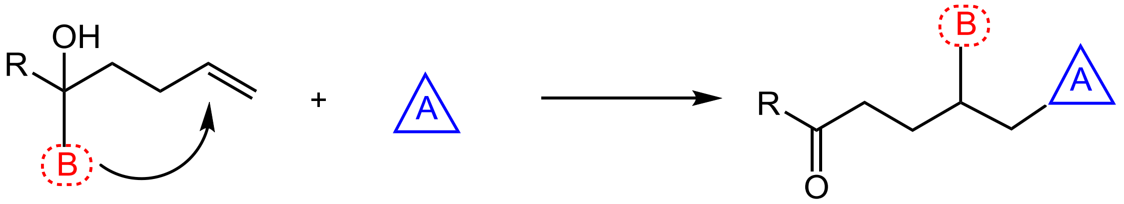
Armido, S. *et al. Chem. Sci.* **2017**, *8,* 6888.



Jiang, B. *et al. Org. Lett.* **2018**, *20,* 3596.

Introduction

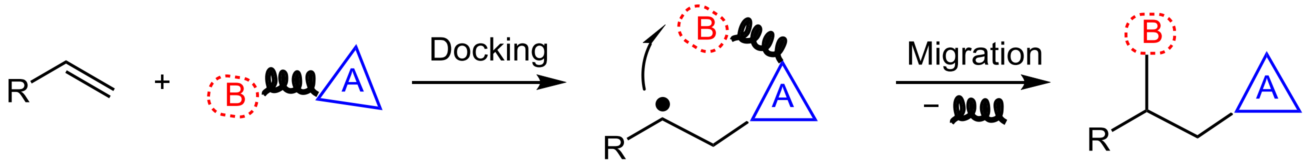
The strategy of intramolecular distal functional group migration



Well-designed substrates
Scope: Unactivated alkenes

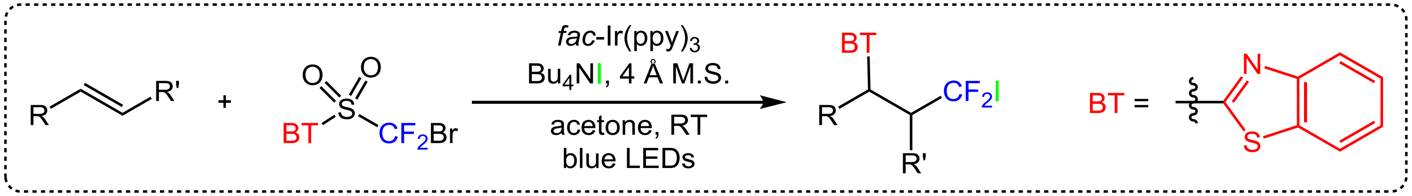
Strategically located tertiary alcohols are employed as substrates that restricts the generality of the protocol.

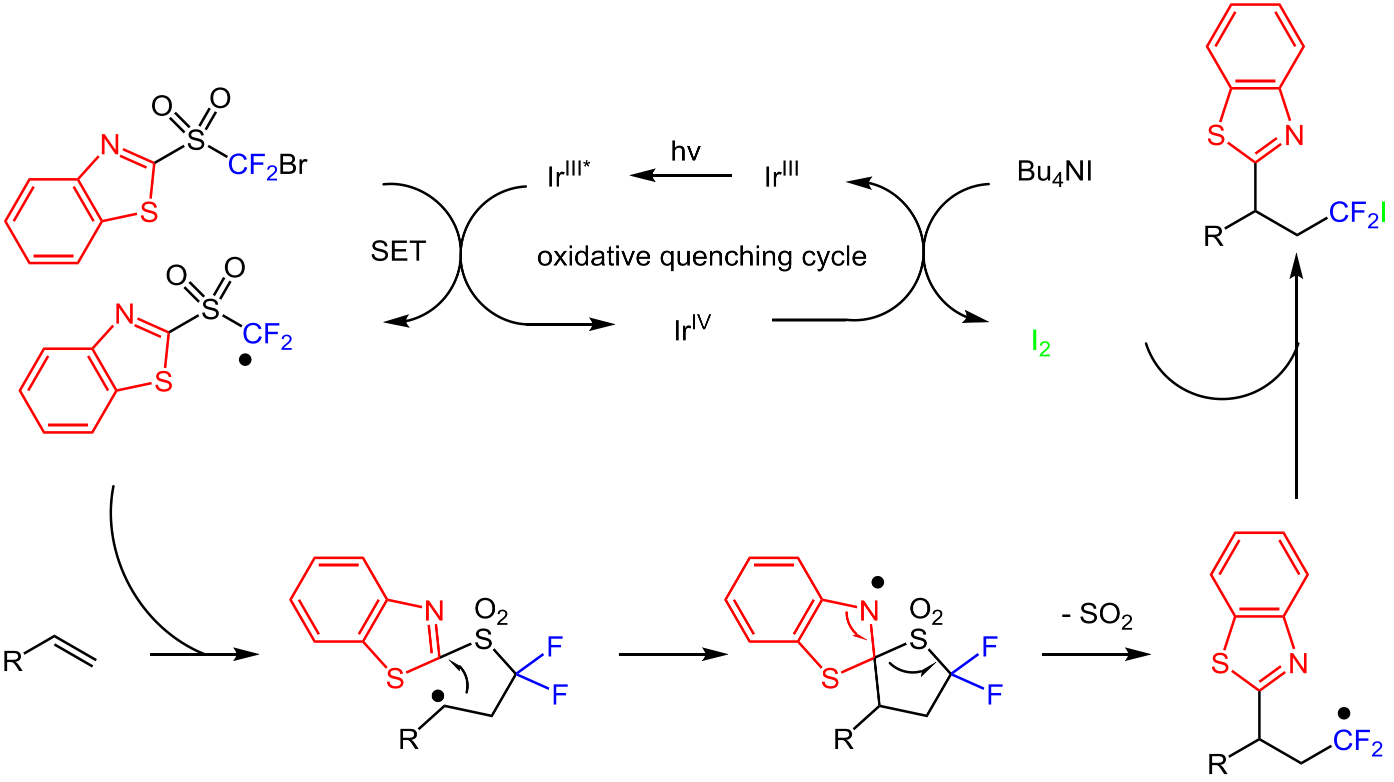
Docking-migration mode



Scope: activated and unactivated alkenes
Broad functional group tolerance
Regio- and stereo-selective control

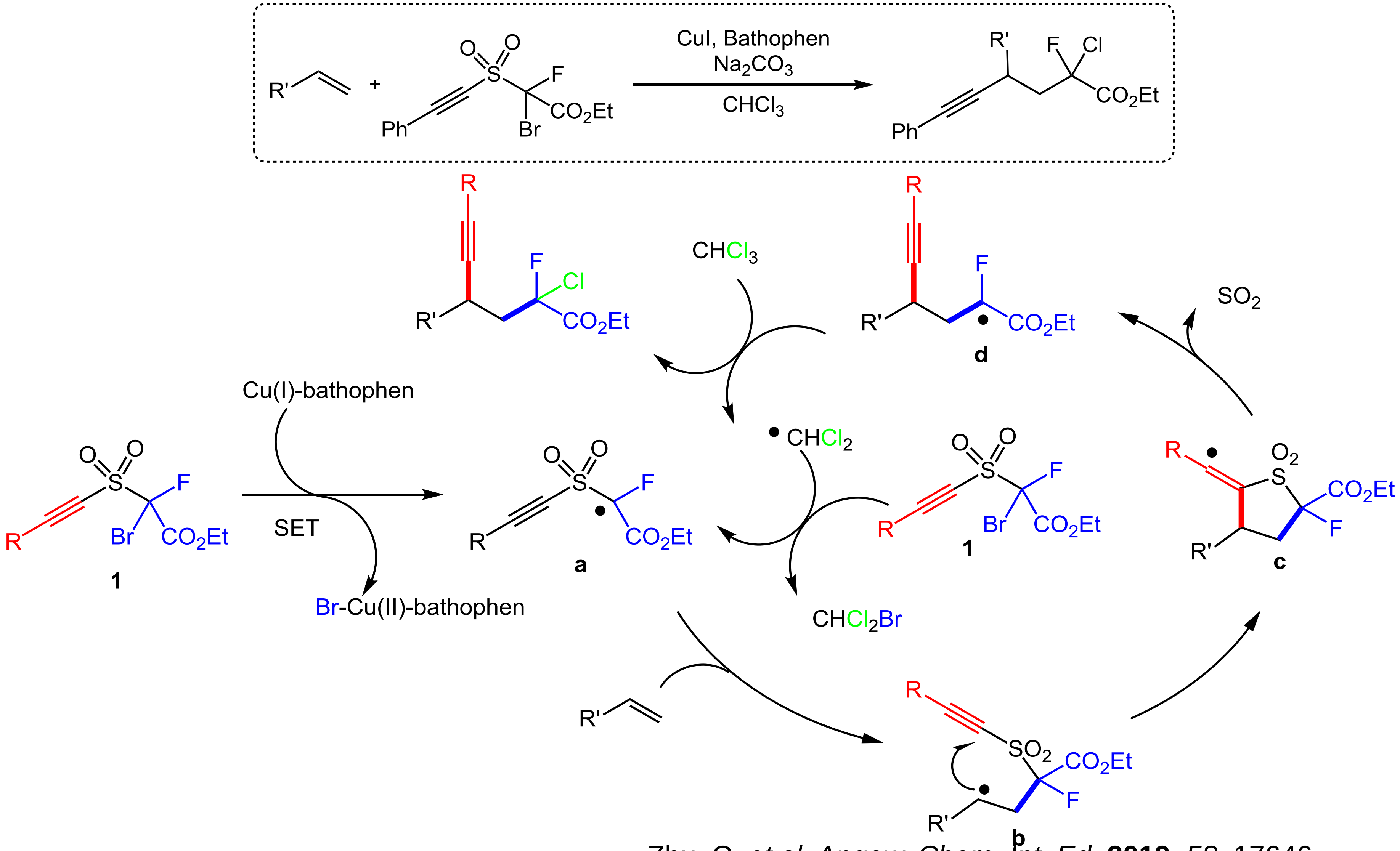
Introduction





Zhu, C. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 17156.

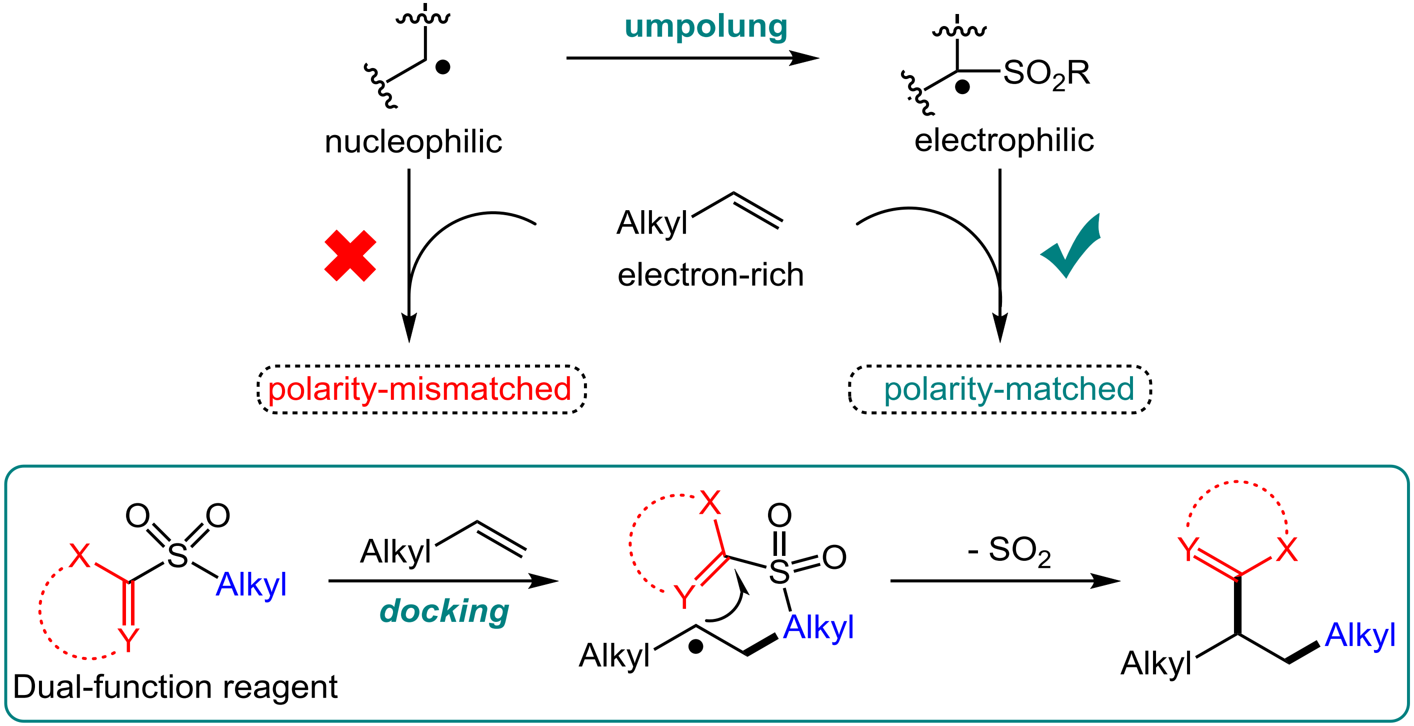
Introduction



Zhu, C. *et al. Angew. Chem. Int. Ed.* **2019**, *58,* 17646.

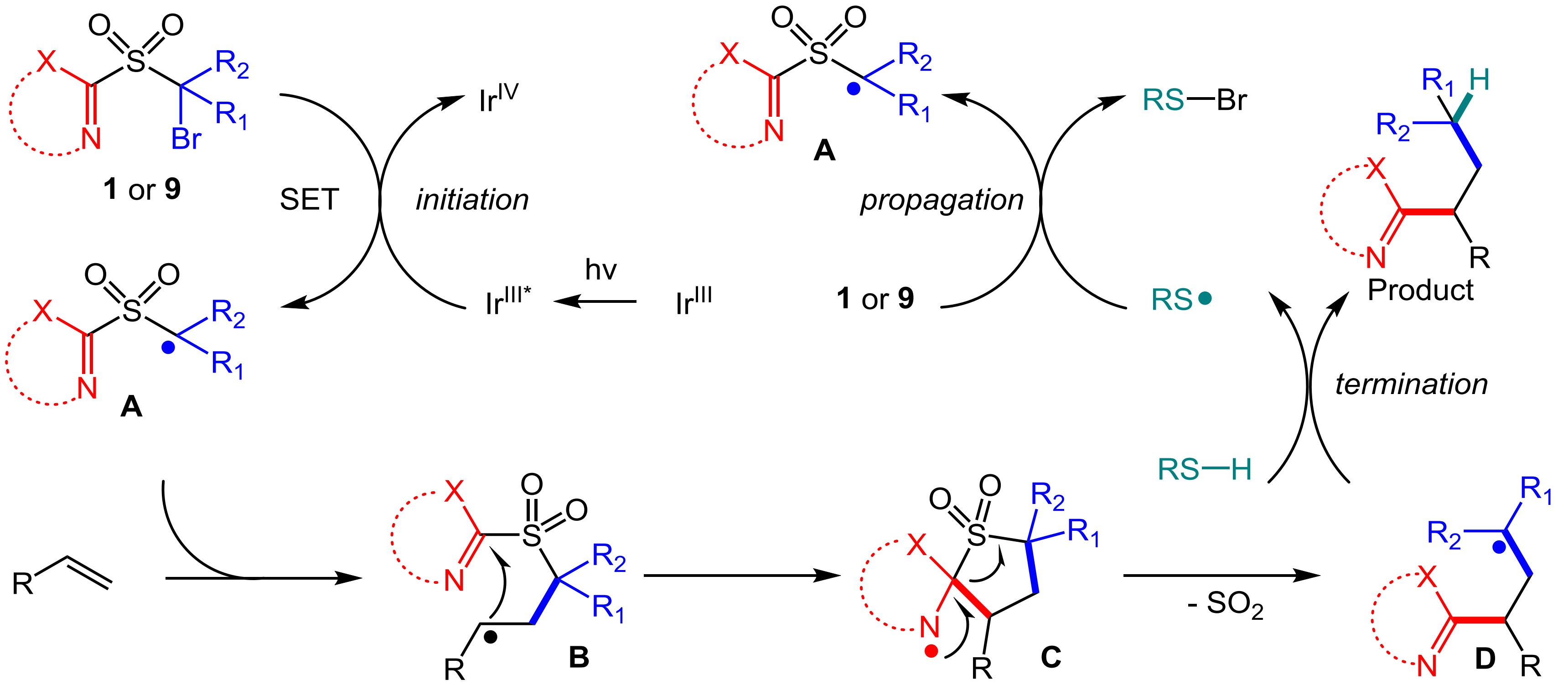
Background and project synopsis

Polarity-Umpolung Strategy

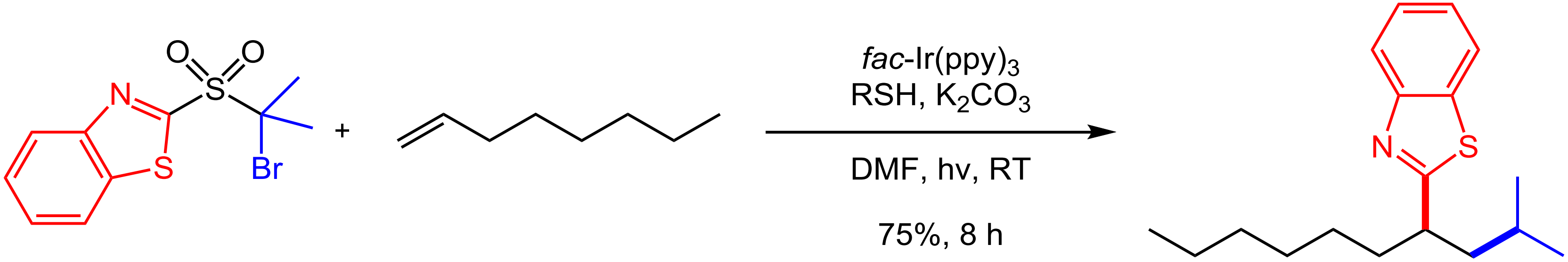


Zhu, C. *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 8195.

Proposed mechanism



Reaction conditions optimization

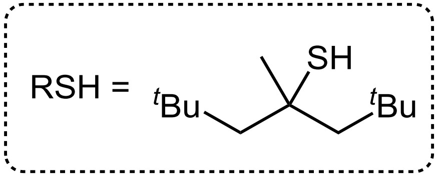


fac-Ir(ppy)$_3$
RSH, K_2CO_3

DMF, hv, RT

75%, 8 h

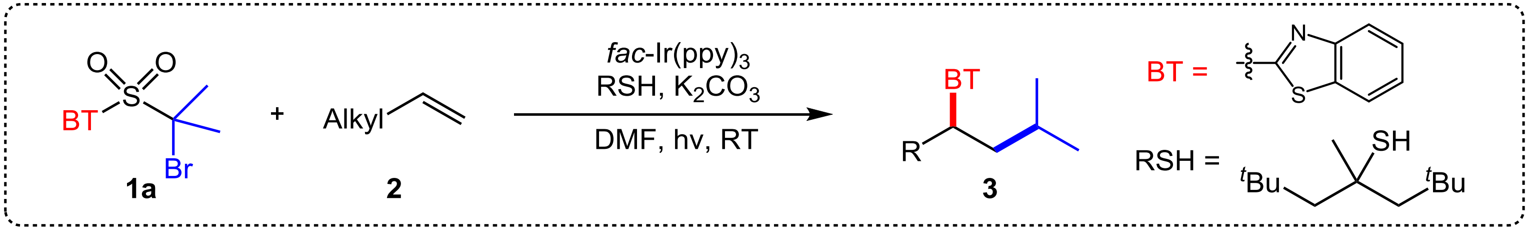
1a **2a** **3a**

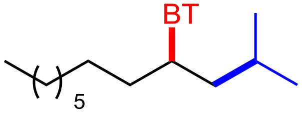


Control Experiments:

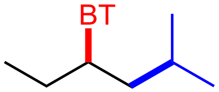
a. no *fac*-Ir(ppy)$_3$	**3a** ND
b. no RSH	messy
c. no K_2CO_3	46% of **3a**
d. no light	**3a** ND

Scope of substrates

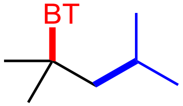




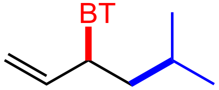
3b, 69%, 3 h



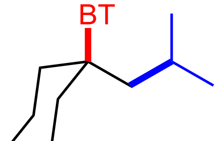
3c, 70%, 5 h



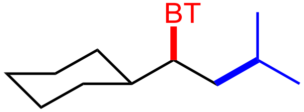
3d, 76%, 5 h



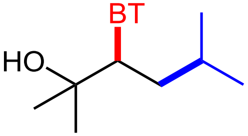
3e, 31%, 5 h



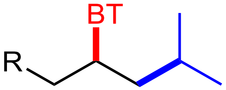
3f, 97%, 4 h



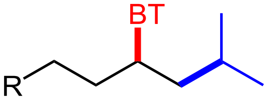
3g, 58%, 5 h



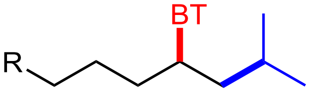
3h, 50%, 4 h



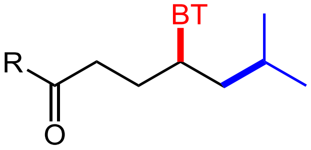
R = TMS, **3i**, 85%, 4 h
R = TBS, **3j**, 85%, 5 h



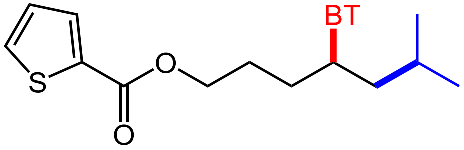
R = CO_2H, **3k**, 88%, 11 h
R = Ph, **3l**, 69%, 8 h



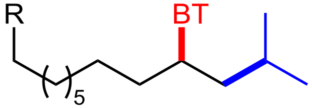
R = OH, **3m**, 83%, 5 h
R = OPh, **3n**, 55%, 5 h
R = OTs, **3o**, 42%, 4 h
R = Br, **3p**, 47%, 10 h
R = NO_2, **3q**, 51%, 5 h
R = $P(O)(OEt)_2$, **3r**, 88%, 4 h



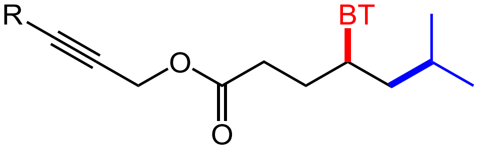
R = Ph, **3s**, 63%, 4 h
R = thienyl, **3t**, 48%, 4 h



3u, 74%, 5 h

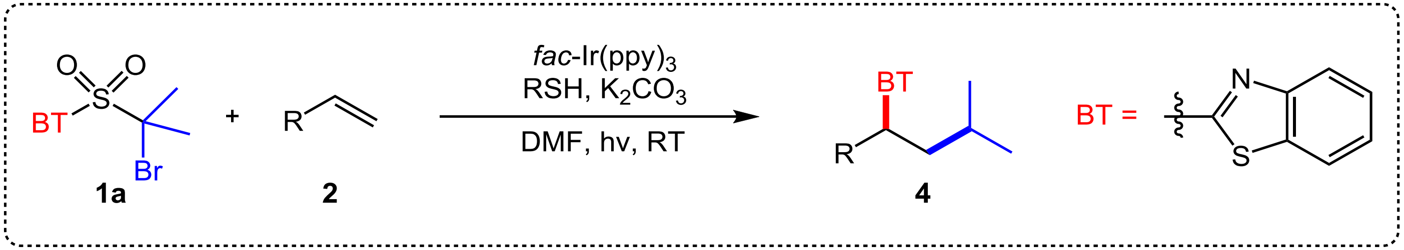


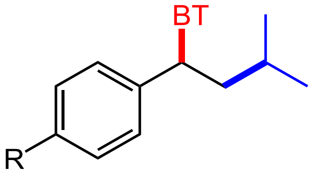
R = CO_2Et, **3v**, 70%, 3 h
R = CHO, **3w**, 44%, 9 h



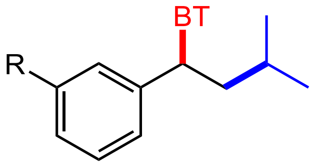
R = CH_3, **3x**, 41%, 4 h
R = H, **3y**, 26%, 5 h

Scope of substrates

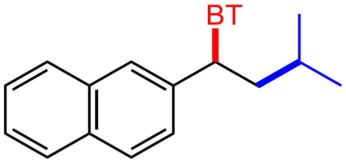




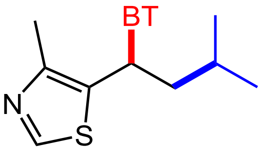
4a, R = H, 81%, 7 h
4b, R = Me, 87%, 8 h
4c, R = ^{t}Bu, 95%, 19 h
4d, R = OMe, 74%, 17 h
4e, R = Ph, 84%, 11 h
4f, R = F, 70%, 9 h
4g, R = Cl, 76%, 9 h
4h, R = Br, 79%, 6 h
4i, R = CF_3, 79%, 7 h
4j, R = CN, 56%, 5 h
4k, R = NO_2, 30%, 4 h
4l, R = OAc, 66%, 6 h
4m, R = CH_2Cl, 62%, 7 h
4n, R = Bpin, 49%, 4 h



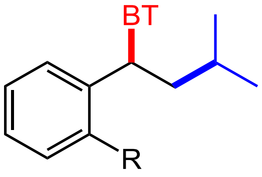
4o, R = OMe, 71%, 17 h
4p, R = Br, 85%, 11 h
4q, R = CF_3, 59%, 6 h



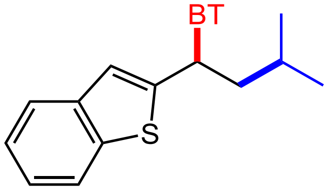
4v, 84%, 24 h



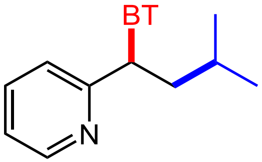
4x, 46%, 6 h



4r, R = Me, 87%, 6 h
4s, R = Br, 78%, 7 h
4t, R = Cl, 72%, 7 h
4u, R = F, 68%, 10 h

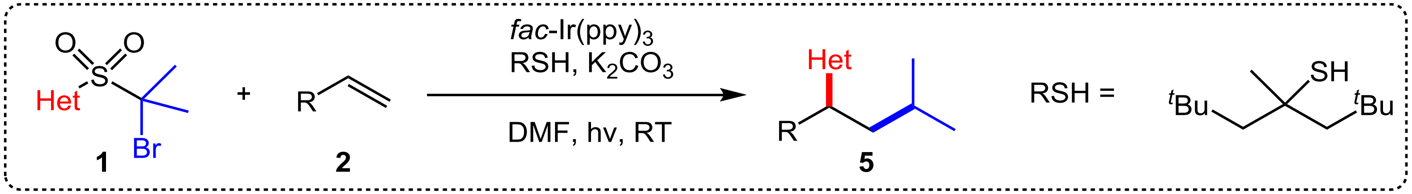


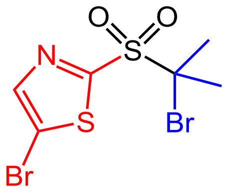
4w, 54%, 6 h



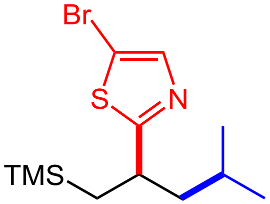
4y, 45%, 18 h

Scope of substrates

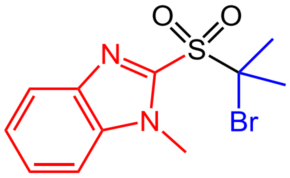




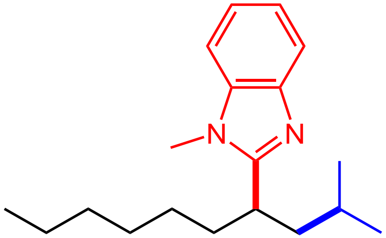
1b



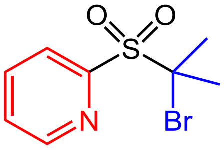
5a, 60%, 4 h



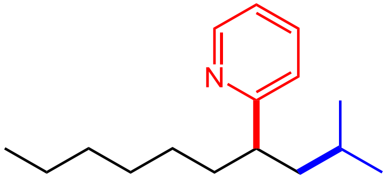
1c



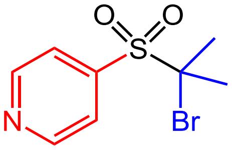
5b, 60%, 4 h



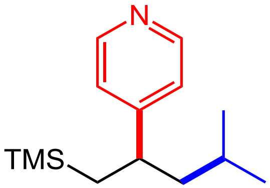
1d



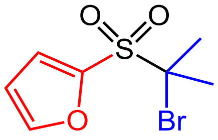
5c, 54%, 4 h



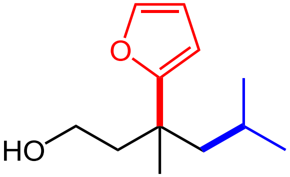
1e



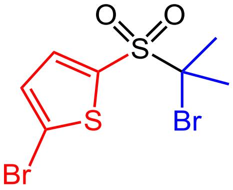
5d, 40%, 3 h



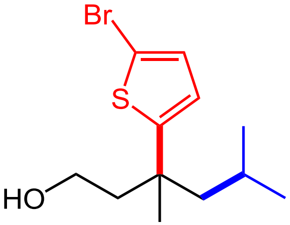
1f



5e, 58%, 4 h

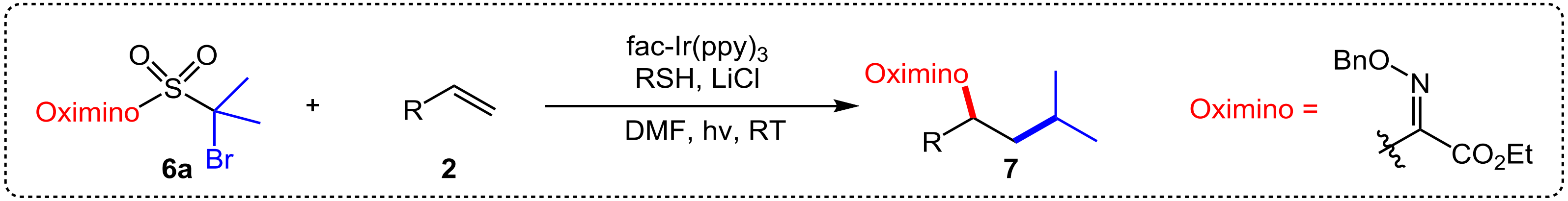


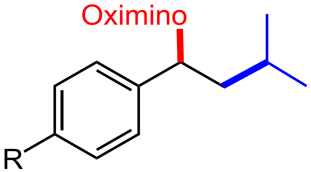
1g



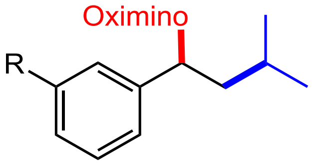
5f, 43%, 4 h

Scope of substrates

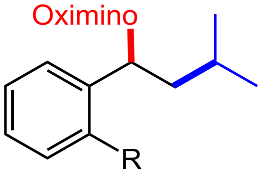




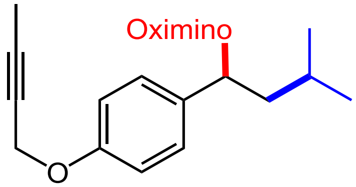
7a, R = H, 88%, 12 h
7b, R = Me, 84%, 12 h
7c, R = ^{t}Bu, 83%, 14 h
7d, R = OMe, 80%, 10 h
7e, R = Ph, 59%, 5 h
7f, R = F, 88%, 12 h
7g, R = Cl, 70%, 11 h
7h, R = Br, 76%, 14 h
7i, R = CF_3, 63%, 11 h
7j, R = OAc, 65%, 14 h
7k, R = CH_2Cl, 80%, 20 h



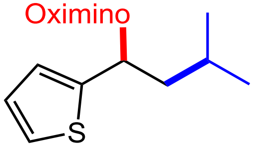
7l, R = OMe, 82%, 14 h
7m, R = Br, 75%, 10 h
7n, R = CF_3, 87%, 12 h



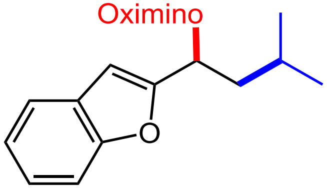
7o, R = Me, 74%, 13 h
7p, R = Cl, 87%, 14 h
7q, R = F, 78%, 11 h



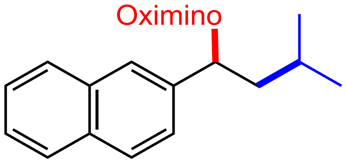
7r, 36%, 17 h



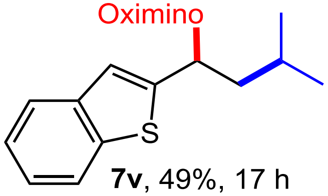
7s, 36%, 20 h



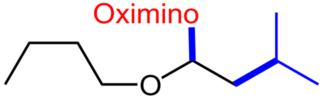
7t, 46%, 17 h



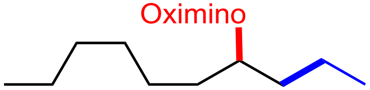
7u, 74%, 12 h



7v, 49%, 17 h

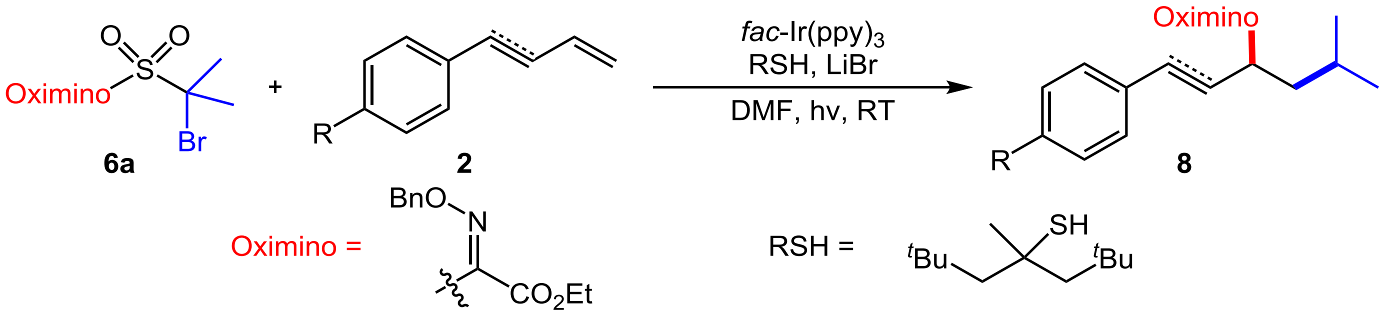


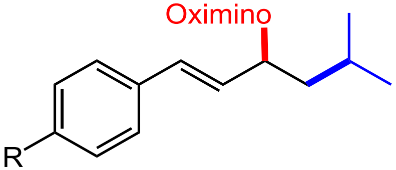
7w, 38%, 18 h



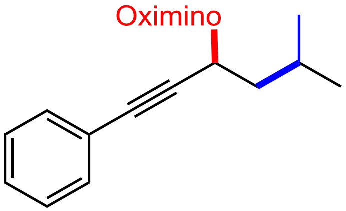
7x, 45%, 14 h

Scope of substrates



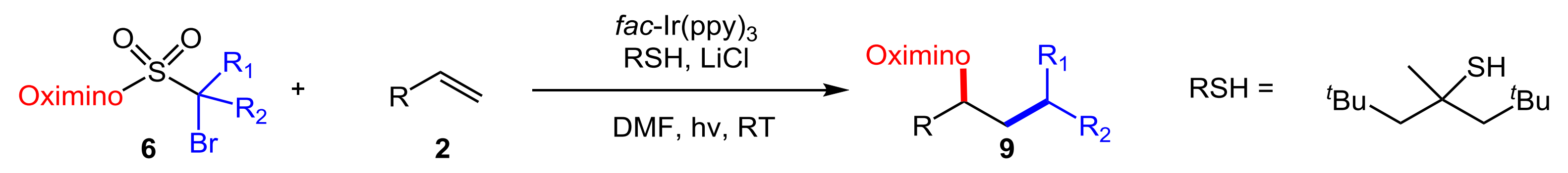


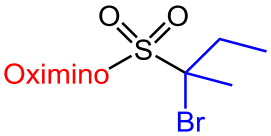
8a, R = H, 48%, 18 h
8b, R = Me, 34%, 18 h
8c, R = CF_3, 46%, 18 h



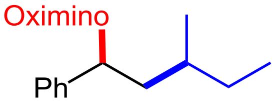
8d, 32%, 12 h

Scope of substrates

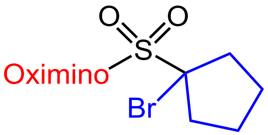




6b



9a, 60%, 14 h



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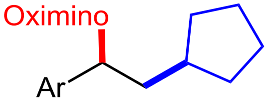
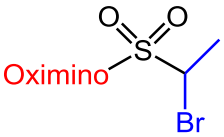
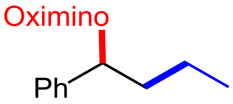


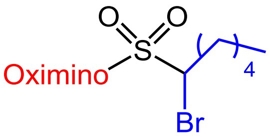
9b, Ar = Ph, 78%, 17 h
9c, Ar = 1-Naphth, 69%, 12 h



6d



9d, R = H, 54%, 17 h



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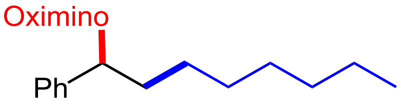
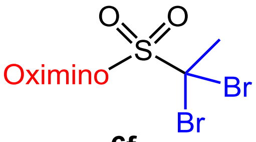
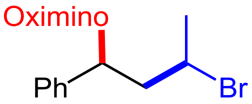


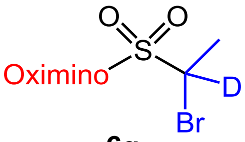
9e, 52%, 17 h



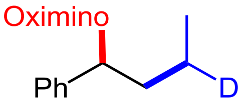
6f



9f, 82%, 17 h



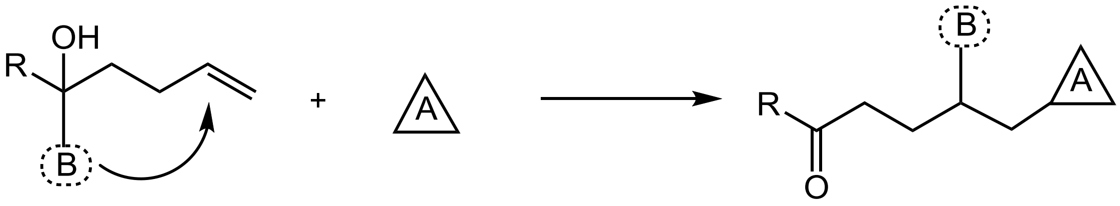
6g



9g, 51%, 17 h

Summary

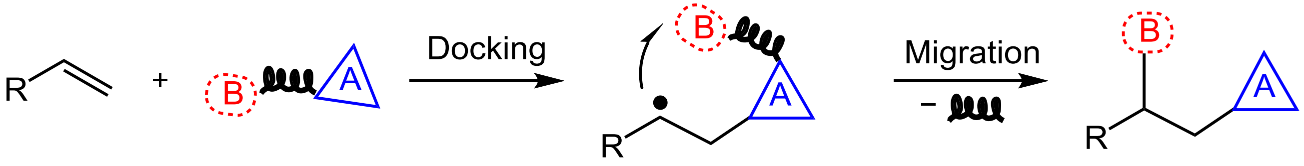
The strategy of intramolecular distal functional group migration



Well-designed substrates
Scope: Unactivated alkenes

Strategically located tertiary alcohols are employed as substrates that restricts the generality of the protocol.

Docking-migration mode



Scope: activated and unactivated alkenes
Broad functional group tolerance
Regio- and stereo-selective control

The first paragraph

写作思路

烯烃双官能化
构建C-C键的重要性

↓

前人工作的受限性

↓

引出非活化烯烃双官
能化构建C-C键

The first paragraph

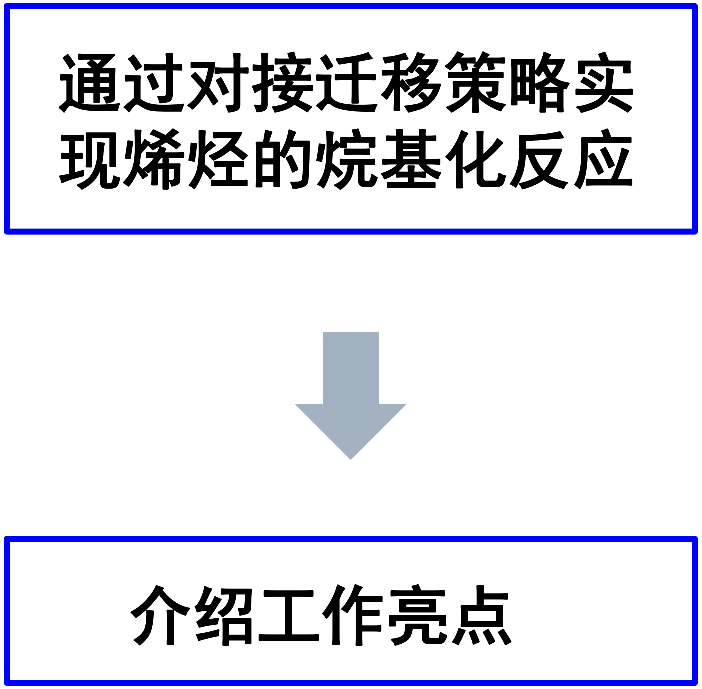
Carbon–carbon bond formation is paramount in synthetic chemistry as C-C bonds constitute the basic framework of organic molecules. Considering that alkenes are abundant and widely available, radical-mediated functionalization of alkenes to construct C-C bonds represents an effective and ingenious tactic. Direct alkylation of alkenes by incorporation of an external alkyl radical into an alkene, leading to a more complex aliphatic scaffold, is of great synthetic value. State-of-the-art methods reveal that such a process mainly proceeds through two modes, the polarity-matched mode and the p–π conjugation assisted mode.

The first paragraph

Mechanistically, the addition of a nucleophilic alkyl radical to an electron-deficient alkene is kinetically favored owing to their matched radical polarity, while the formation of a benzylic radical intermediate stabilized by p–π conjugation is thermodynamically preferred. Both approaches suffer from limited substrate scope, in which activated alkenes are generally required. In contrast, the incorporation of nonspecific alkyl radicals into unactivated alkenes surmounts the substrate limitation, thus substantially increasing product diversity. Borne out of pragmatic consideration, this approach is more anticipated, yet remains unmet because of the mismatched polarity.

The last paragraph

写作思路



通过对接迁移策略实现烯烃的烷基化反应

介绍工作亮点

The last paragraph

A novel “polarity umpolung” strategy has been developed for radical alkylation of alkenes. Activated and unactivated alkenes, including many complex natural products and drug derivatives, are readily functionalized by a docking and migration pathway to efficiently afford valuable alkylated products. Along with alkylation, either an heteroaryl or oximino group is concomitantly incorporated into the alkenes. The reaction features mild reaction conditions, broad functional-group tolerance, and high product diversity. Given the ubiquity of alkenes as building blocks and easy accessibility of the difunctional alkylating reagents, this method offers an efficient approach for extending aliphatic scaffoldings.

Representative examples

In contrast, the incorporation of nonspecific alkyl radicals into unactivated alkenes surmounts the substrate limitation, thus substantially increasing product diversity. (克服)

Borne out of pragmatic consideration, this approach is more anticipated, yet remains unmet because of the mismatched polarity. (综合考虑)

Herein, we disclose the proof-of-principle for this hypothesis. (证明该假设的原理)

The reaction was messy either in the absence of tert-dodecylthiol or with the use of other thiols. (混乱)

Thanks
for your attention