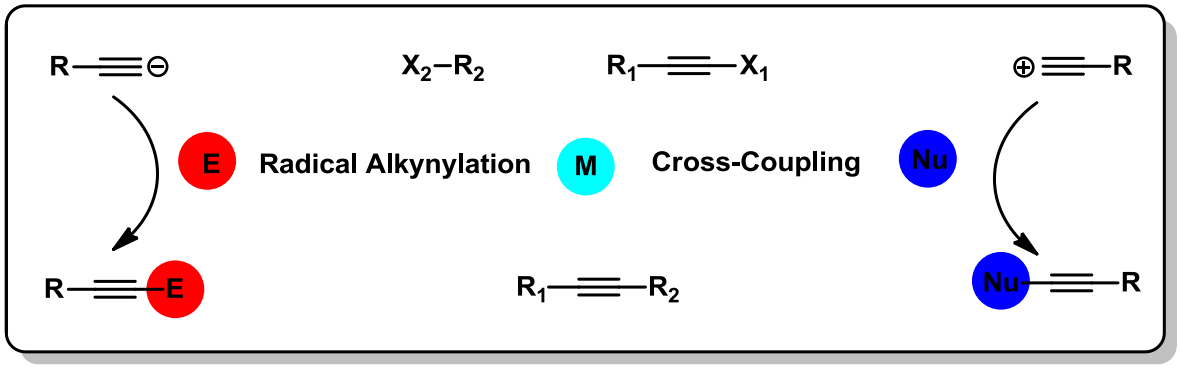
Recent Developments in Alkynylation

--New approaches to introduce an alkynyl group



Reporter: Zhao-feng Wang

Supervisor: Yong Huang

2013-03-27

Recent Developments in Alkynylation

Contents

Recent Developments in Alkynylation

Introduction -- Structure and Bonding

Linear Acetylenic Scaffolds

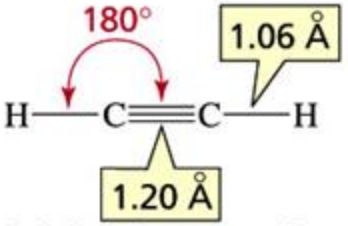
$pK_a \cong 25$

Total bond strength: 839 kJ/mol

C-Cσ bond: 369 kJ/mol

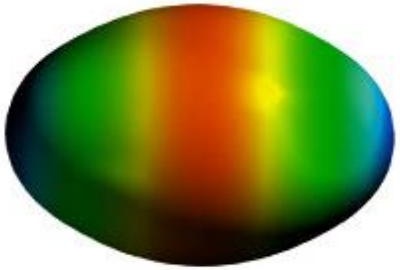
1st C-Cπ bond: 268 kJ/mol

2nd C-Cπ bond :202 kJ/mo



a triple bond consists of one σ bond and two π bonds

ball-and-stick model of ethyne

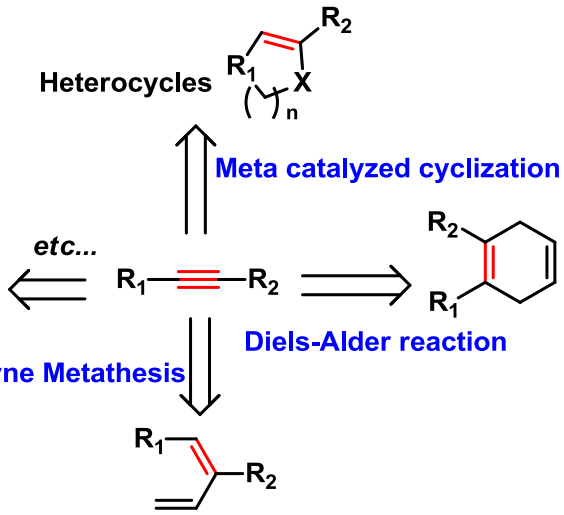


electrostatic potential map for ethyne

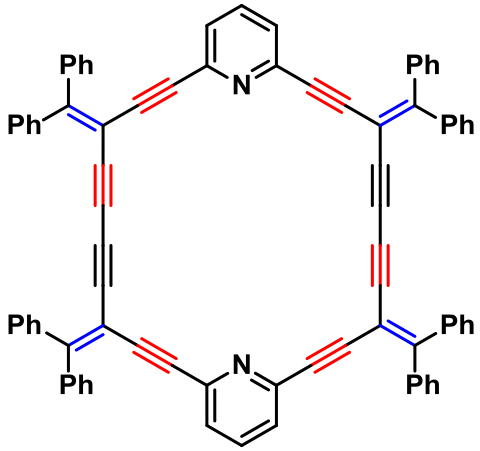
Picture downloaded from http://en.wikipedia.org

Recent Developments in Alkynylation

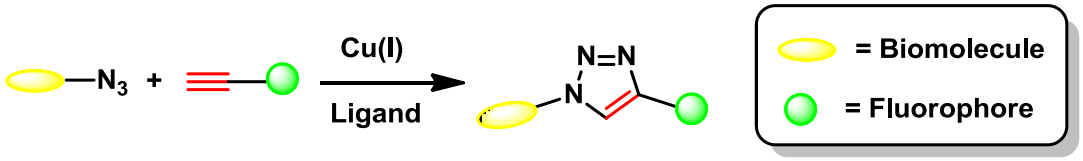
Introduction -- Why we need to introduce an alkynyl group?



versatile building blocks in organic synthesis



Arylene-Acetylene nanostructure



click chemistry for biomolecular labeling

Tykwinsky, R. R. *et al. Synlett* **2004**, 182-184.
Q. Lin *et al. Chem. Commun.* **2010**, *46,* 1589-1600

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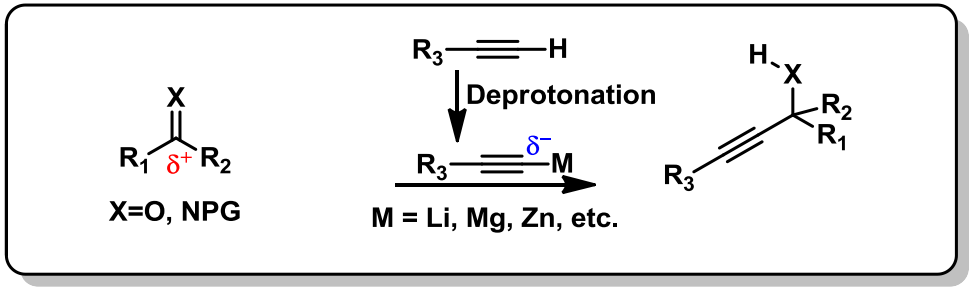
5. Summary and outlook

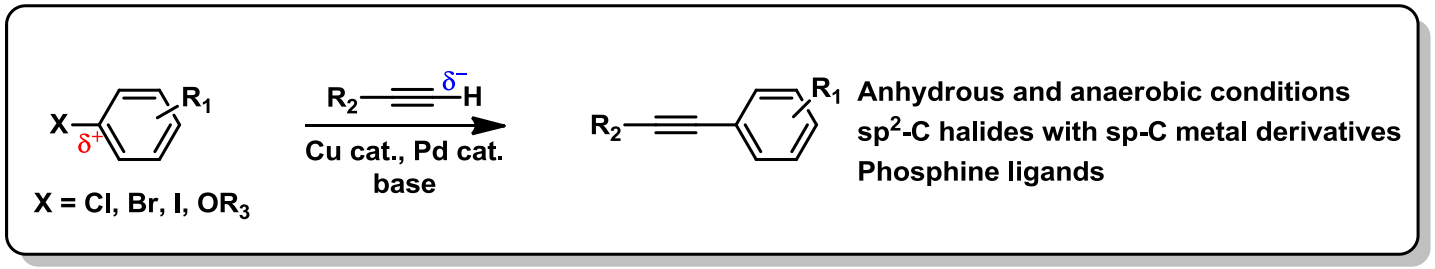
Recent Developments in Alkynylation

Nucleophilic alkynylation: Classic text book approach

Addition of Alkyne Nucleophiles to Carbonyl Groups



Sonogashira coupling of aryl halides and acetylenes

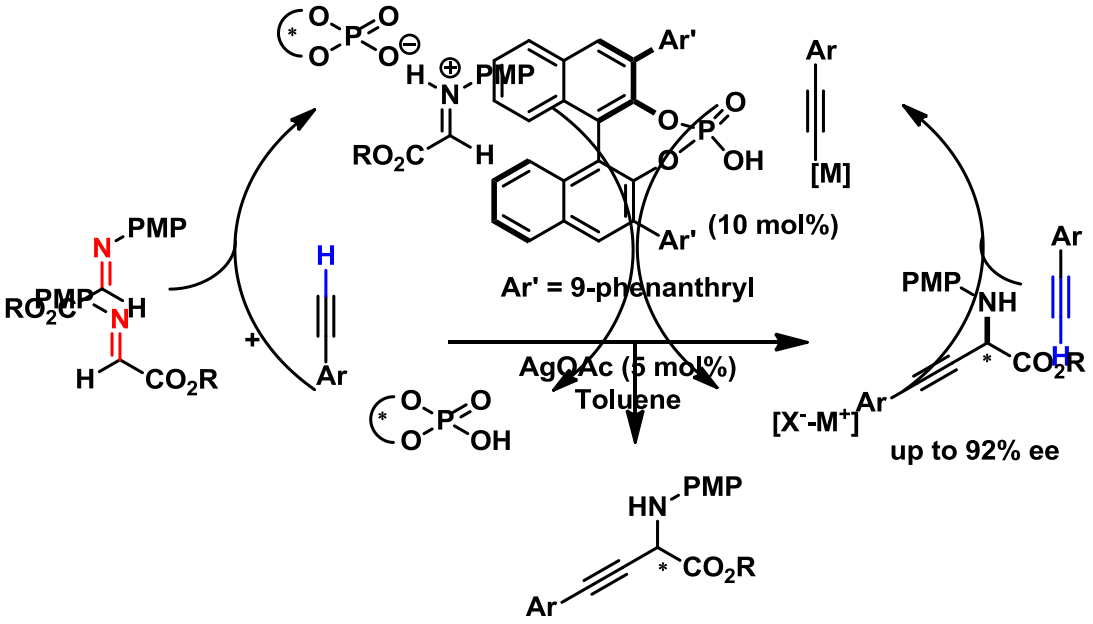


J. Waser *et al. Chem. Soc. Rev.* **2012**, *41*, 4165–4179

Recent Developments in Alkynylation

Nucleophilic alkynylation

Asymmetric alkynylation of α-imino esters via synergistic catalysis strategy



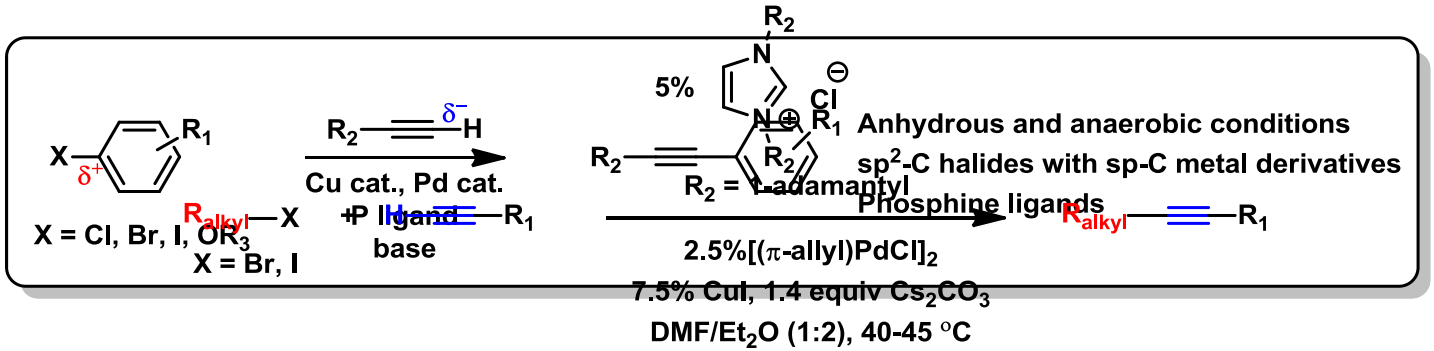
Combined enantioselective Brønsted acid and metal-catalyzed alkynylation of α-imino esters

M. Rueping *et al. Angew. Chem., Int. Ed.* **2007**, *46*, 6903-6906

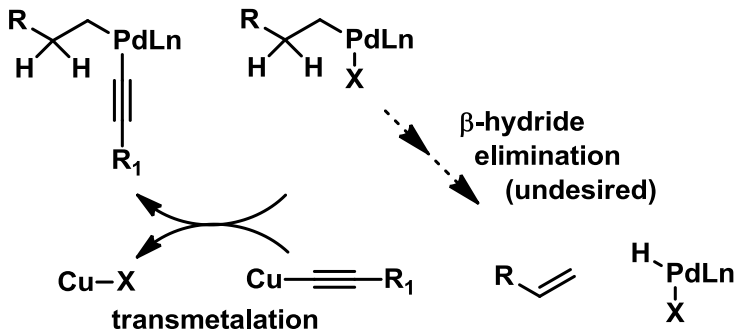
Recent Developments in Alkynylation

Nucleophilic alkynylation

Sonogashira coupling of Sp^2 halides and acetylenes



The first applications of carbene ligands in sonogashira reactions of unactivated alkyl halides



M. Eckhardt, G.-C. Fu *et al. J. Am. Chem. Soc.* **2003**, *125*, 13642-13643

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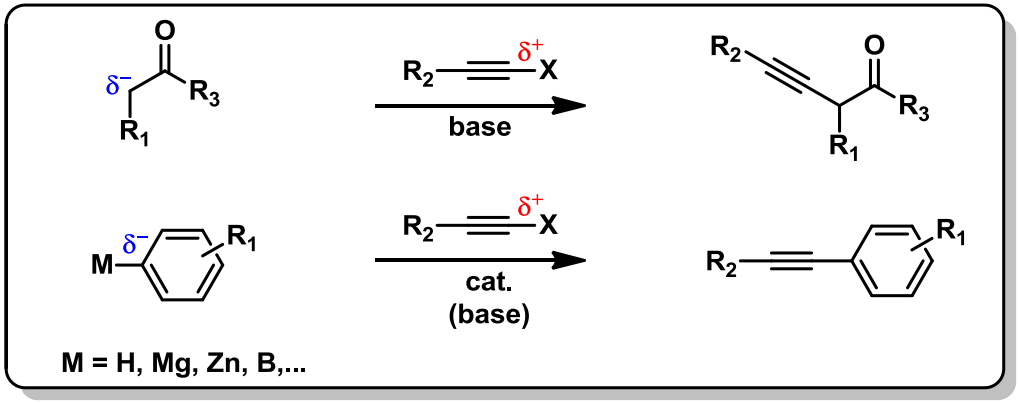
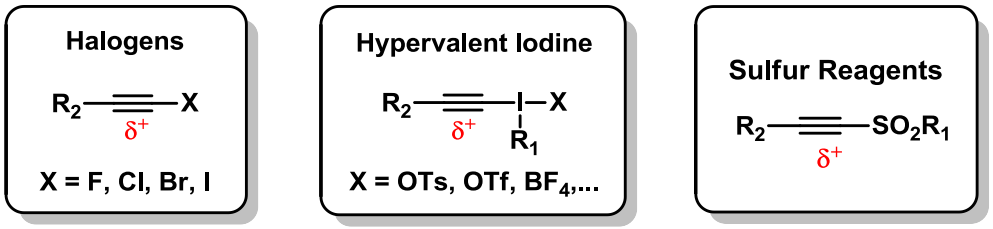
Recent Developments in Alkynylation

Electrophilic alkynylation : The dark side of acetylene chemistry

Addition of alkynes on a nucleophilic position



Electrophilic alkynylation reagents

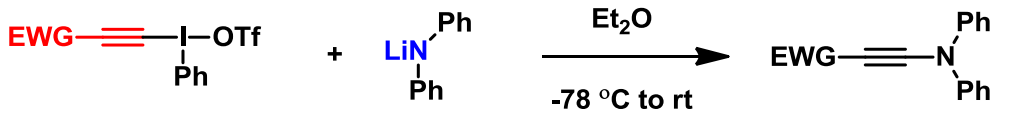


J. Waser *et al. Chem. Soc. Rev.* **2012**, *41*, 4165–4179

Recent Developments in Alkynylation

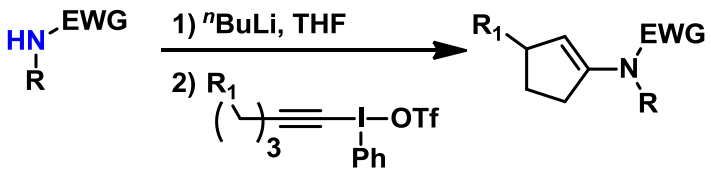
Electrophilic alkynylation : Heteroatom alkynylation

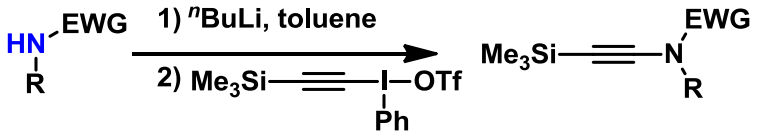
C-N bond formation: first ynamine synthesis

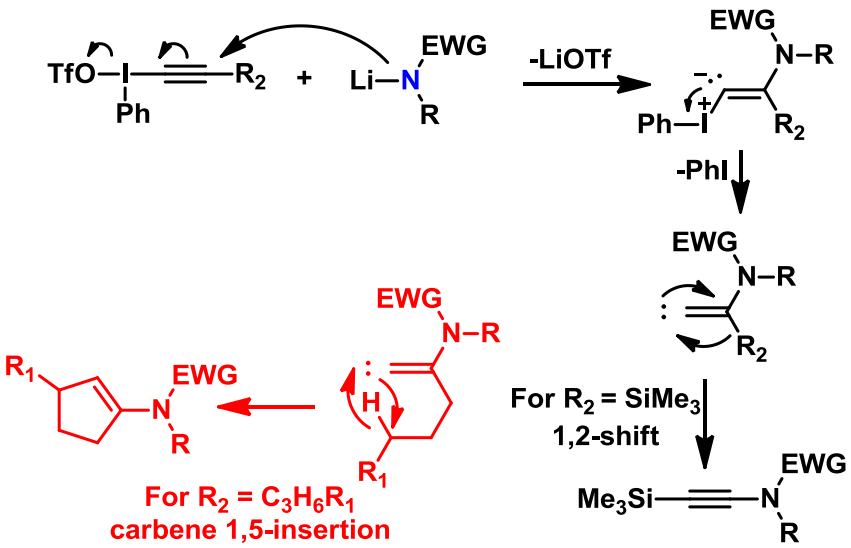


push-pull ynamines

Extended methodology to ynamide





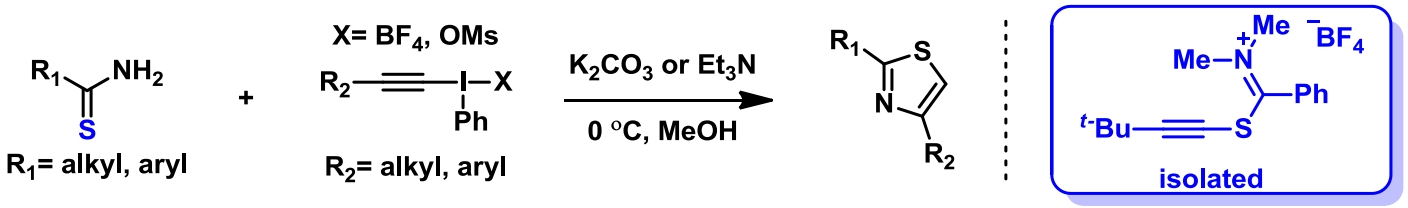


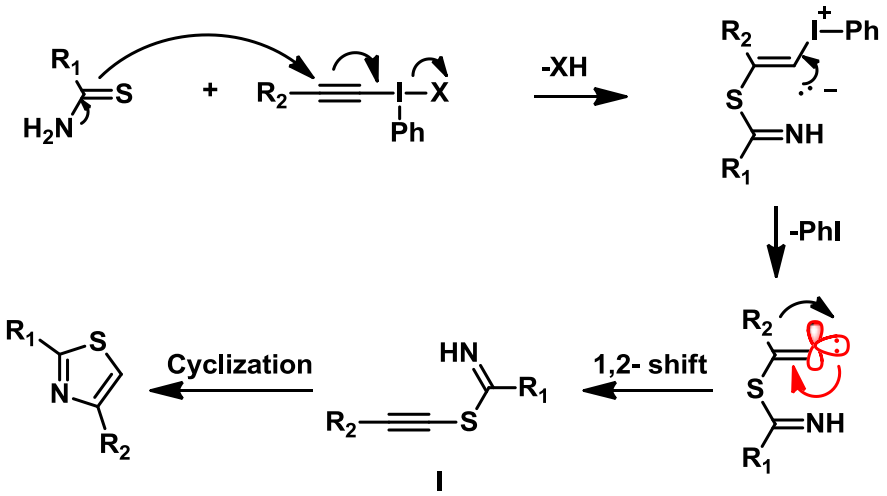
P. J. Stang *et al. Synthesis* **1994**,1255–1256
K. S. Feldmen *et al. J. Org. Chem.***1996**, *61*, 5440–5452
A. T. Stengel *et al. Angew. Chem., Int. Ed.* ***1998***, *37*,489–492

Recent Developments in Alkynylation

Electrophilic alkynylation : Heteroatom alkynylation

C-S bond formation: regiospecific thiazole synthesis using alkynyliodonium salts



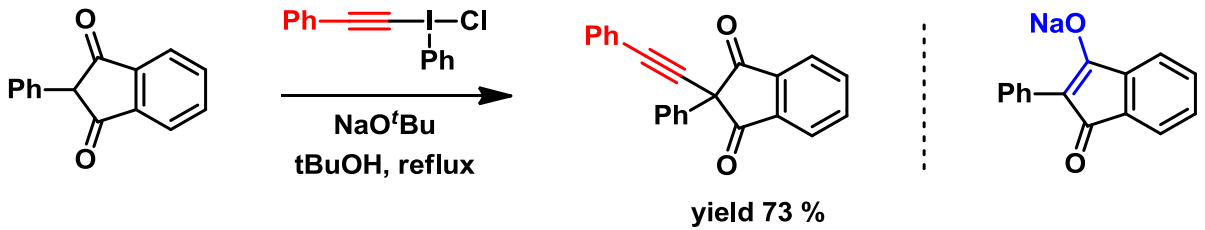


P. Wipf *et al. J. Org. Chem.* **1996**, *61*, 8004–8005
M. Ochiai *et al. Angew. Chem., Int. Ed*. **2005**, *44*, 6896–6899

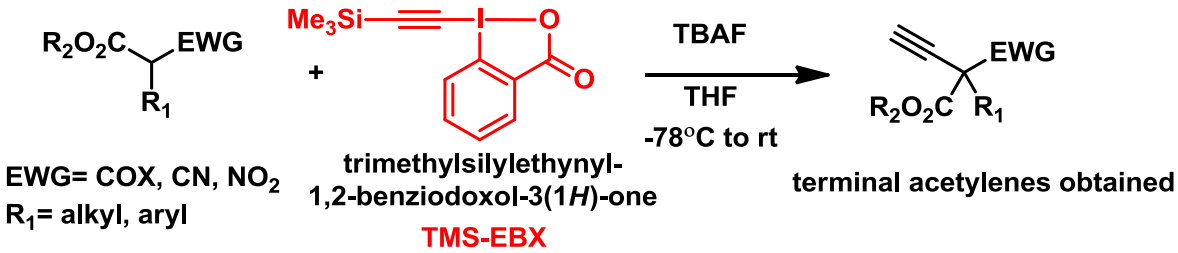
Recent Developments in Alkynylation

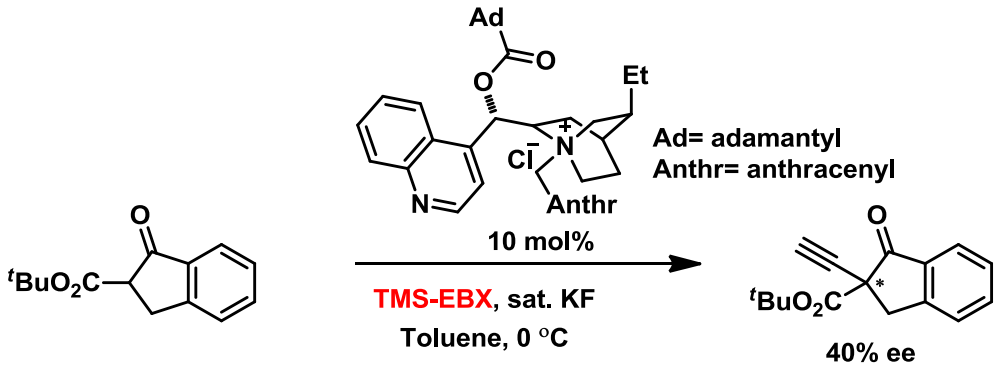
Electrophilic alkynylation : Enolate alkynylation

First alkynyliodonium salt reacted with the enolate



Improvement of the methodology involving novel hypervalent iodine reagents



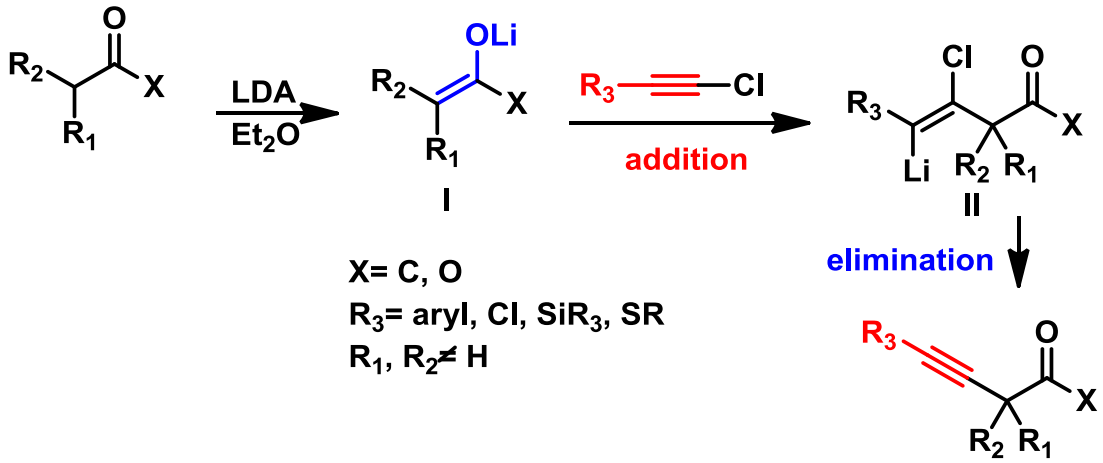


S. A. Galton *et al. J. Org. Chem*. **1965**, *30*, 1930–1934
J. Waser *et al. Chem.–Eur. J.* **2010**, *16*, 9457–9461

Recent Developments in Alkynylation

Electrophilic alkynylation : Enolate alkynylation

Alkynylation of non-stabilized enolates using chloroacetylenes

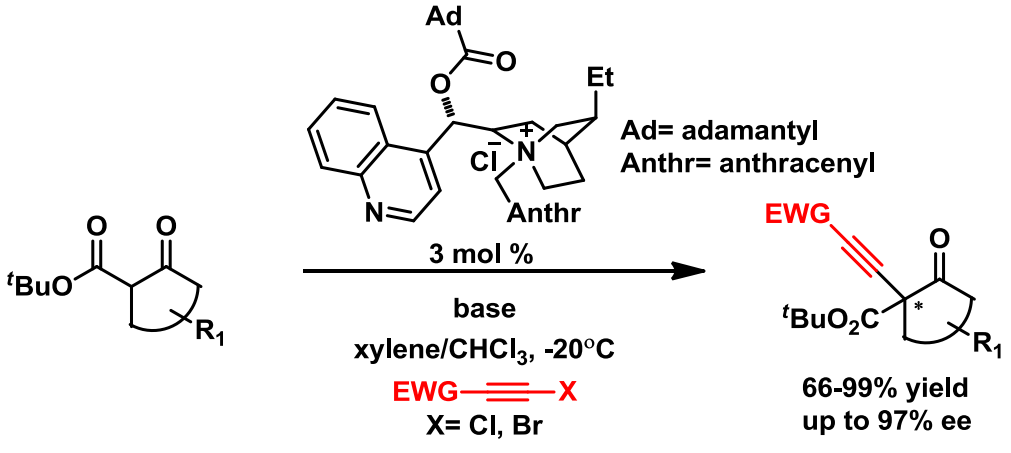


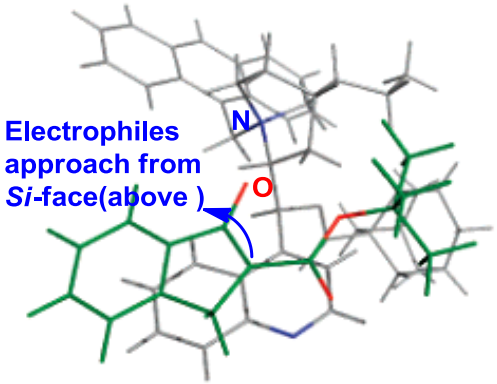
A. S. Kende *et al. J. Am. Chem. Soc.***1984**, *106,* 3551–3562
A. J. T. Pinhey *et al. J. Chem. Soc. Perkin Trans. 1,* **1997**, 1465–1468.

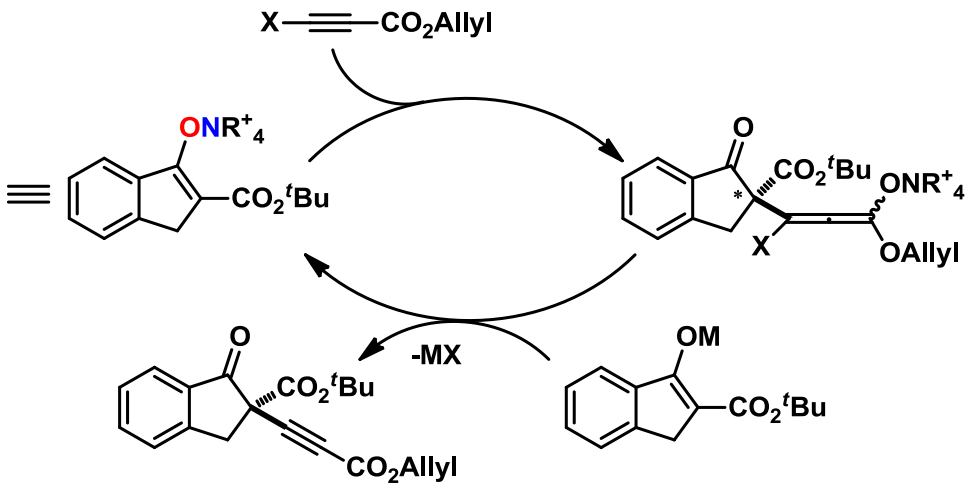
Recent Developments in Alkynylation

Electrophilic alkynylation : Enolate alkynylation

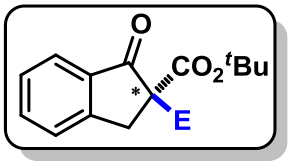
Highly enantioselective electrophilic alkynylation







Electrophile	ee (%)
Br—≡—CO_2Allyl	96
Ph, Cl, O	90
O, Me	95
Ph, Br	98

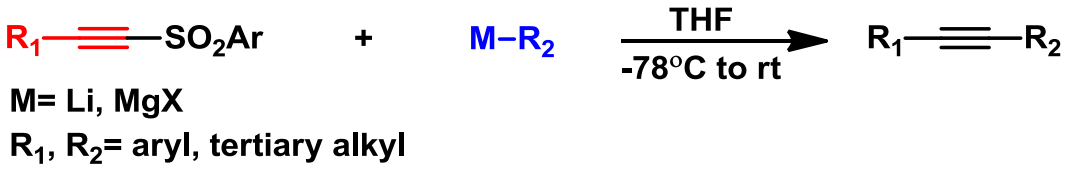


K. A. Jørgensen *et al. J. Am. Chem. Soc*. **2007**, *129*, 441-449

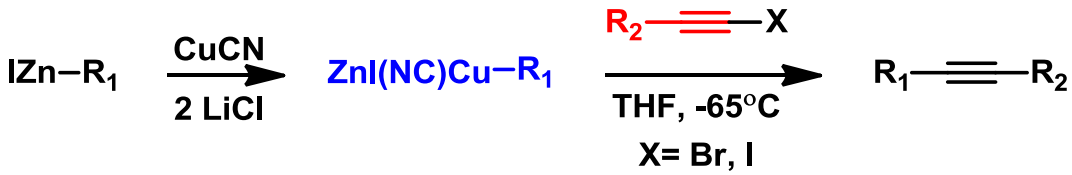
Recent Developments in Alkynylation

Electrophilic alkynylation : Alkynylation of organometallic nucleophiles

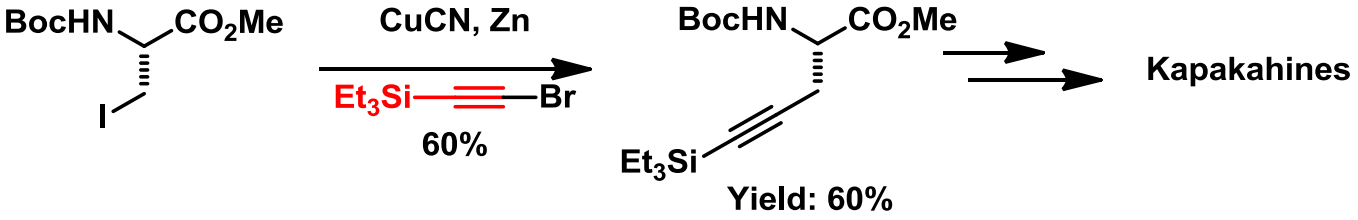
Pioneering work using alkynyl sulfones



Efficient synthesis of aliphatic acetylenes based on a mixed Zn–Cu reagent



Organocopper reagent as nucleophile in total synthesis



W. E. Truce *et al. J. Org. Chem*. **1979,** *44*, 3444–3445
P. Knochel *et al. Tetrahedron Lett.* **1989,** *30*,4799–4802.
P. S. Baran *et al. J. Am.Chem. Soc.* **2010**, *132*, 7119–7137.

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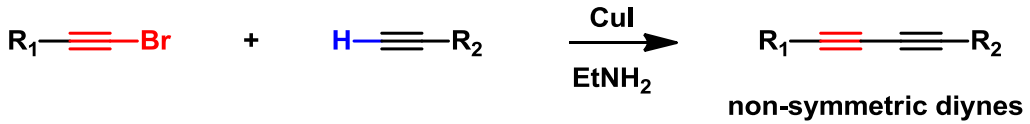
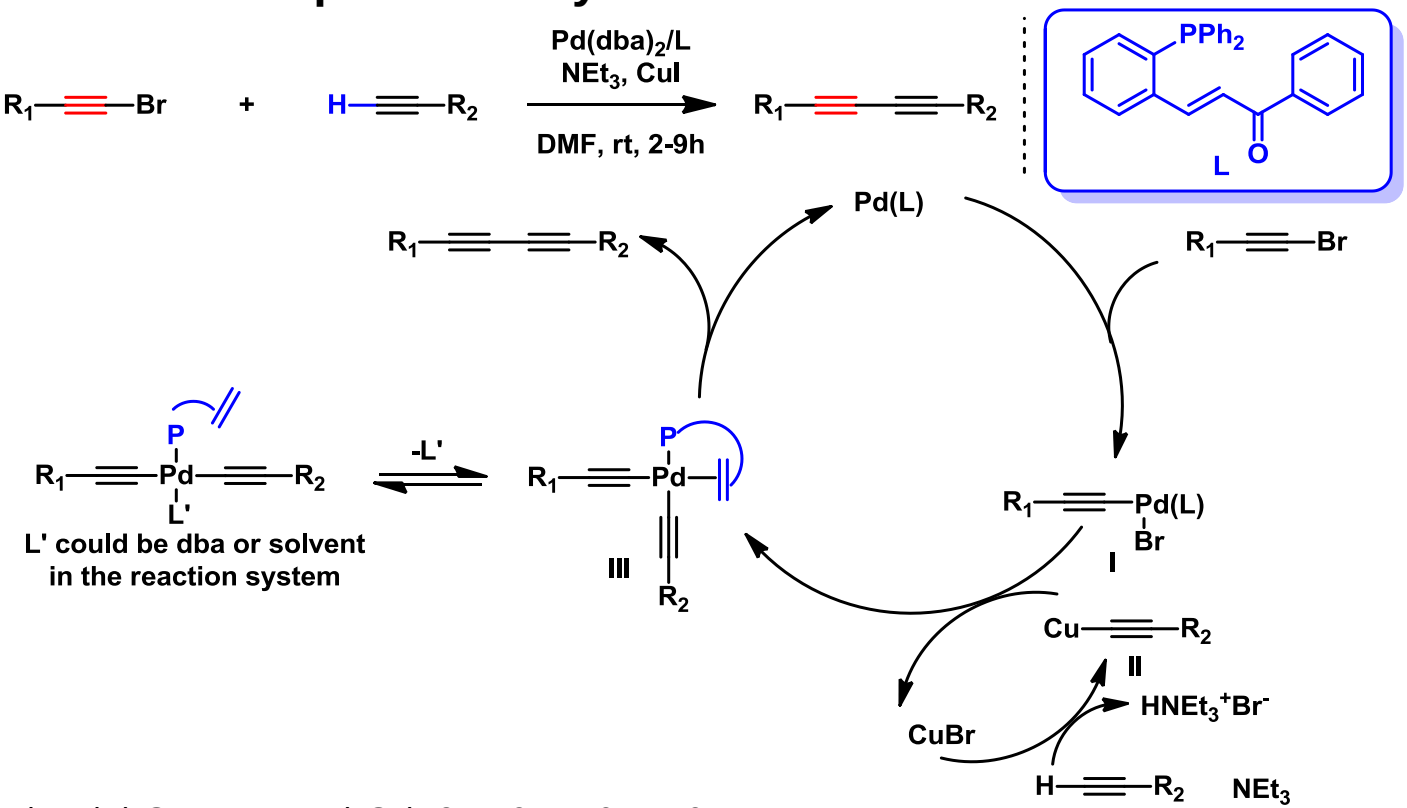
Electrophilic alkynylation : Alkynylation of C(sp)–H

Cadiot–Chodkiewicz alkynylation of terminal alkynes



Palladium could be a superior catalyst



W. Chodkiewicz *et al. Hebd. Seances Acad. Sci.* **1955**, *241,* 1055–1057.
A.-W. Lei *et al. J. Am. Chem. Soc.* **2008**, *130,* 14713–14720

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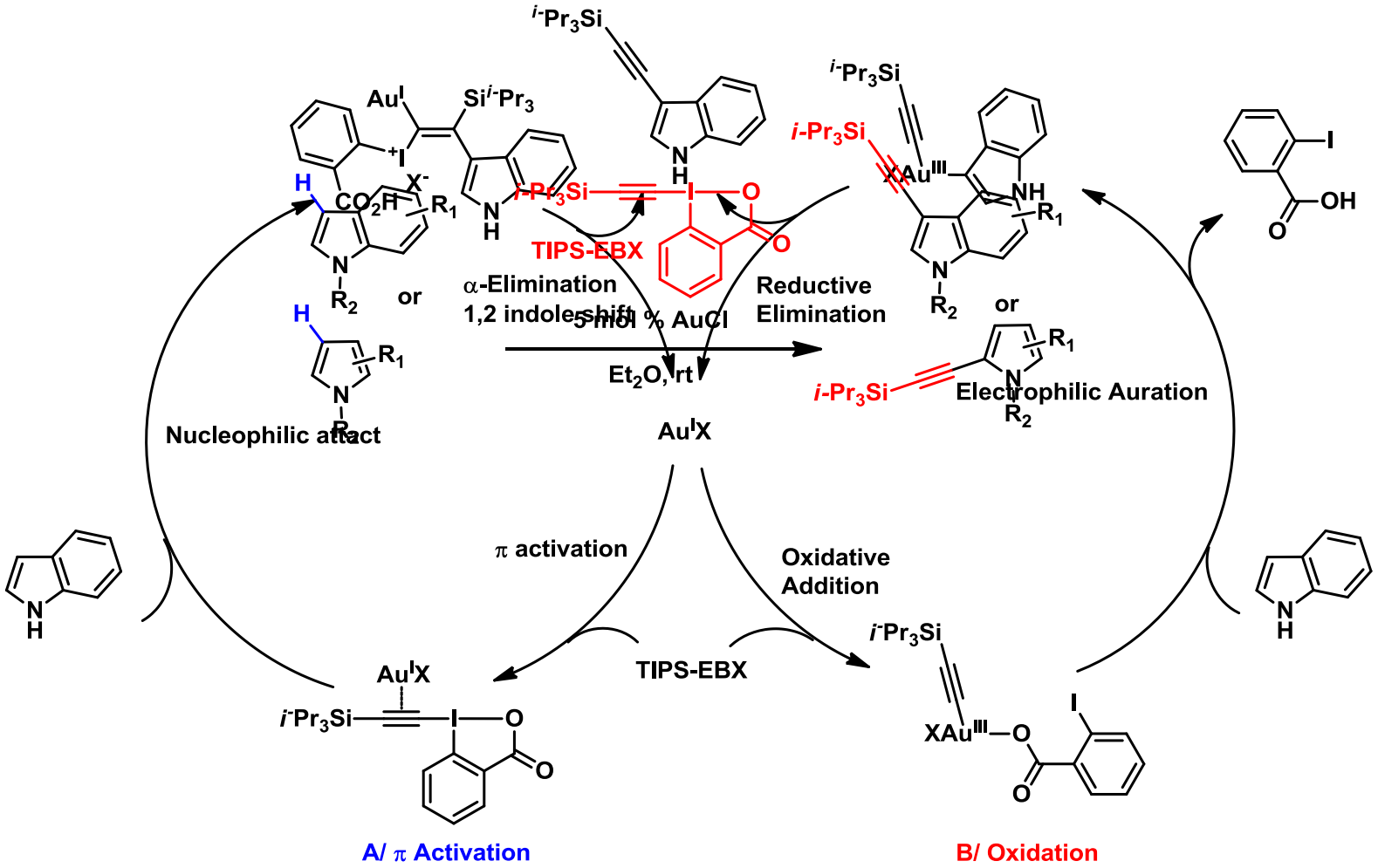
Electrophilic alkynylation : Alkynylation of C(sp^2)–H

Gold-catalyzed alkynylation of indoles and pyrroles using alkynyl benziodoxolone

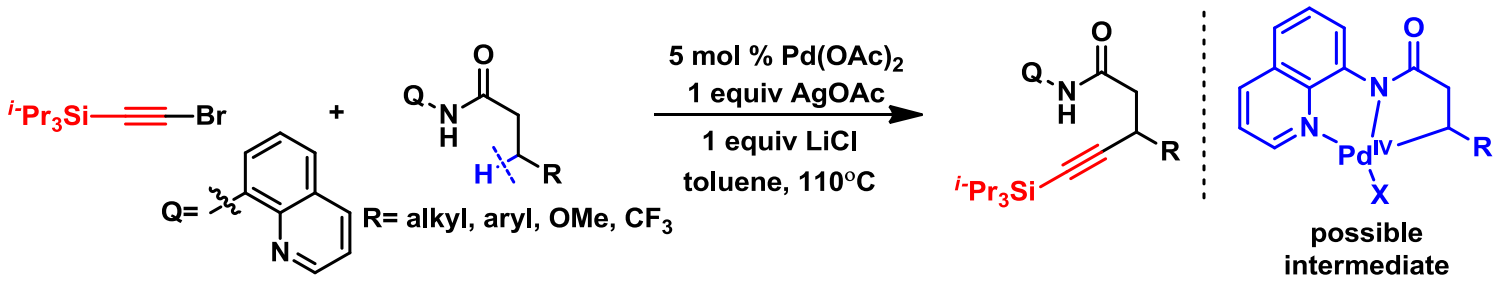


J. Waser *et al. Angew. Chem., Int. Ed*. **2009**, *48*, 9346–9349

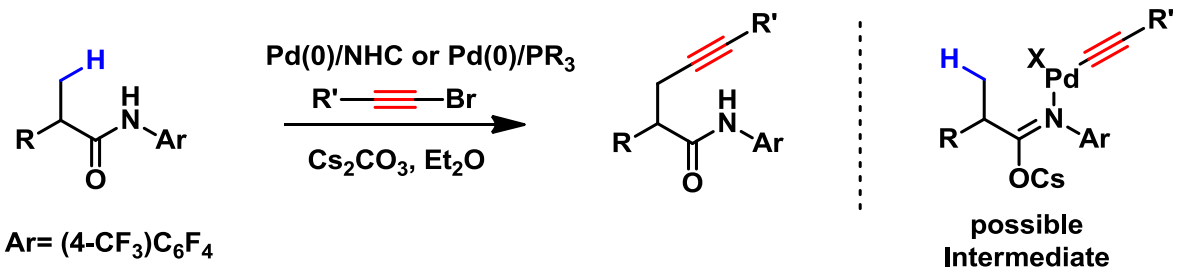
Recent Developments in Alkynylation

Electrophilic alkynylation : Alkynylation of C(sp^3)–H

First Palladium(II)-catalyzed β-C(sp^3)−H bond alkynylation



Palladium(0)-catalyzed primary β-C(sp3)−H bond alkynylation



N. Chatani *et al. J. Am. Chem. Soc*. **2011**, *133,* 12984–12986
J.-Q. Yu *et al. J. Am. Chem. Soc*. **2013,** *135* , 3387–3390

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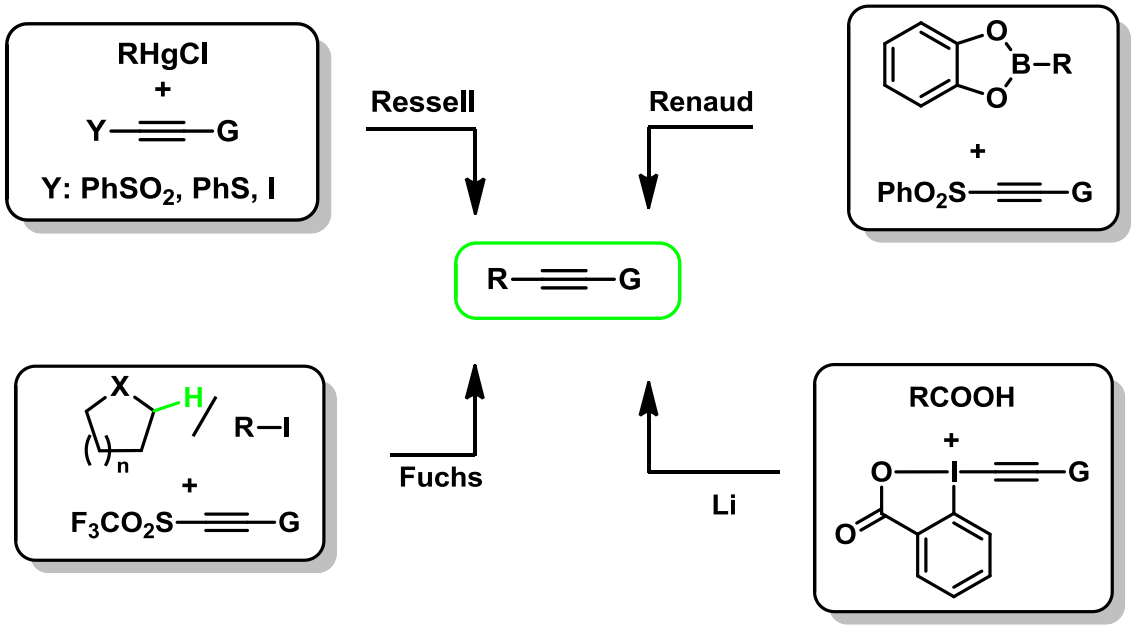
Radical C-alkynylation

Overview of radical C-alkynylation reactions

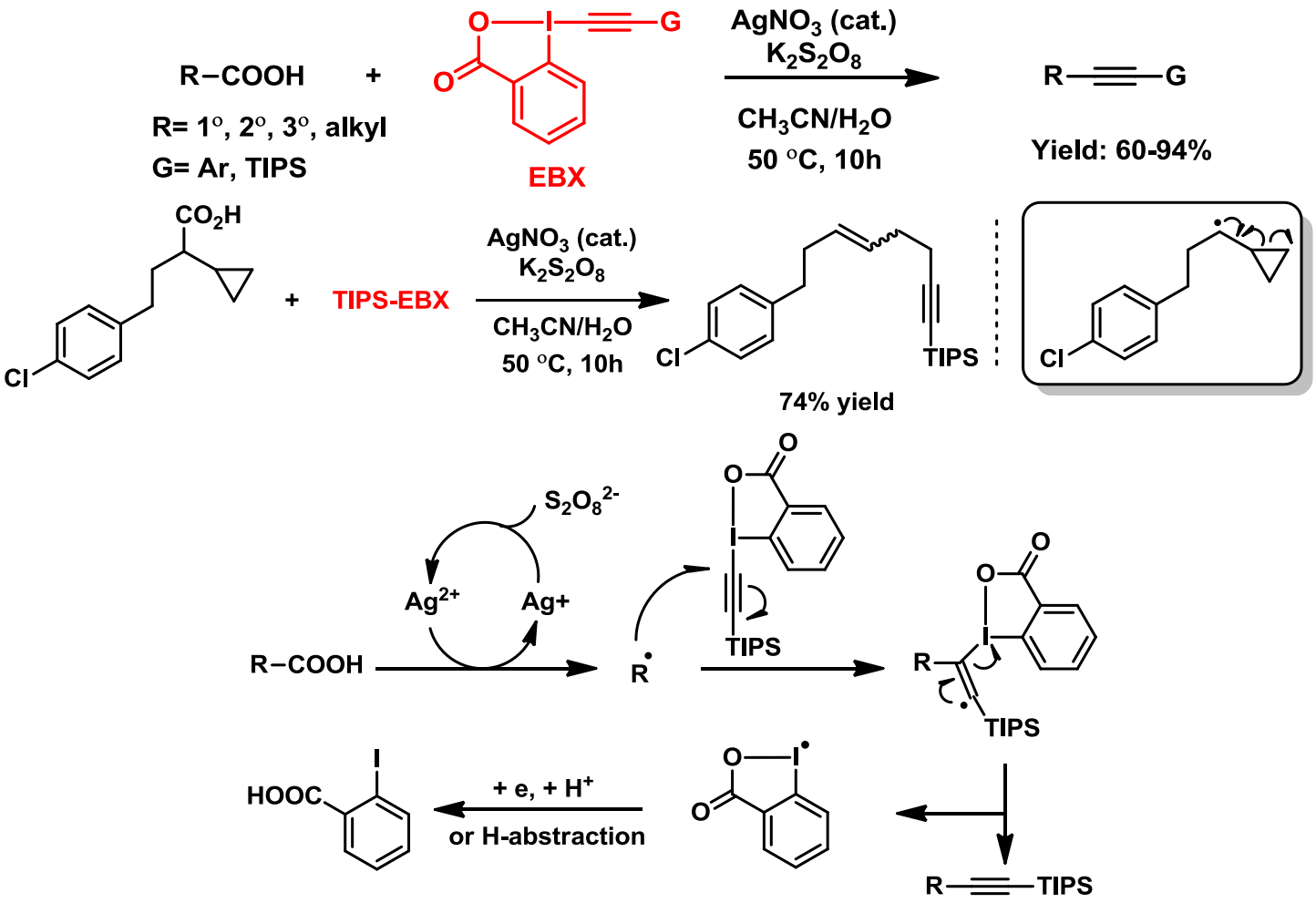


G. A. Russell *et al. Tetrahedron Lett.* **1986**, *27*, 3479-3482
P. L. Fuchs *et al. J. Am. Chem. Soc.* **1996**, *118*, 4486-4487
P. Renaud *et al. Angew. Chem., Int. Ed.* **2006**, *45*, 5847-5849
C.-Z. Li *et al. J. Am. Chem. Soc.* **2012,** *134,* 14330−14333

Recent Developments in Alkynylation

Radical C-alkynylation

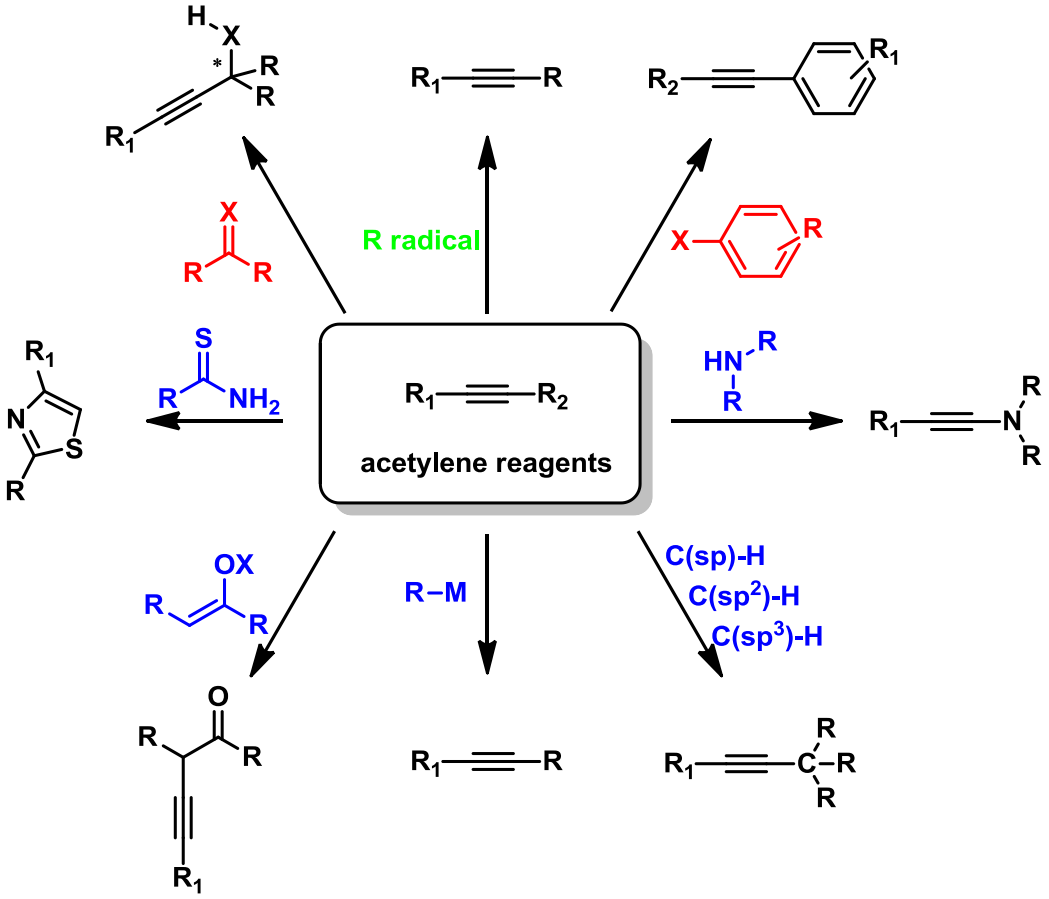
Radical-mediated C(sp^3) - C(sp) coupling



C.-Z. Li *et al. J. Am. Chem. Soc.* **2012,** *134,* 14330−14333

Recent Developments in Alkynylation

Summary



Recent Developments in Alkynylation

Acknowledgement

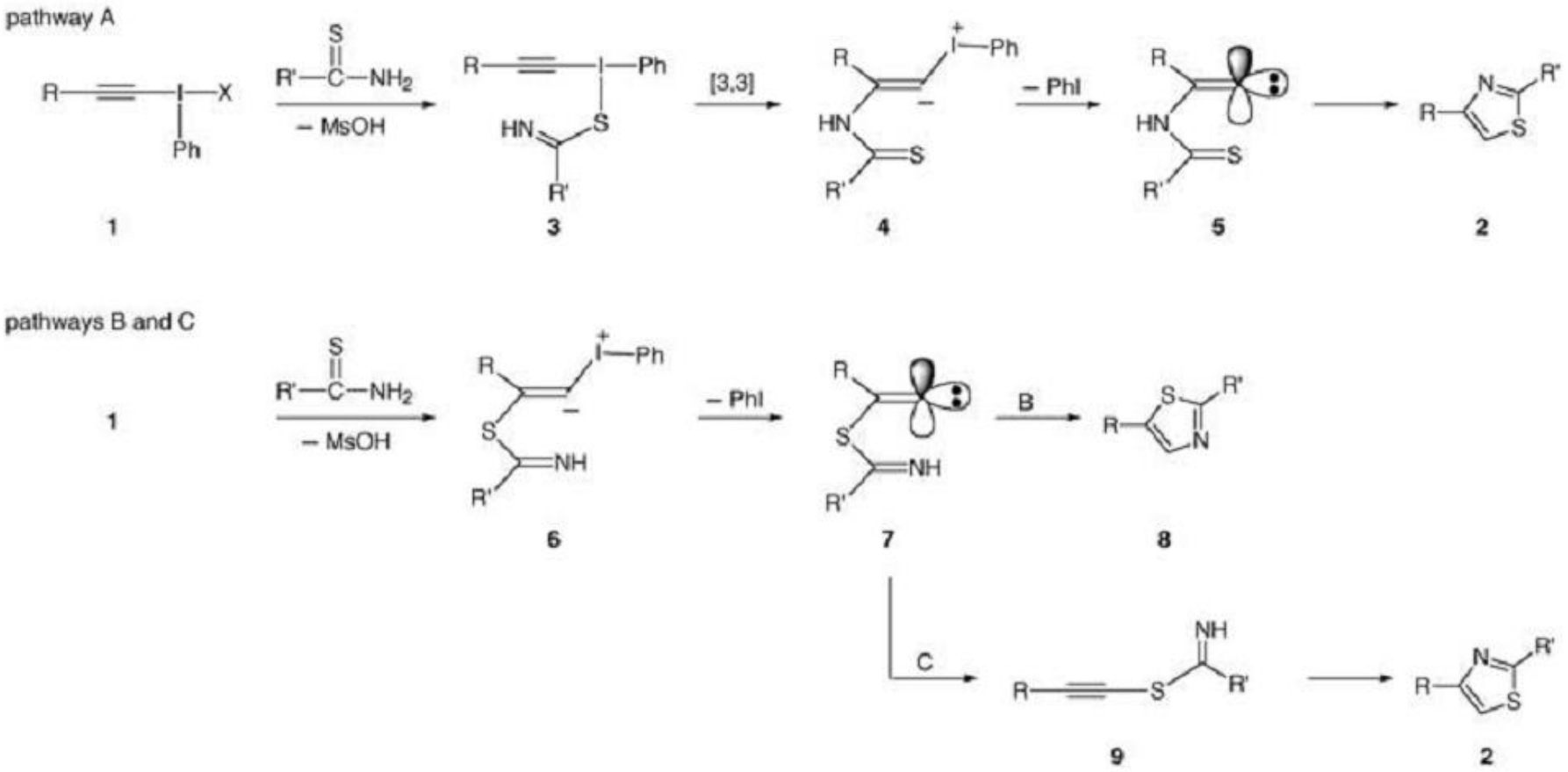
Prof. Yong Huang

All my labmates in E201

All the members in SCBB


Thank you!

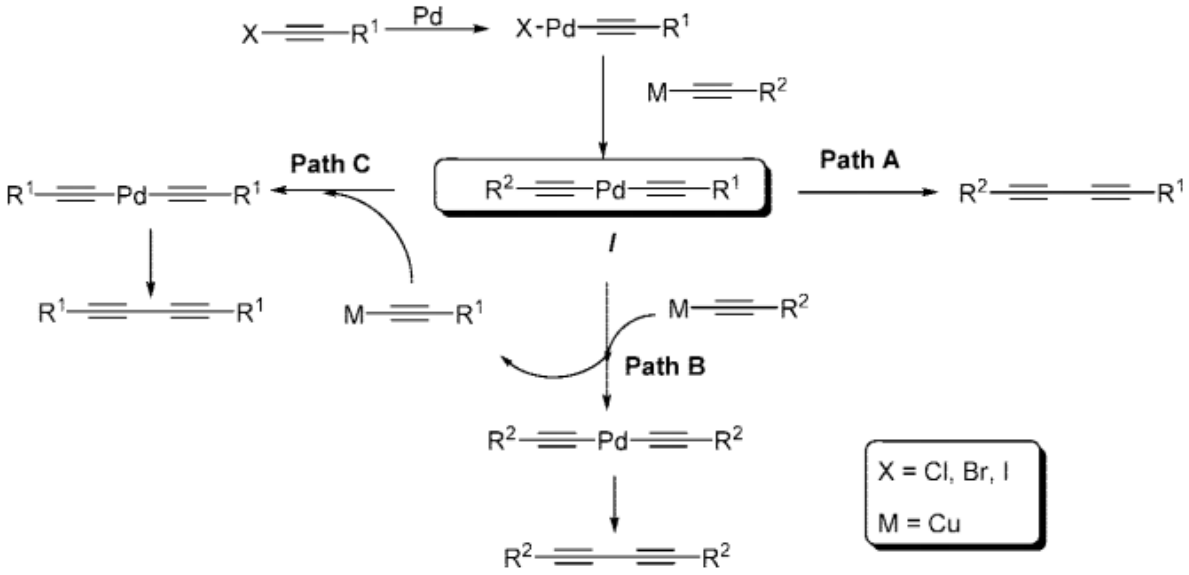
Supporting information



Scheme 2. Possible reaction mechanisms.

Supporting information

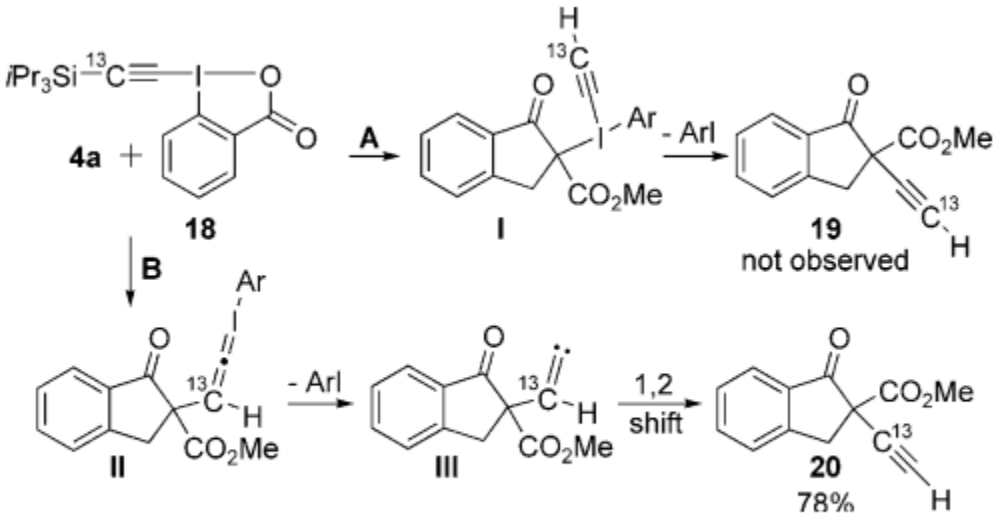
Scheme 2. Proposed Pathways of Palladium-Catalyzed C(sp)−C(sp) Coupling



Supporting information

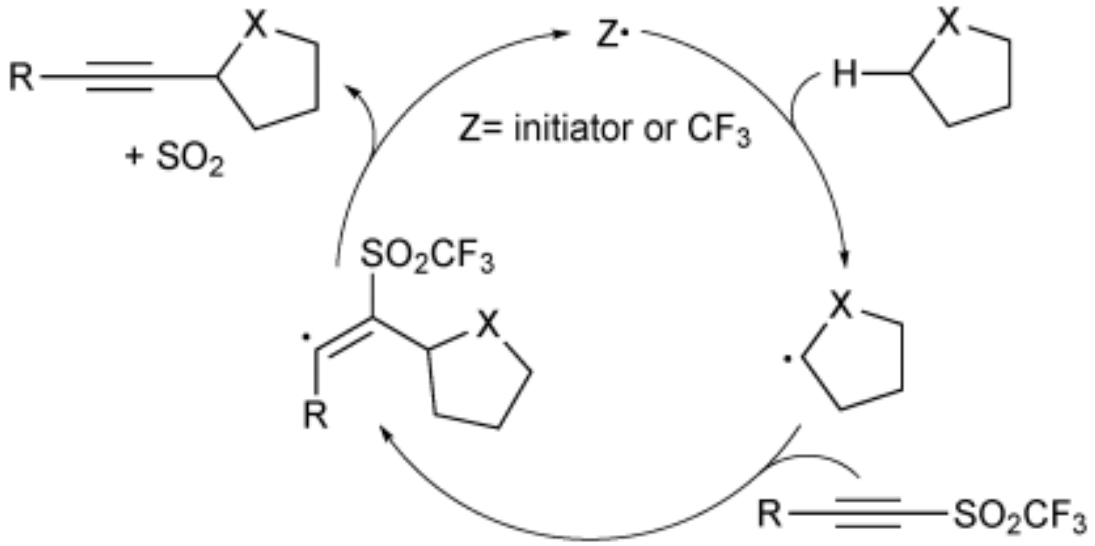
General Procedures for the Coupling Reactions.

To an ovendried Schlenk tube with a magnetic stir bar were added Pd(dba)2 (11.5 mg, 0.02 mmol), L1 ligand (7.9 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol). DMF (1 mL) was added via a syringe. The system was vacuumed with an oil pump at 0 ° C and filled with nitrogen, and this was repeated five times. After the mixture was stirred under nitrogen for about 10 min, alkyne (0.6 mmol) was added via a microliter and stirred for another 5 min. 1-Bromoalkyne was added last via a microliter syringe. The system was stirred at room temperature for 10 h. Upon completion, 4 mL of brine was added, and the mixture was extracted by ethyl acetate (3 mL × 3). The product was obtained by flash column chromatography.



Scheme 3. Possible mechanisms for the ethynylation reaction and labeling experiment (Ar = phenyl-2-carboxylate).

Scheme 65 Radical alkynylation of sp^3 C–H bonds using alkynyl triflones.



Scheme 66 Mechanism of the radical alkynylation.