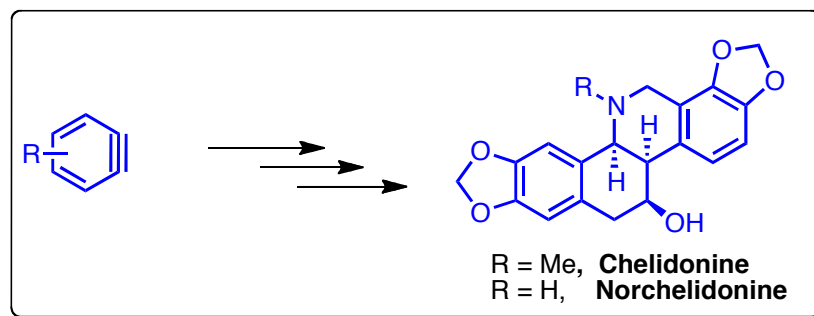


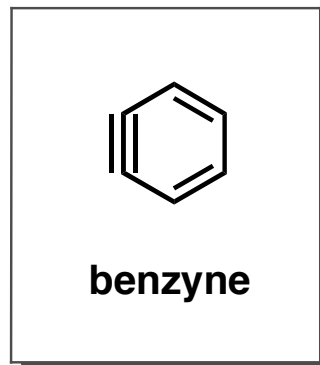
Total Synthesis of Chelidonine and Norchelidonine via An Enamide-Benzyne-[2+2] Cycloaddition Cascade

Zhi-Xiong Ma, John B. Feltenberger and Richard P. Hsung *Org. Lett.*, **2012**, 14, 2742-2745



Current Literature Presentation
Jaideep Saha
06.09.2012

Benzyne: An Overview

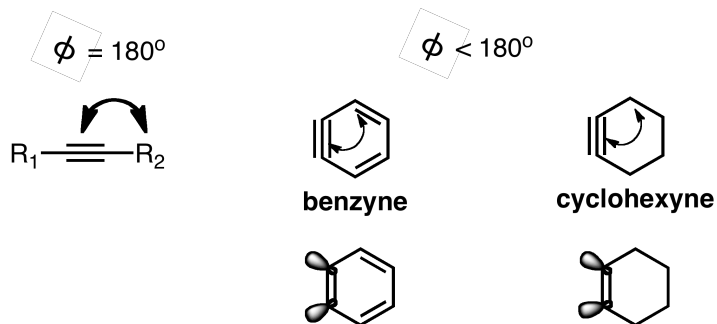


- ✓ A possible existence of benzyne was considered by **Wittig** in a reaction of fluoro benzene with phenyl lithium in 1942.
- ✓ J. D. Roberts first proposed the structure of benzyne in 1953.
- ✓ Till date, over 75 natural products have been synthesized that utilized functionalized arynes to generate key intermediates in the synthesis.

J. Am. Chem. Soc. **1953**, 75, 3290
Chem. Rev. **2012**, ASAP

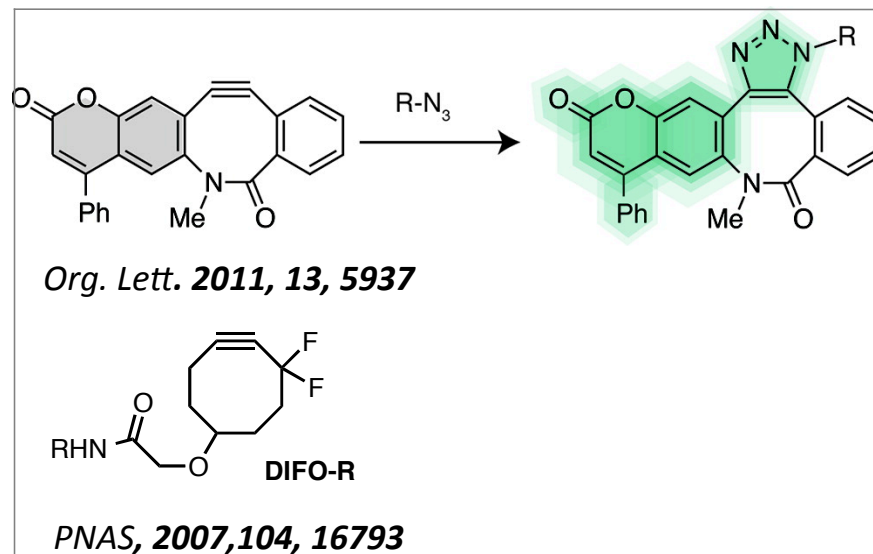
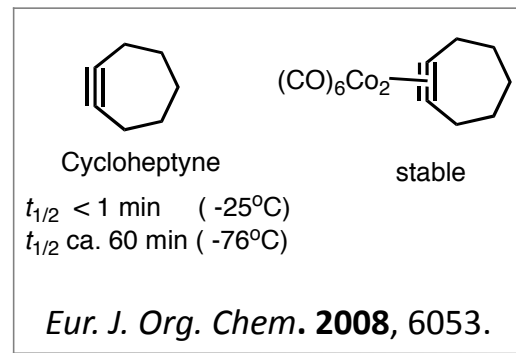
Arynes and related molecules: Structure and Reactivity

Geometrical angle versus hybridization angle



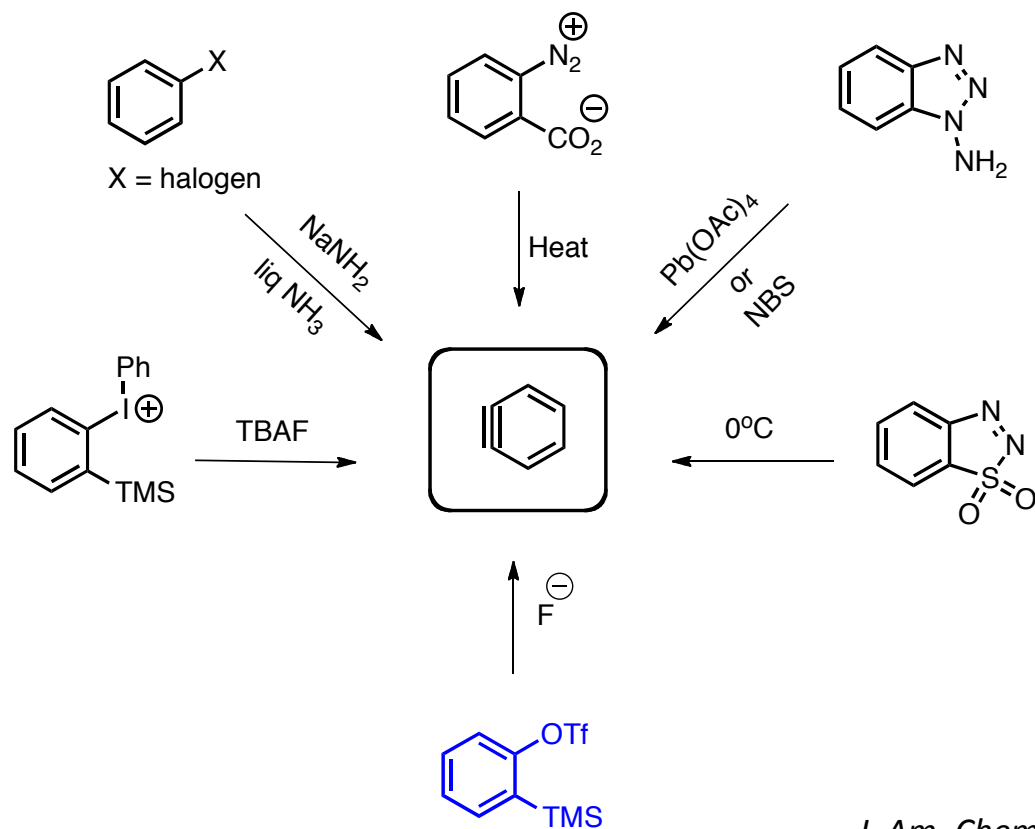
Electrophilic

Bond Energy: Acetylene 76 Kcal/ mol
 Cyclohexyne 35 Kcal/ mol



Angew.Chem. Int. Ed. **2012**, *51*, 3766

Different methods for the preparation of Benzyne

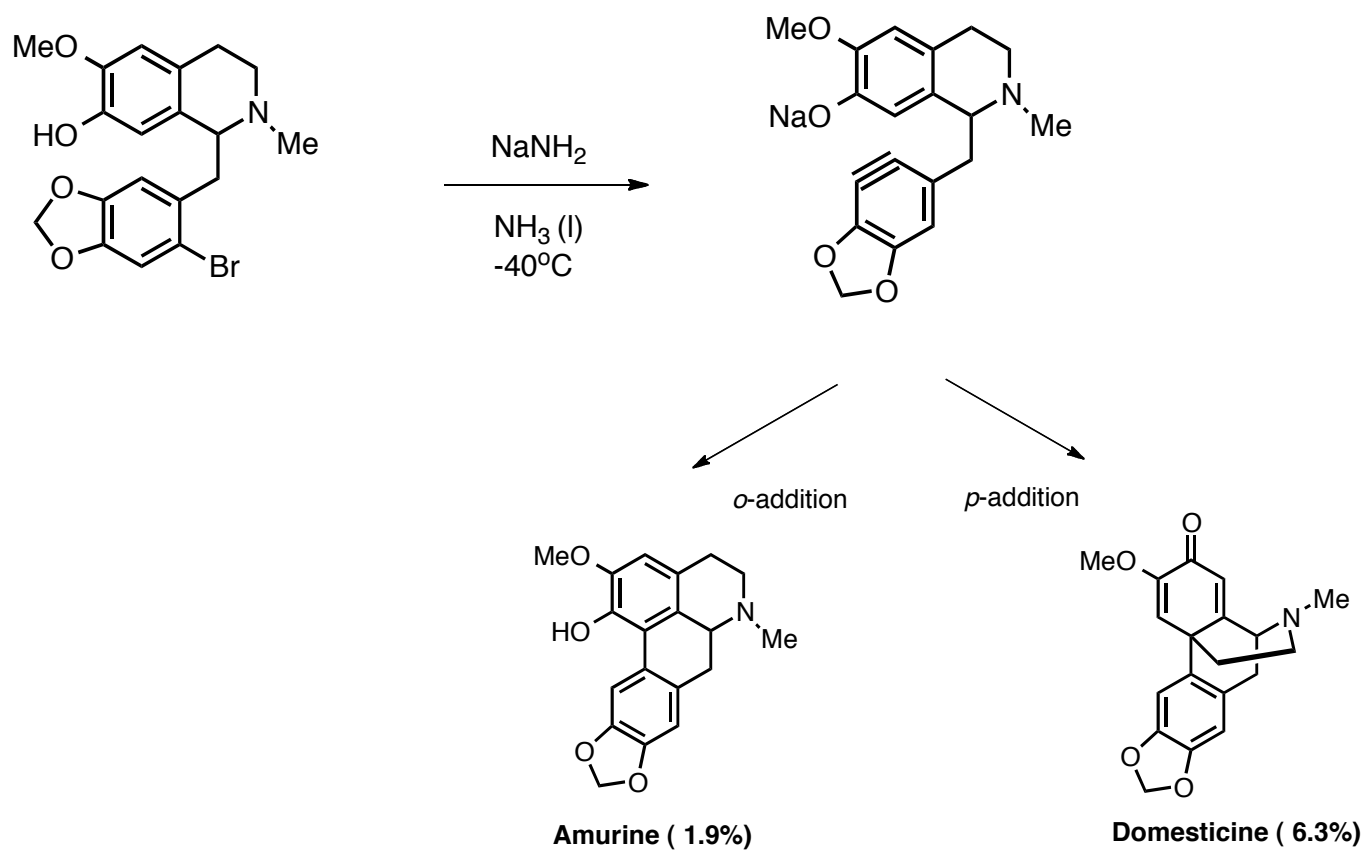


J. Am. Chem. Soc. **1953**, 75, 3290
Angew. Chem. Int. Ed. **1965**, 4, 239
Tetrahedron. **2000**, 56, 1013
Chem. Lett. **1983**, 1211

Classification of the Reaction Manifolds:

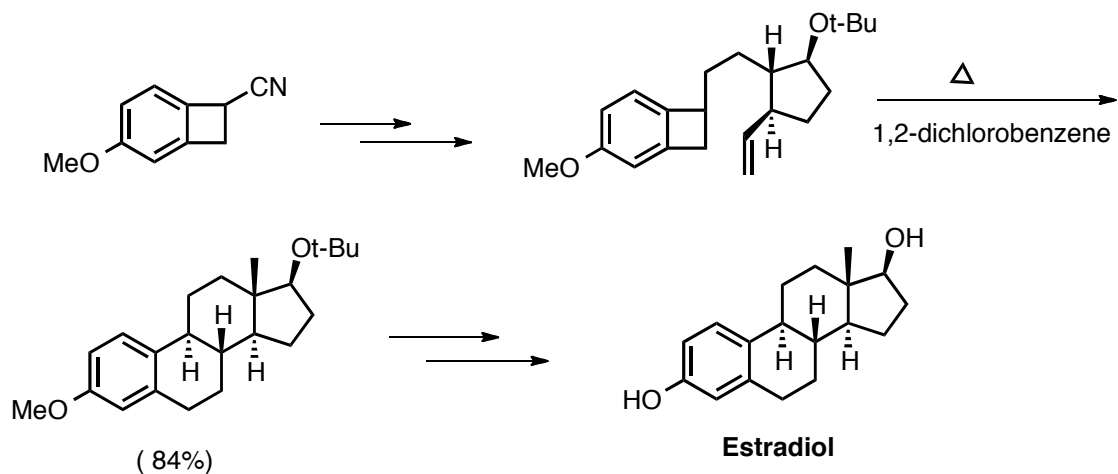
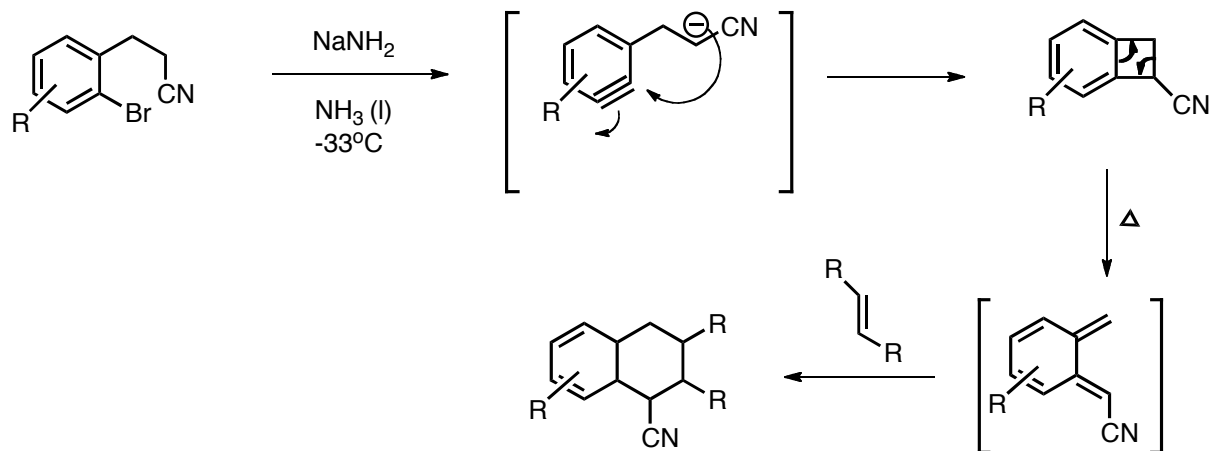
1. Synthetic strategies involving nucleophilic addition onto arynes.
2. Strategies based on Insertion reaction.
3. Cycloaddition Reactions.
4. Multicomponent Reactions.

Nucleophilic addition : Synthesis of Domesticin and Amurine



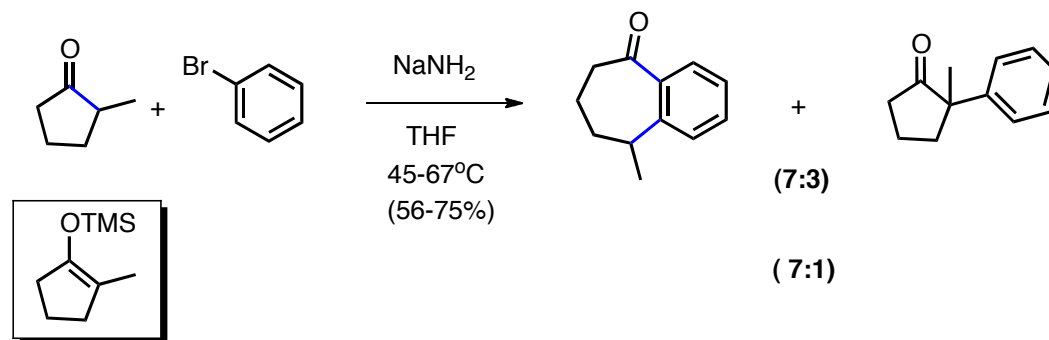
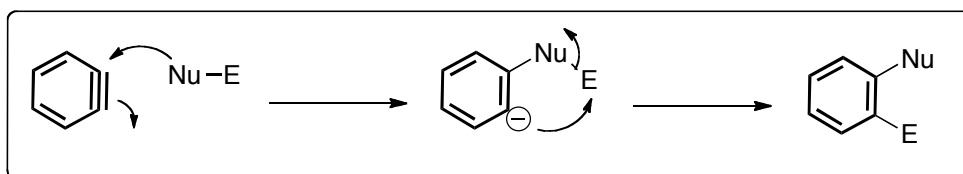
J. Chem. Soc. C. **1971**, 2712.
Heterocycles. **1976**, 4, 1013

Benzocyclobutane via Intramolecular Nitrile Acylation: Application in the Synthesis of Estradiol

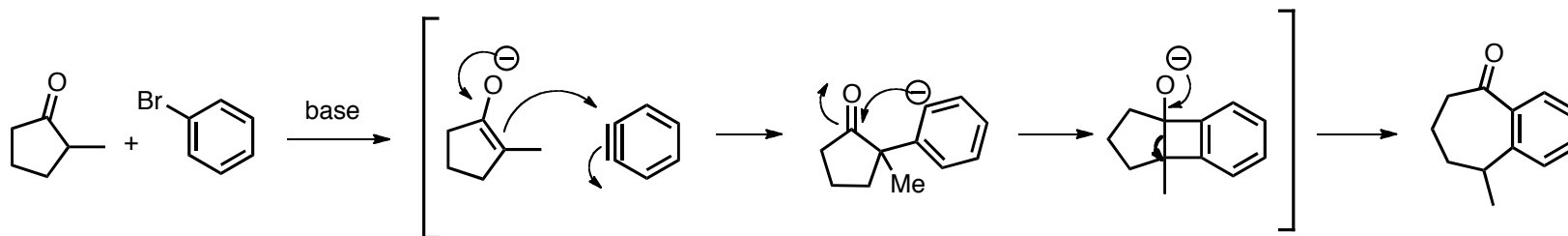


J. Am. Chem. Soc. **1978**, 10, 6218

Carbon-Carbon Bond Insertion of Benzyne



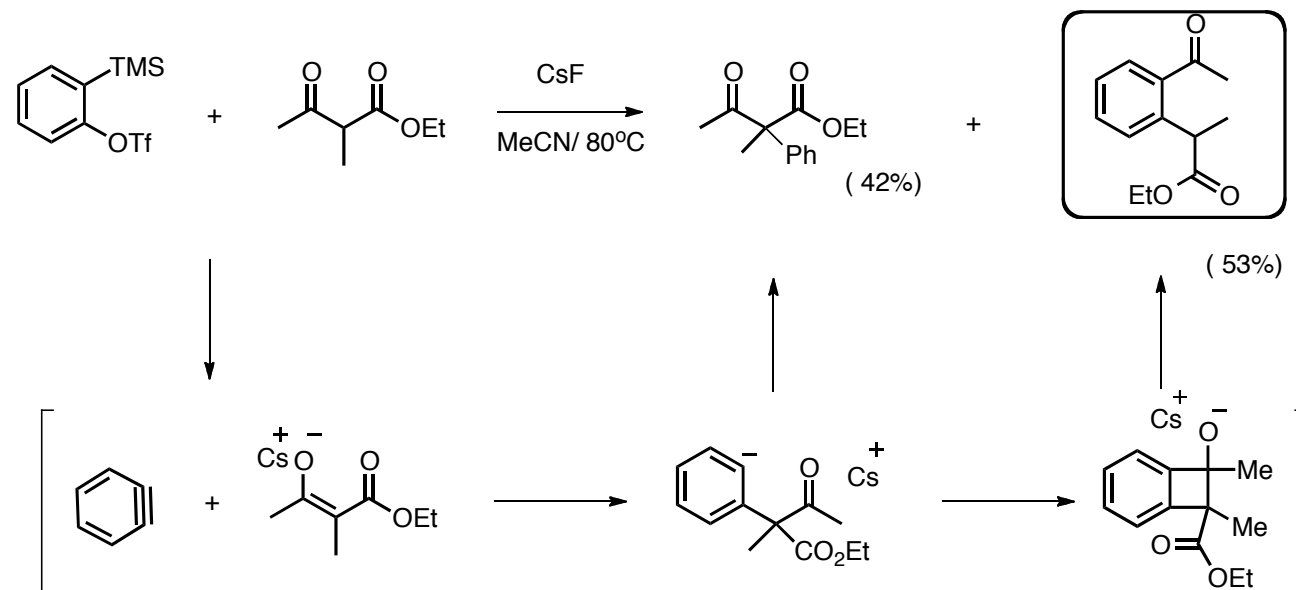
Mechanism:



J. Am. Chem. Soc. **1994**, 116, 9471

Carbon-Carbon Bond Insertion of Benzyne

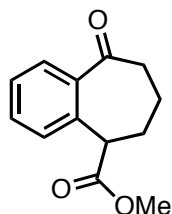
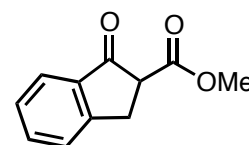
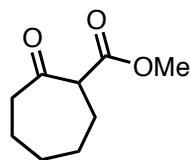
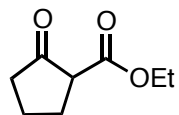
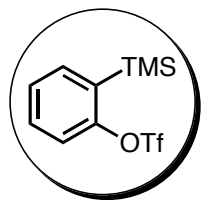
Acyl-Alkylation of Aryne



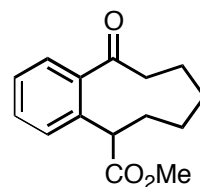
J. Am. Chem. Soc. **2005**, 127, 5340

Carbon-Carbon Bond Insertion of Benzyne

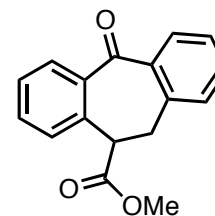
Substrate scope:



(50%)

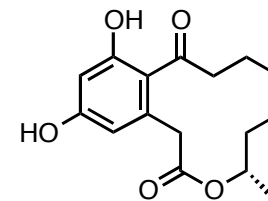
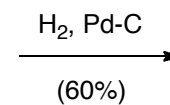
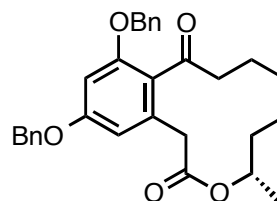
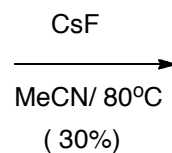
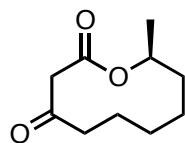
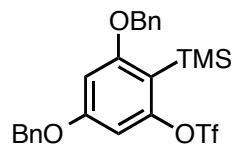


(69%)



(61%)

Application in the Enantioselective Synthesis of (-) Curvularin

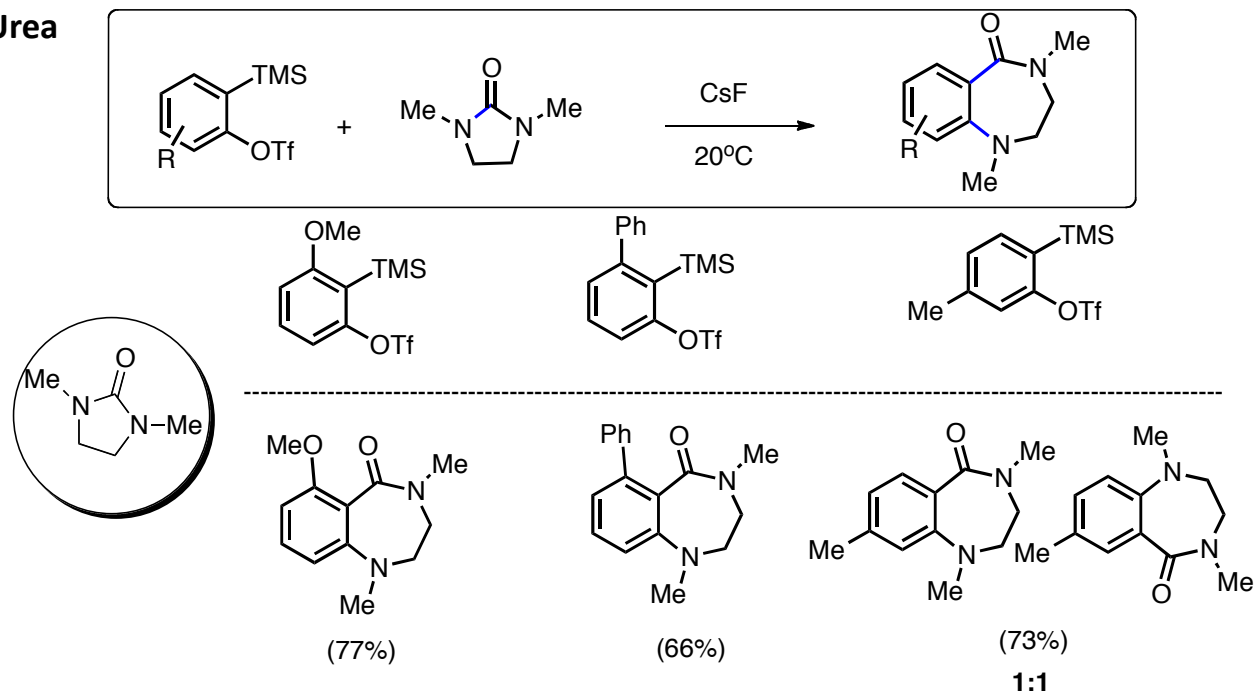


(-) Curvularin

Org. Lett. **2010**, *12*, 1612

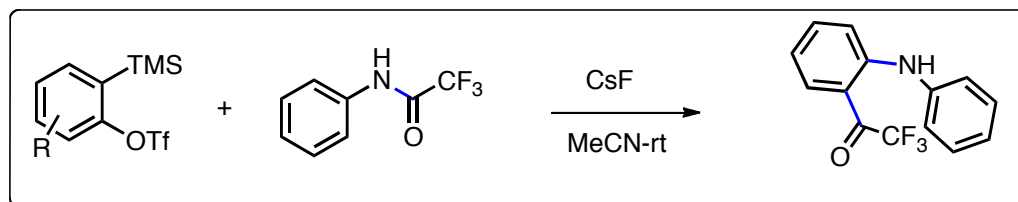
Carbon-Carbon Bond Insertion of Benzyne

Addition of Urea



Angew. Chem. Int. Ed. **2002**, 41, 3247

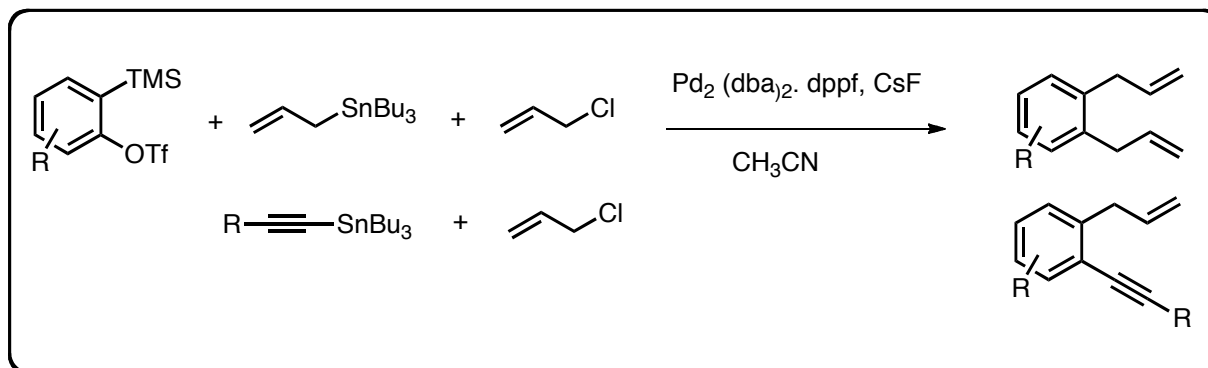
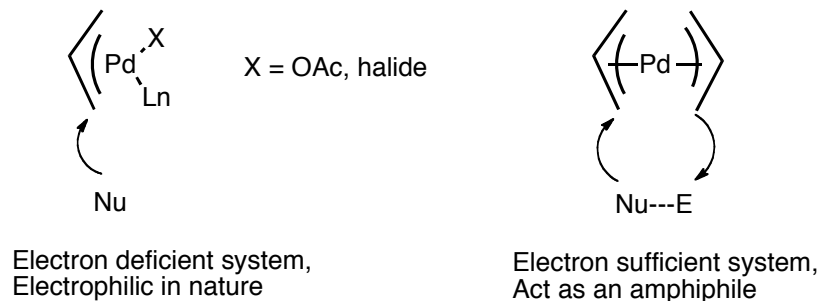
Addition of Amide



J. Am. Chem. Soc. **2005**, 127, 13112

Metal Mediated Functionalization/ Insertion Reactions of Benzynes

Difference in reactivity of mono and bis π -allylpalladium complexes

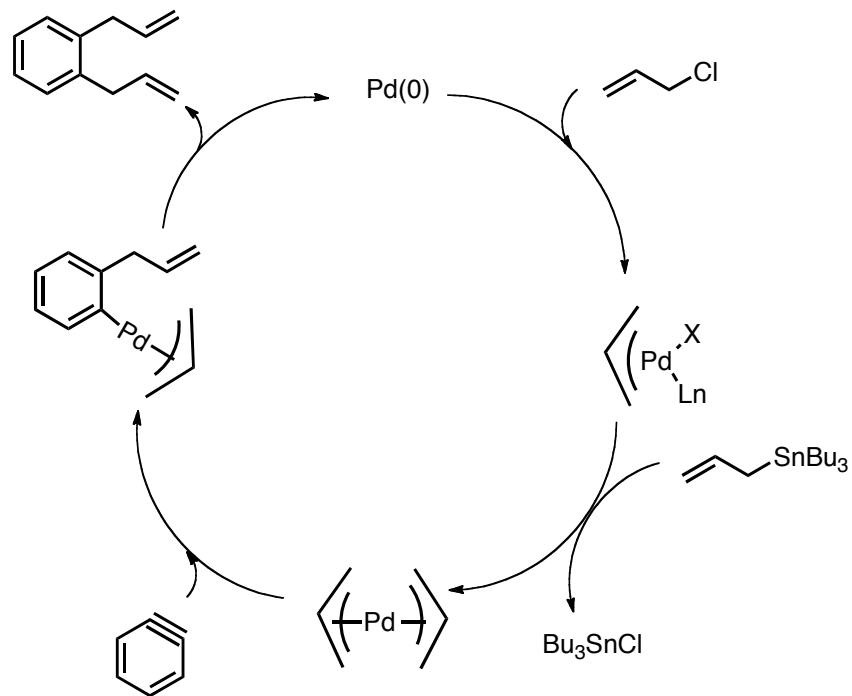


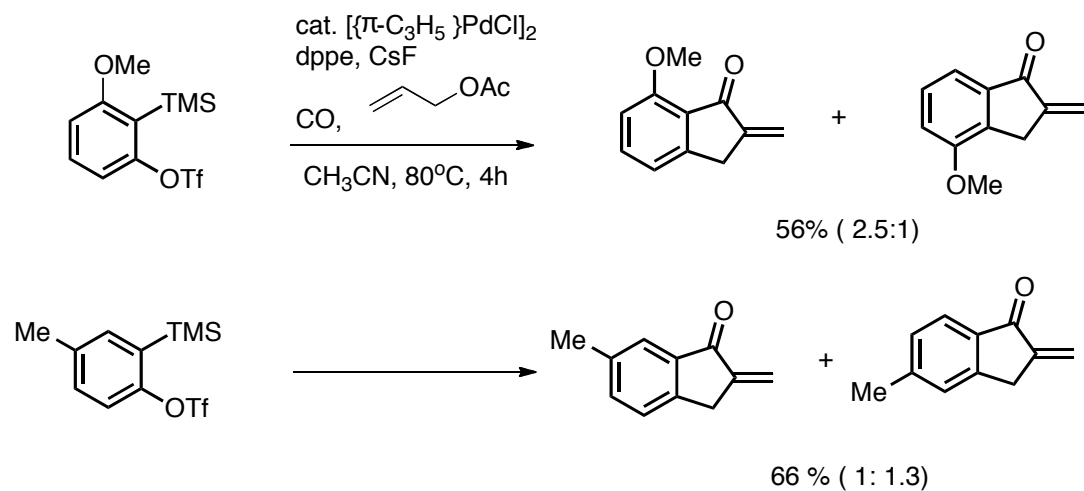
Org. Lett. **2008**, 10, 2393

Tet. Lett. **2000**, 41, 729

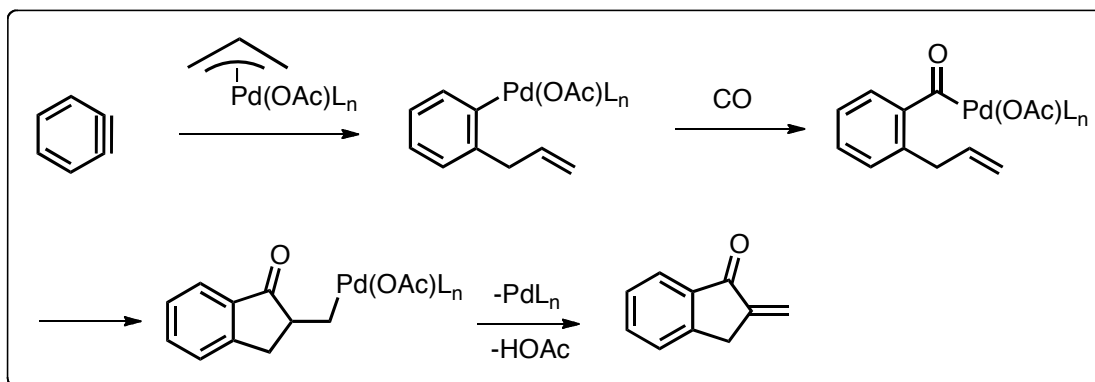
Carbon-Carbon Bond Insertion of Benzyne

Mechanism for bis allylation of aryne



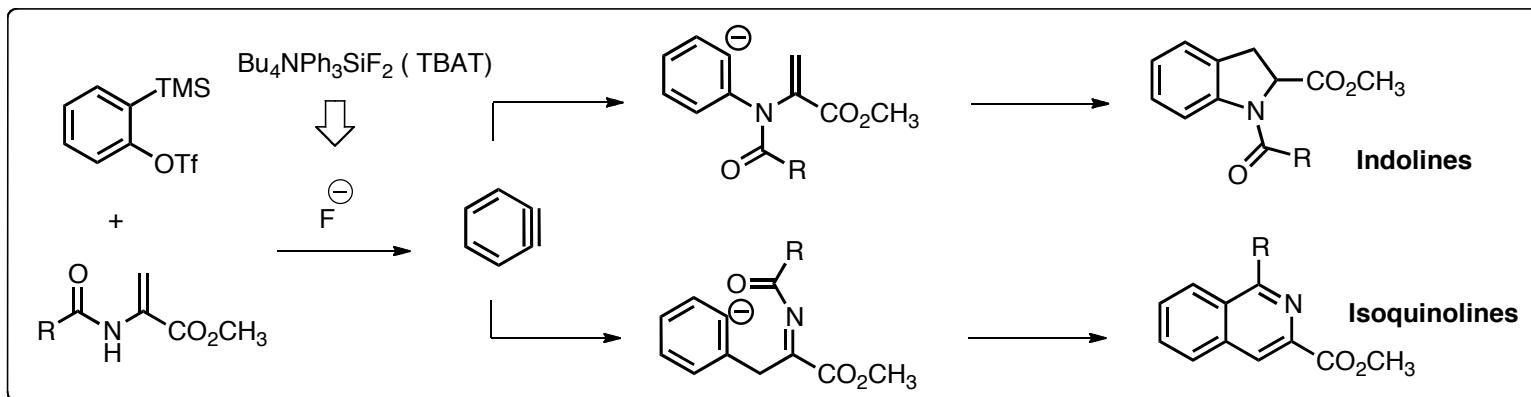


Mechanism:



J. Am. Chem. Soc. **2001**, 123, 12686

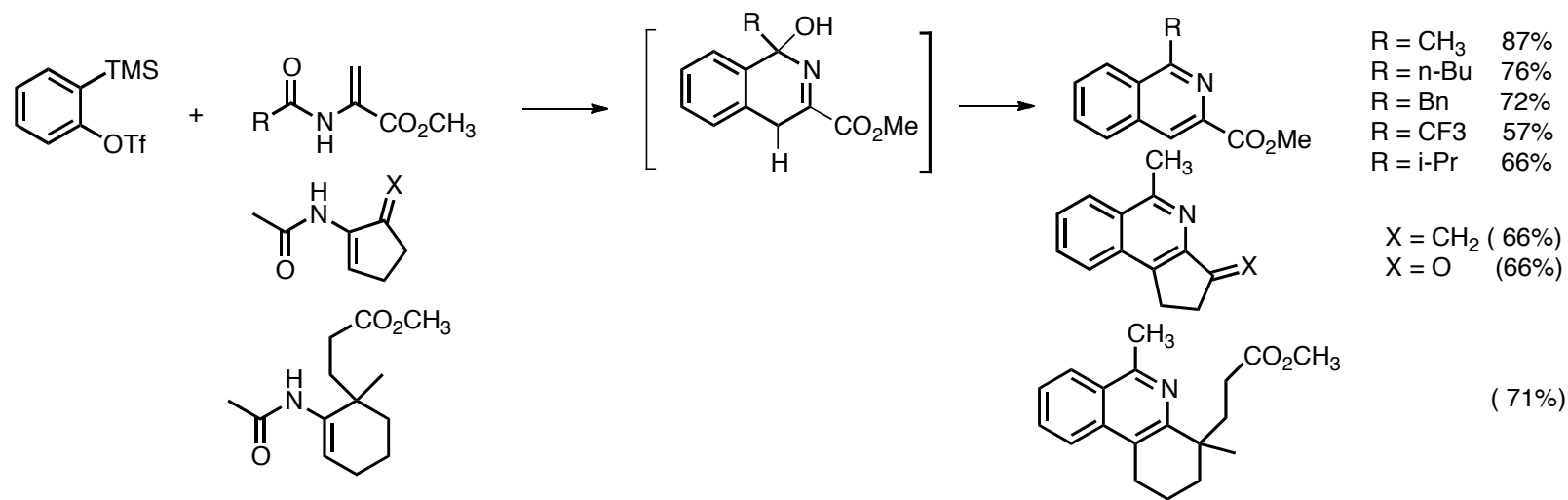
Aryne Annulation by Cycloaddition Reaction



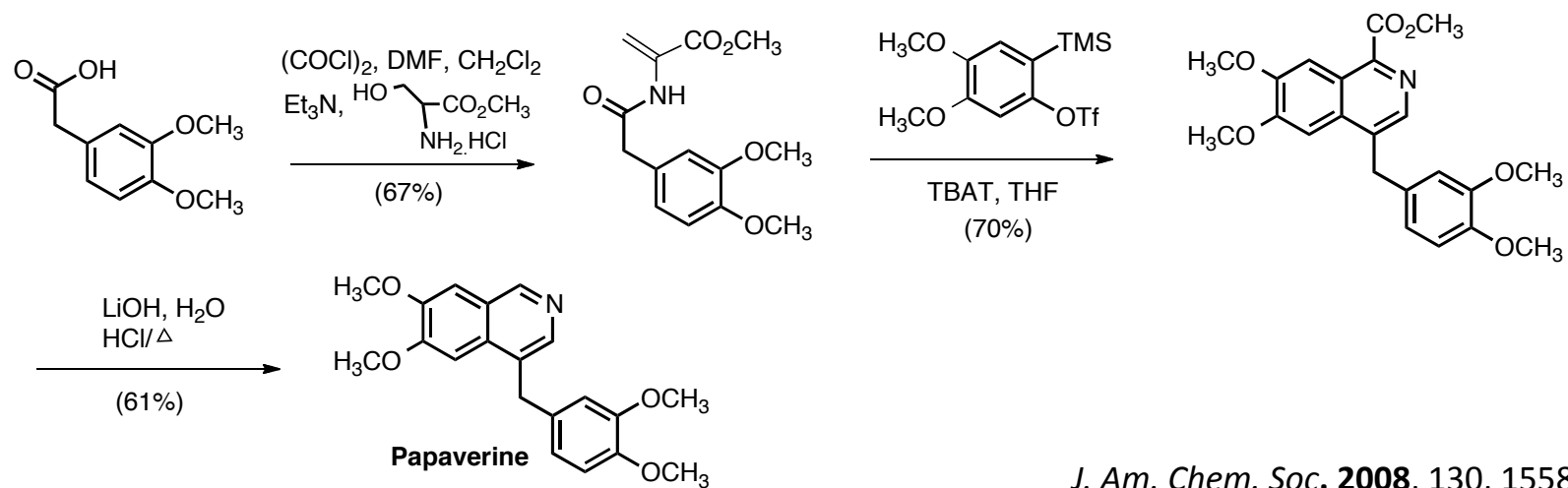
entry	silyl aryl triflate	ene carbamate	product	yield
1				61%
2				49% ^b
3				39%
4				40%

J. Am. Chem. Soc. **2008**, 130, 1558

Aryne Annulation by Cycloaddition Reaction

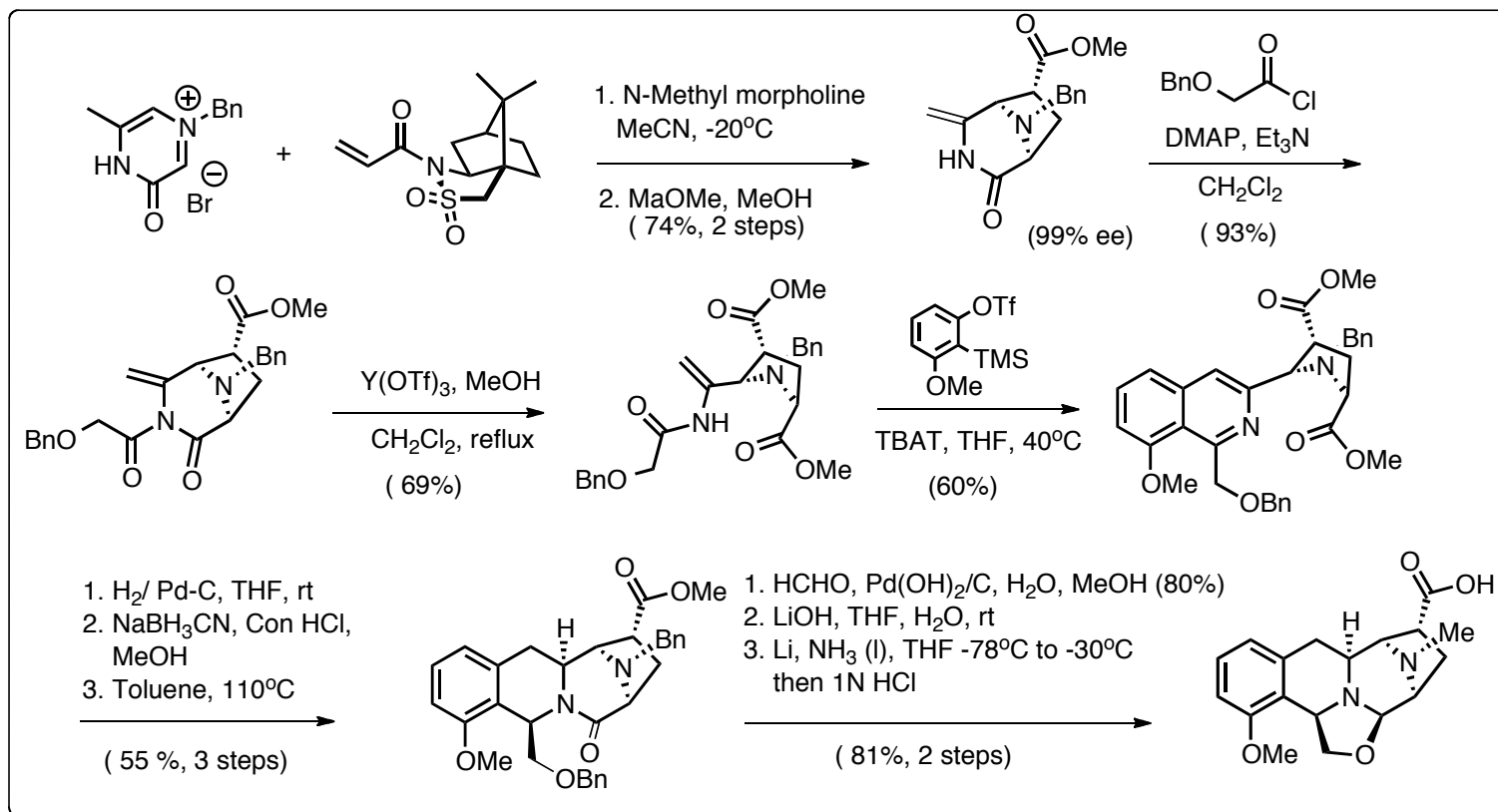
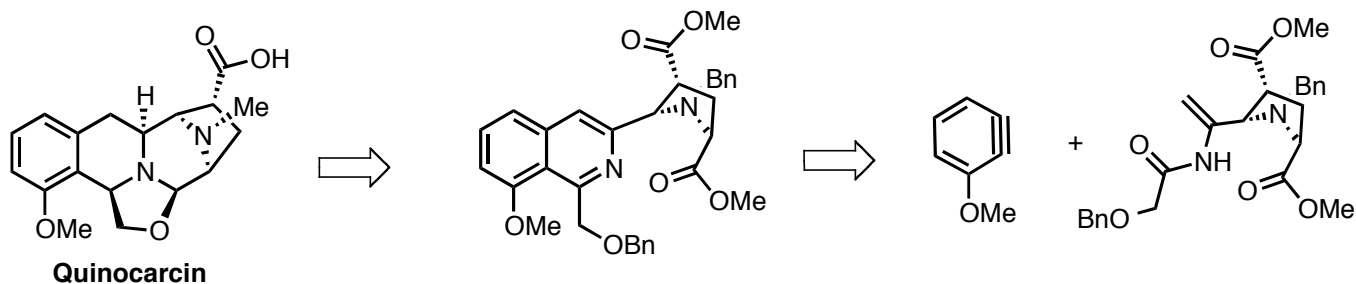


Synthesis of Papaverine

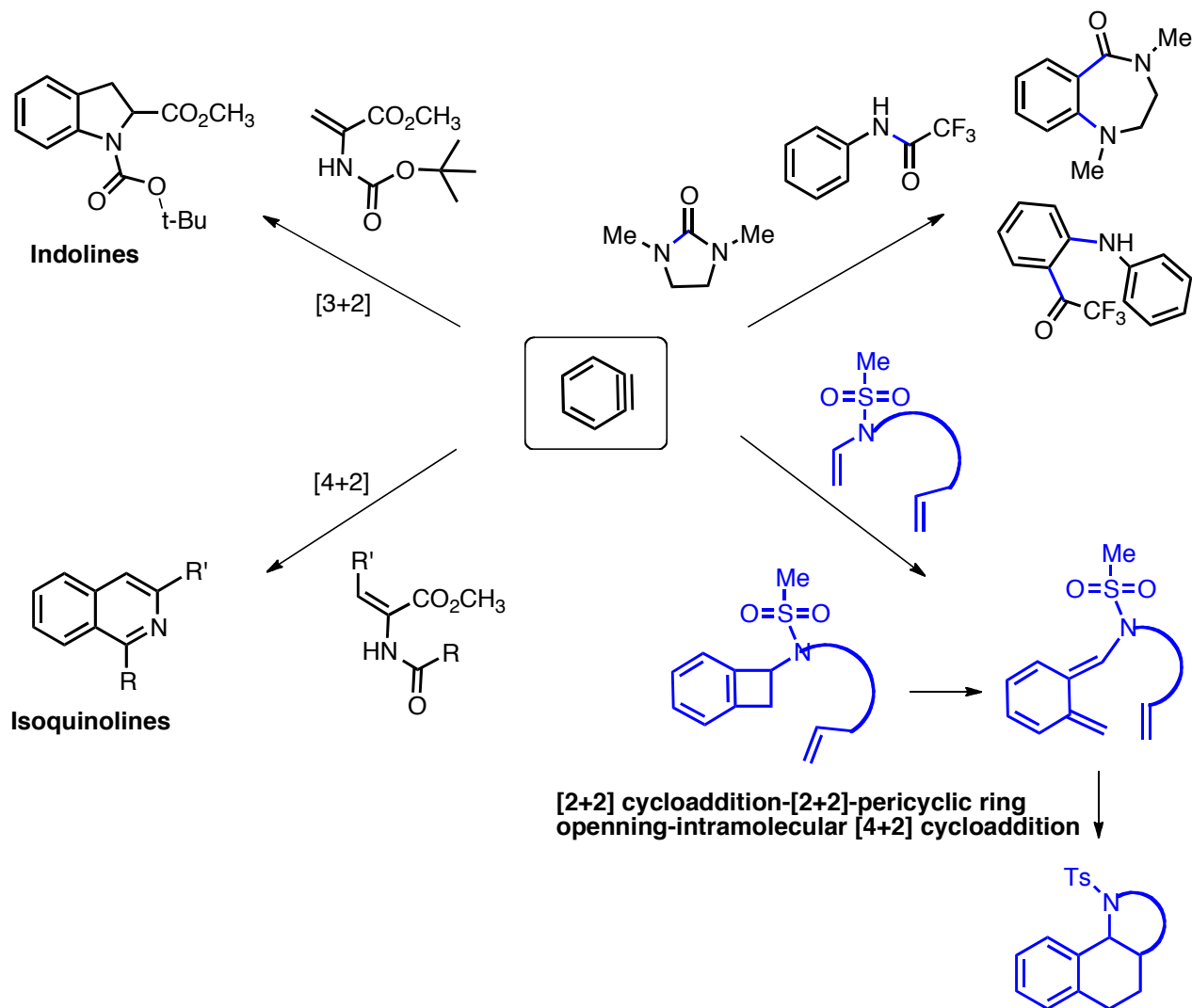


J. Am. Chem. Soc. **2008**, 130, 1558

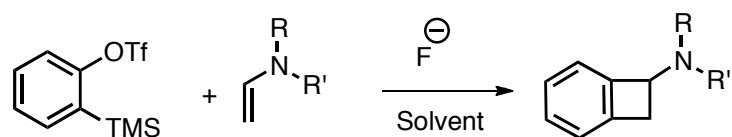
Application: Total Synthesis of Quinocarcin



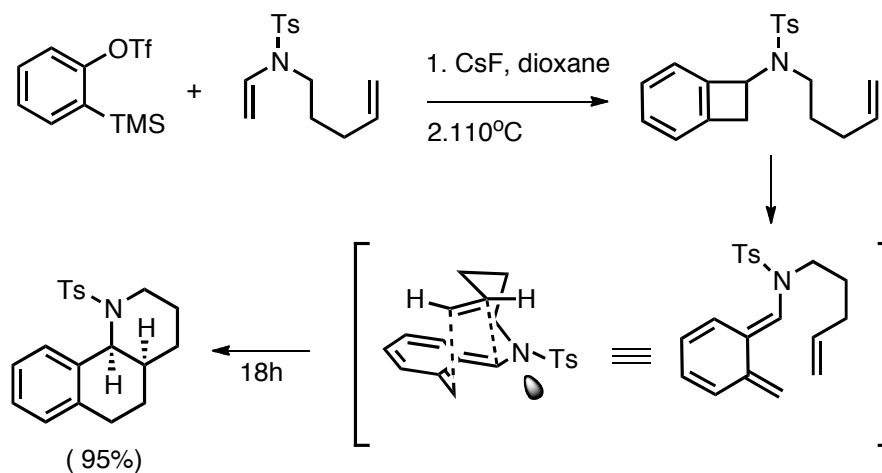
Reaction Diversity of Arynes with Amides and Related Substrates



Method Development for Tandem [2+2]-Cycloaddition-Pericyclic-Ring Opening-N-Tethered IMDA

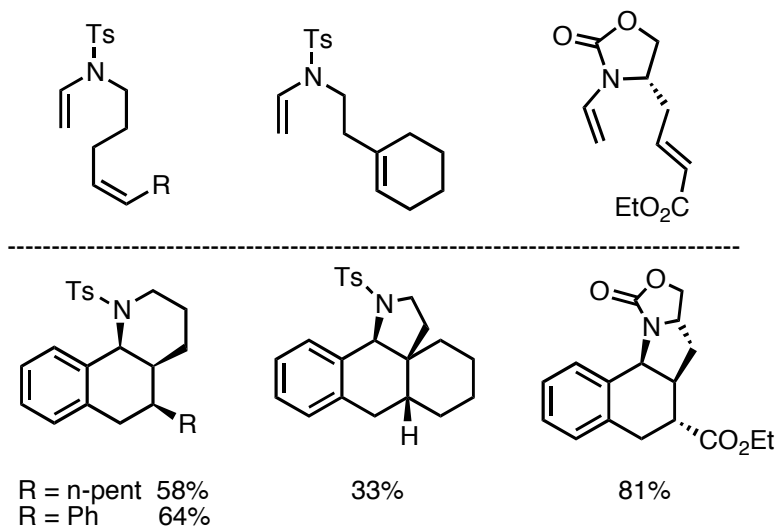


entry	enamide	amido-benzocyclobutanes	yield [%]
1.			63
2.			63
3.			95
4.			64 (dr 1:1)

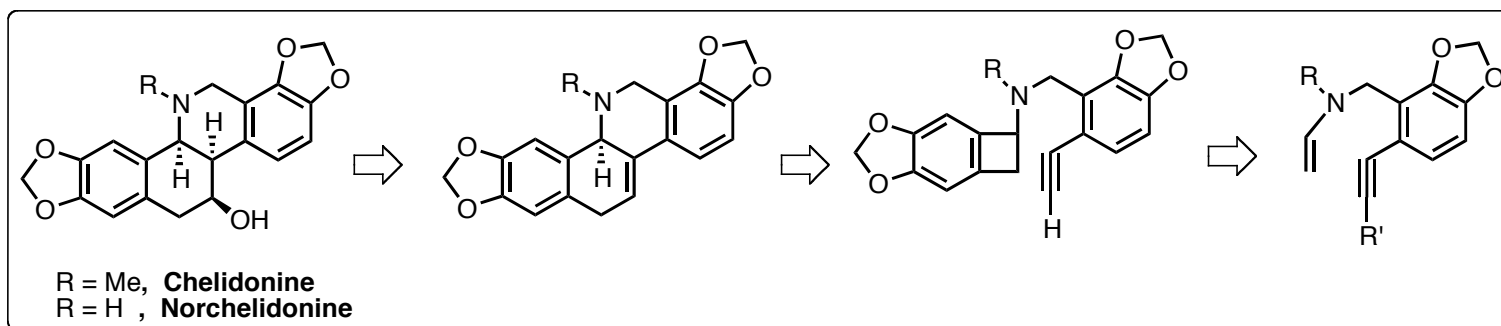


Org. Lett. **2009**, *11*, 3666

Total Synthesis of Chelidonium and Norchelidonium

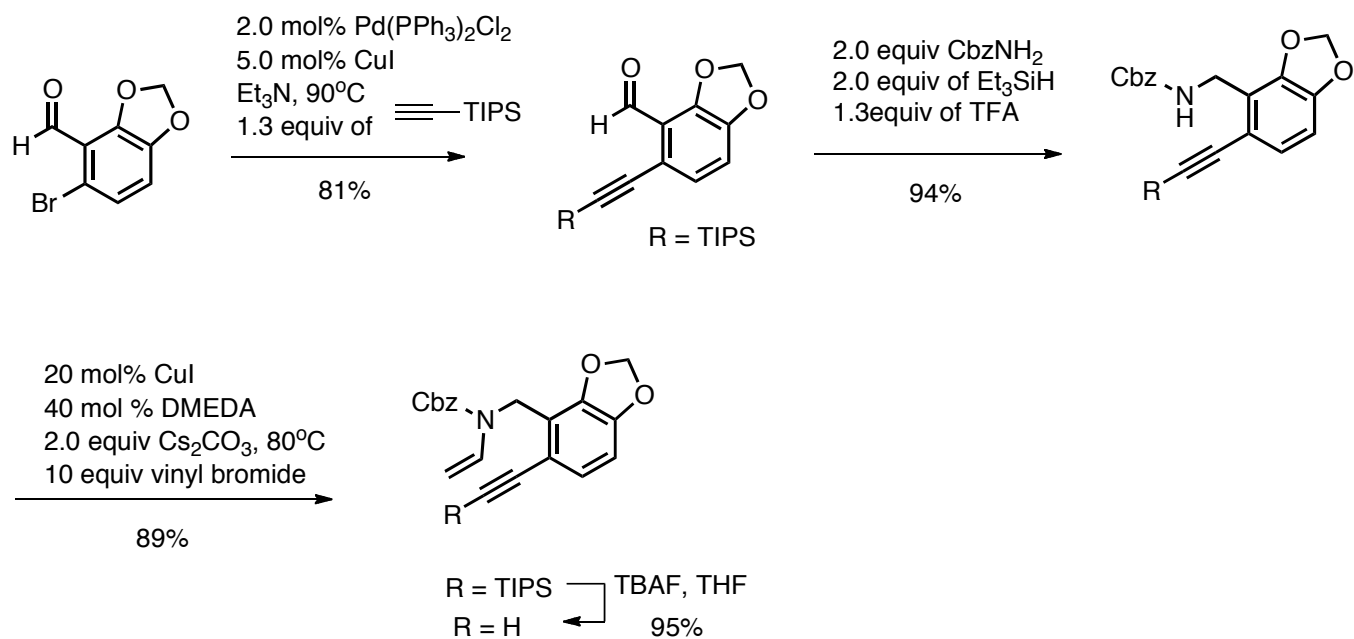


Retrosynthesis of Chelidonium:



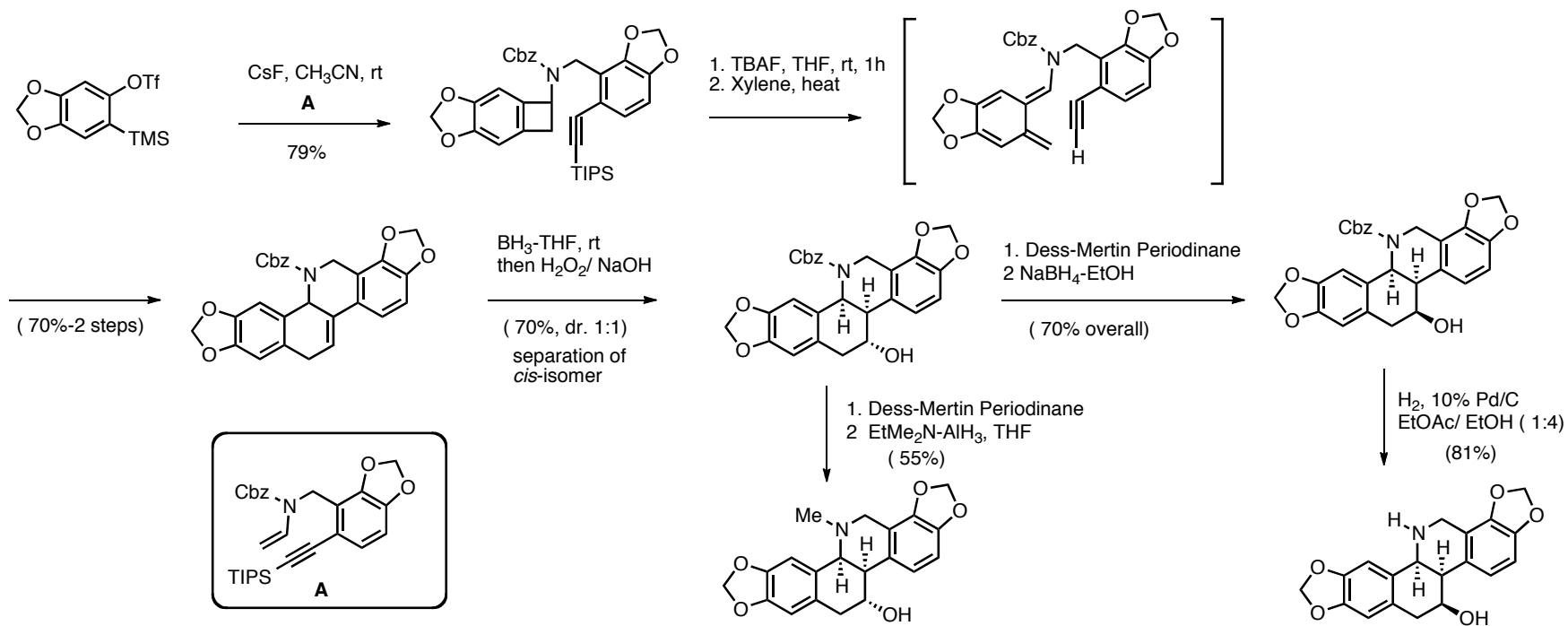
Org. Lett., **2012**, *14*, 2742-2745

Synthesis of Enamide Fragment

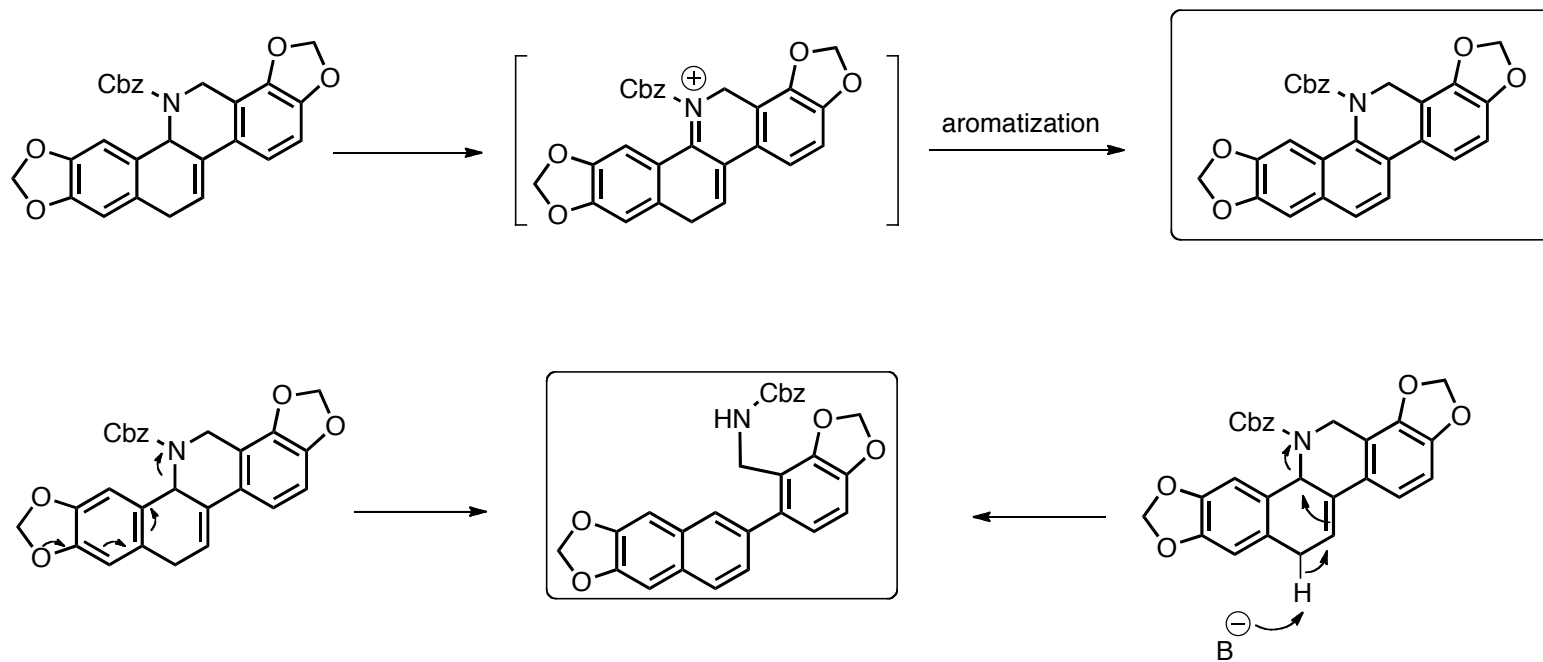


Org. Lett., **2012**, 14, 2742-2745

Completion of the Total Synthesis



Side Reactions



Org. Lett., **2012**, *14*, 2742-2745

Summary

- ✓ A New reaction manifold had been demonstrated utilizing [2+2] cycloaddition cascade coupled with IMDA reaction.
- ✓ The aryne based methodology utilized in the current context can be extended further for the synthesis of other alkaloid natural products