Catalytic Enantioselective Synthesis of Amino Skipped Diynes

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Checker: Shubo Hu
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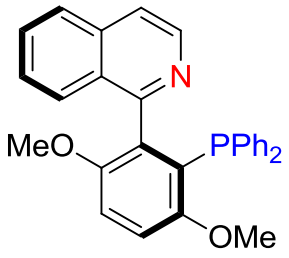
Aponick, A. *et al.*
J. Am. Chem. Soc. **2016**, *138*, 2150-2153.

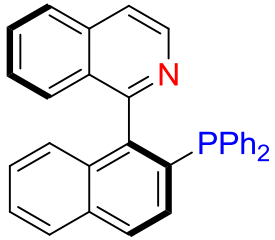
Website: http://aponick.chem.ufl.edu/Aponick_Research/

Contents

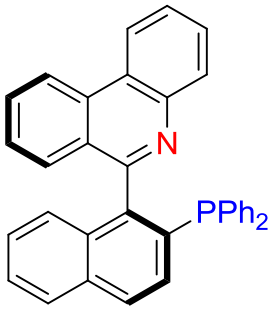
Axially Chiral Heterobidentate N,P-Ligands



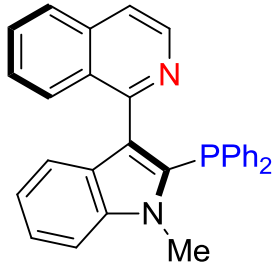
racemize ($t_{1/2}$ < 1h)
at ambient temperature
Brown (1992)



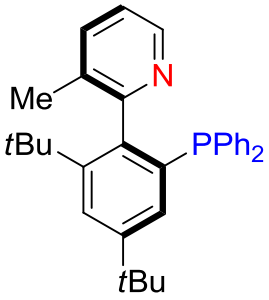
QUINAP
Brown (1993)



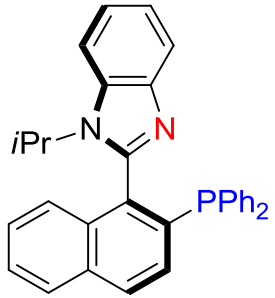
PHENAP
Brown (1995)



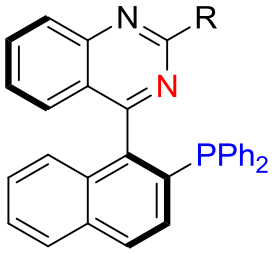
racemize ($t_{1/2}$ < 1.5 h)
at ambient temperature
Brown (1997)



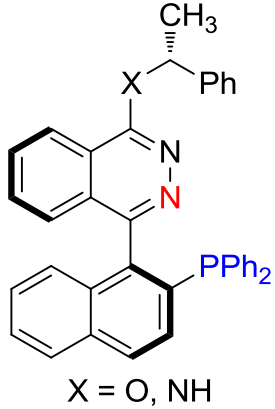
PyPhos
Chan (2002)



BIMNAP
Altenbach (2002)



Quinazolinap
Guiry (2004)



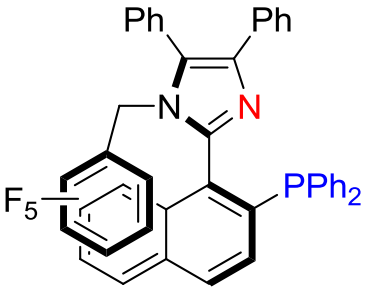
X = O, NH
PINAP
Carreira (2004)

Brown, J. M. *et al. Tetrahedron: Asymmetry* **1992**, *3*, 17; *Tetrahedron: Asymmetry* **1993**, *4*, 743; *Tetrahedron: Asymmetry* **1995**, *6*, 2597; *Tetrahedron* **1997**, *53*, 4035; Chan, K. S. *et al. J. Org. Chem.* **2002**, *67*, 2769; Altenbach, H. J. *et al. Tetrahedron: Asymmetry* **2002**, *13*, 137; Guiry, P. J. *et al. J. Org. Chem.* **2004**, *69*, 6572; Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 5971.

Axially Chiral Heterobidentate N,P-Ligands

The challenge of ligand design: increasing the barrier to rotation.

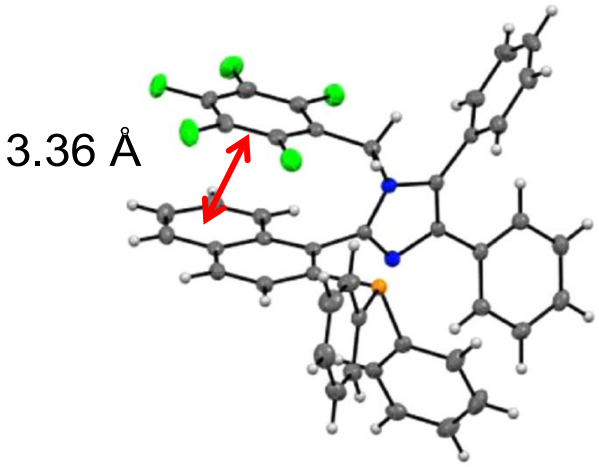
- ✓ Stabilizing the chiral ground state conformation:
  Bulky *ortho*-substituents
- ✓ Destabilizing the planar transition state:
  π-stacking interactions

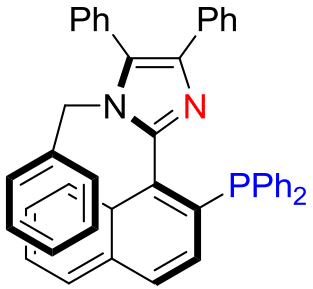


StackPhos

Aponick (2013)

98% ee, $t_{1/2}$ = 8.7 h
at 75 °C in CH_2ClCH_2Cl





$\Delta\Delta G^{\ddagger}_{75\,^{\circ}C}$ = 2.2 kcal/mol

52% ee, $t_{1/2}$ = 22 min
at 75 °C in CH_2ClCH_2Cl

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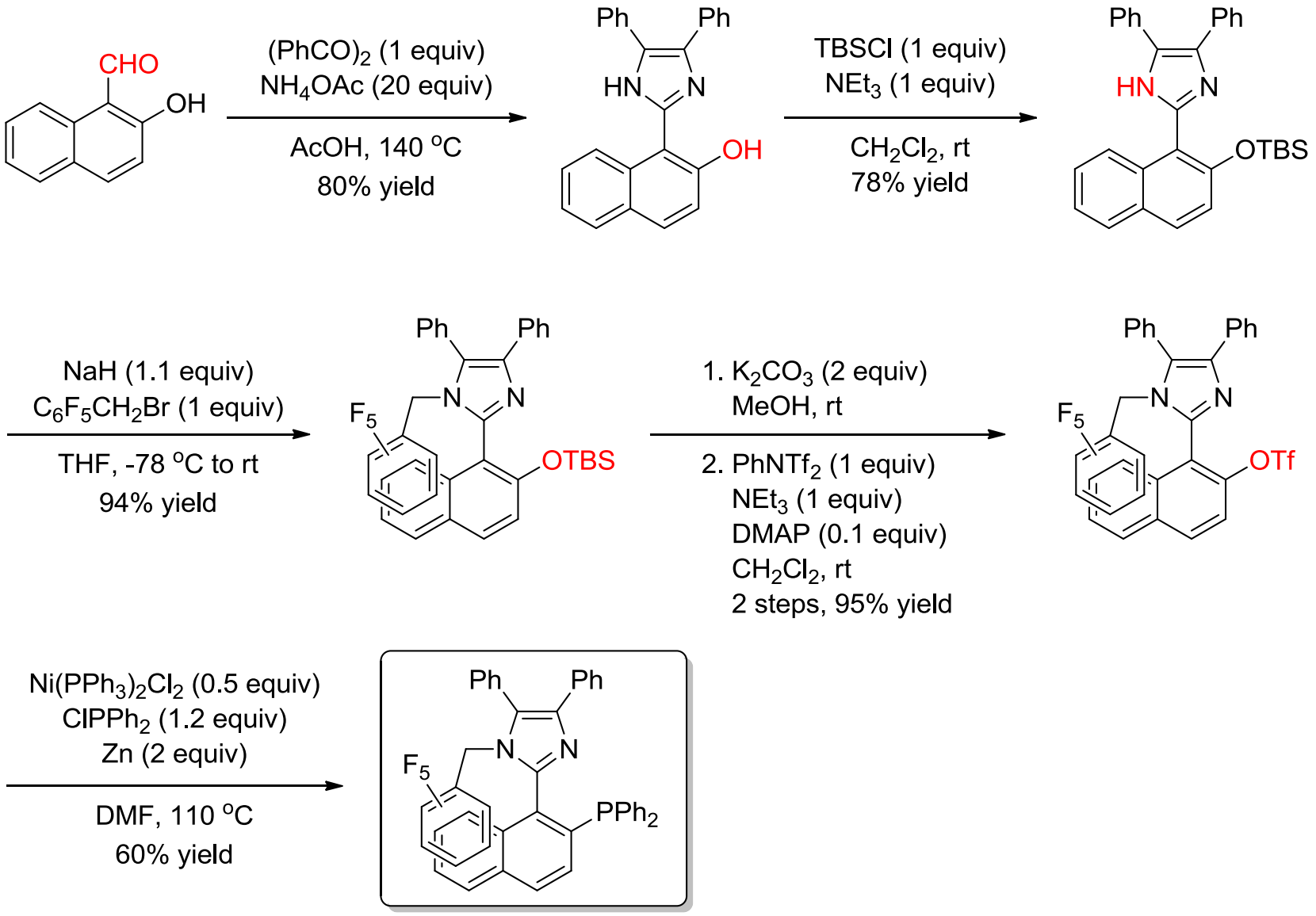
Synthesis of Imidazole-Based Racemic P,N-Ligand



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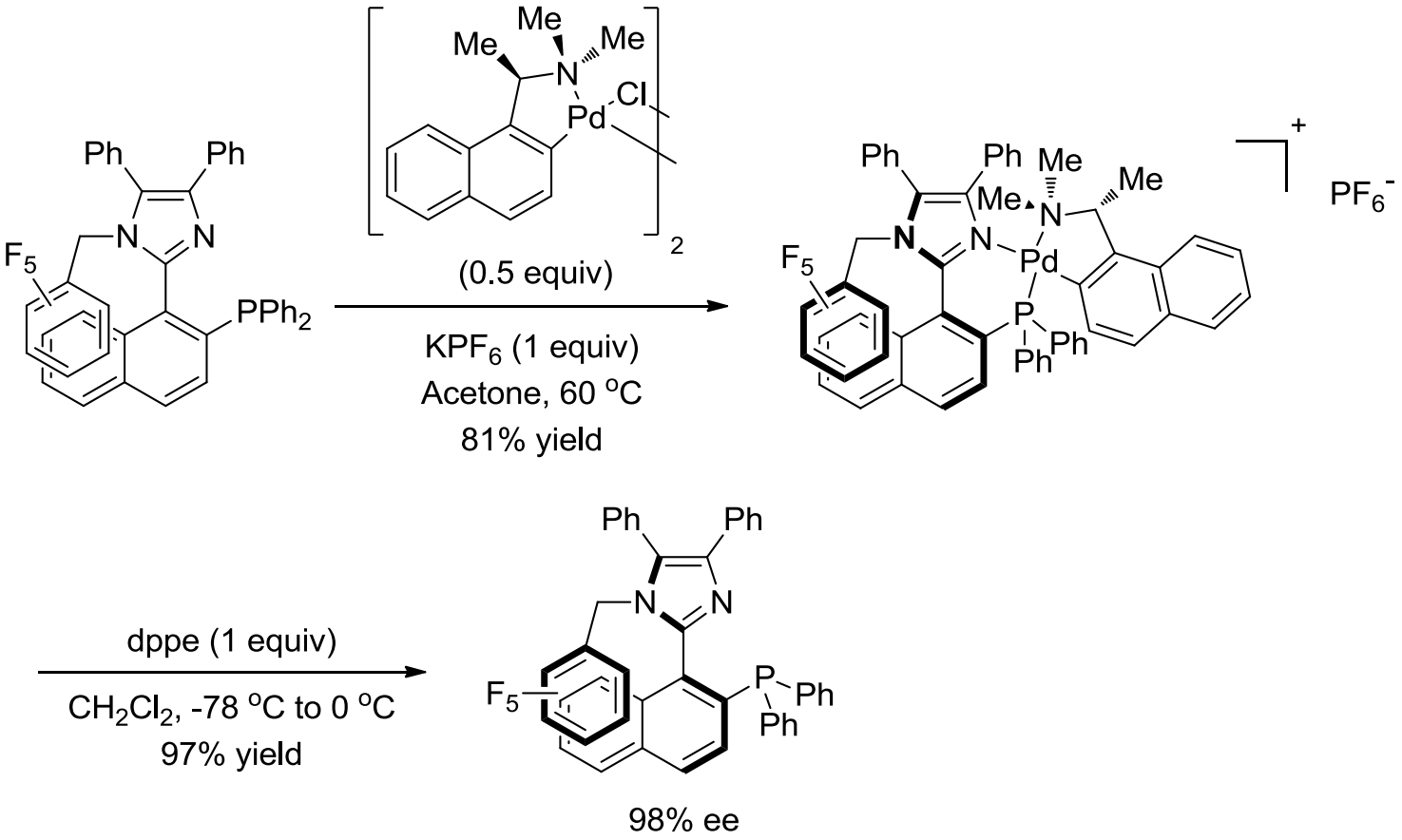
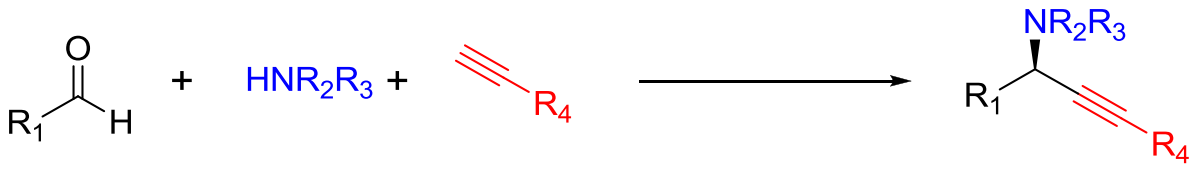
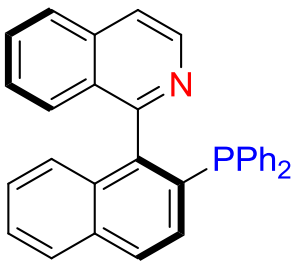
Deracemization of Imidazole-Based P,N-Ligand

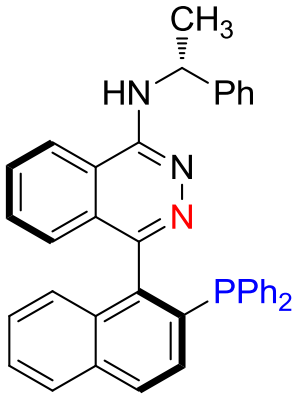


Enantioselective A^3-Coupling Reaction

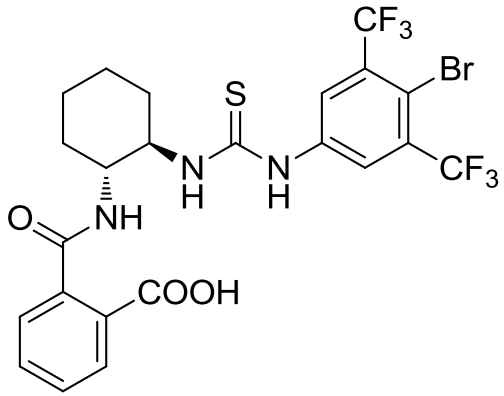




CuBr/QUINAP
Knochel (2003)



CuBr/PINAP
Carreira (2004)



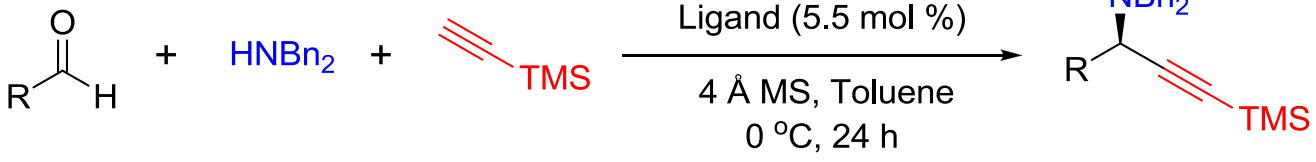
CuI/Acid-Thiourea
Seidel (2015)

- Extended reaction time of 5 days to a week
- Aromatic aldehydes: the most challenging substrates

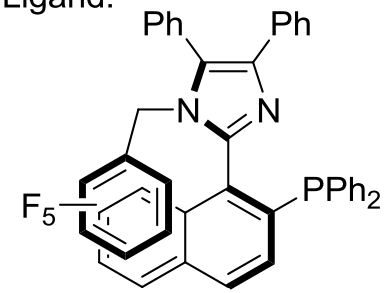
- Recent work

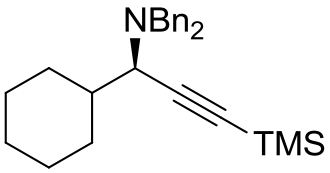
Knochel, P. *et al. Angew. Chem. Int. Ed.* **2003**, *42*, 5763; Carreira, E. M. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 5971; *Org. Lett.* **2006**, *8*, 2437; Seidel, D. *et al. J. Am. Chem. Soc.* **2015**, *137*, 4650.

Enantioselective A^3-Coupling Reaction

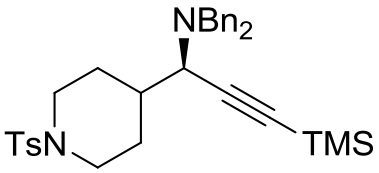


Ligand:

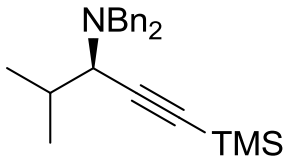




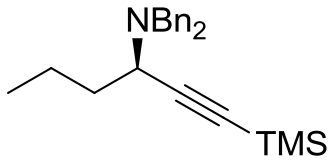
95% yield, 97% ee



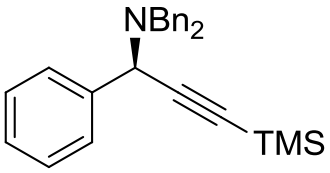
94% yield, 91% ee



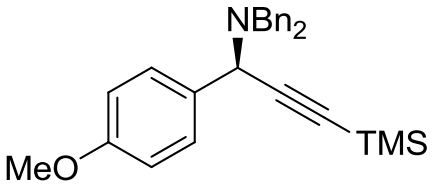
92% yield, 95% ee



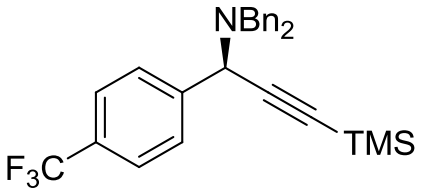
92% yield, 89% ee



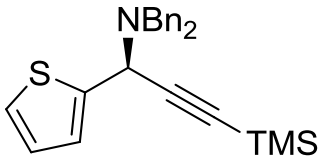
80% yield, 94% ee



77% yield[a], 94% ee



0 °C, 15% yield[a], 95% ee
22 °C, 70% yield, 92% ee



60% yield[a], 94% ee

[a] Reaction allowed to run for 4 days at 0 °C.

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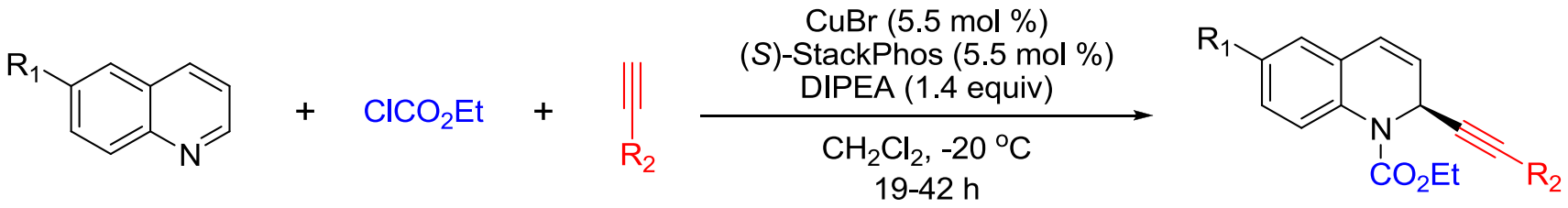
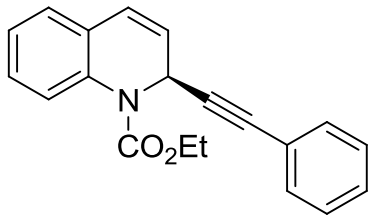
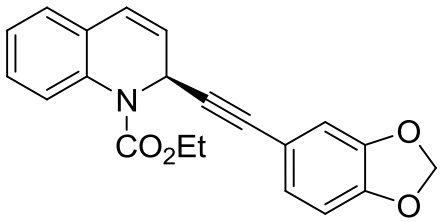
Enantioselective Alkynylation of Quinolinium Salts

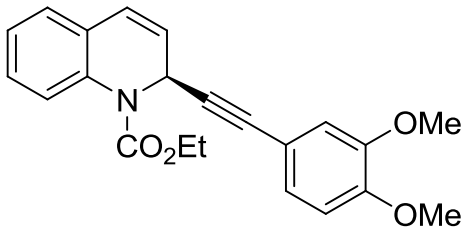




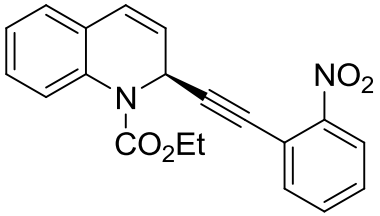
74% yield, 98% ee



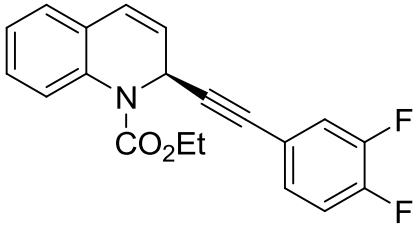
74% yield, 98% ee



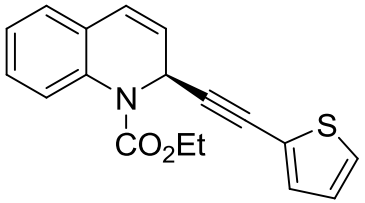
86% yield, 96% ee



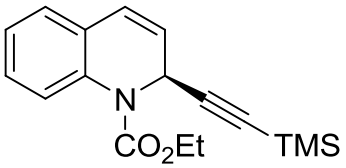
68% yield, 96% ee



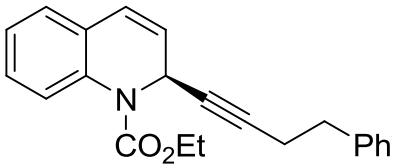
70% yield, 96% ee



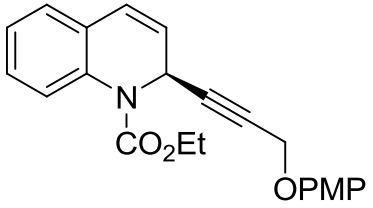
67% yield, 90% ee



75% yield, 96% ee



62% yield, 95% ee



75% yield, 91% ee

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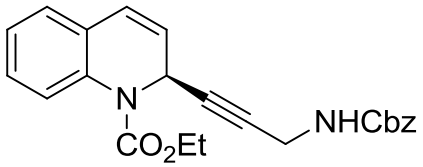
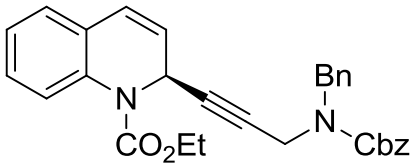
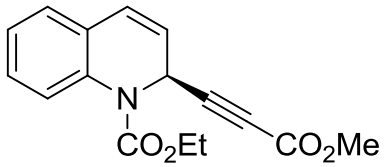
Enantioselective Alkynylation of Quinolinium Salts



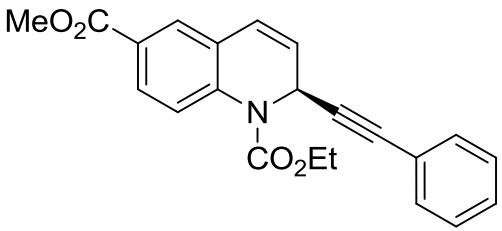
45% yield, 90% ee



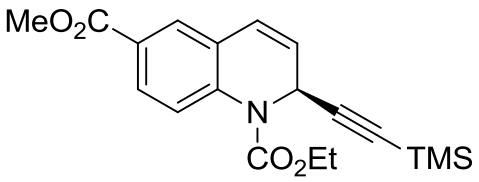
62% yield, 90% ee



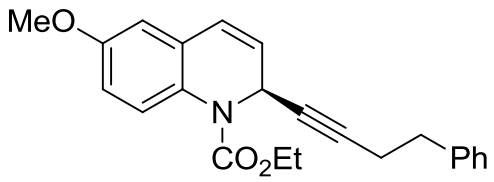
70% yield, 92% ee



66% yield, 96% ee

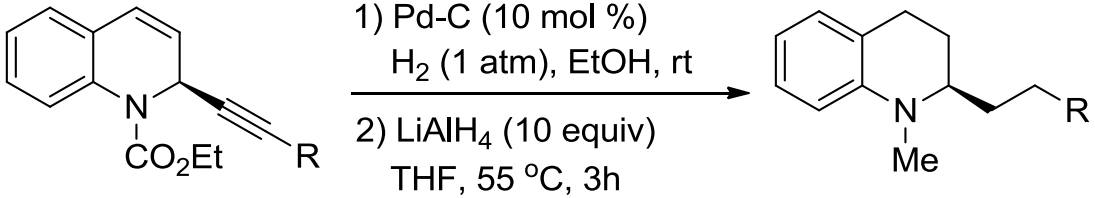


66% yield, 97% ee

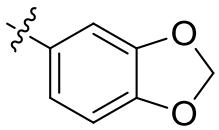


77% yield, 92% ee

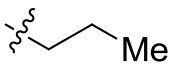
Assignment of absolute configuration by alkaloid synthesis



R =

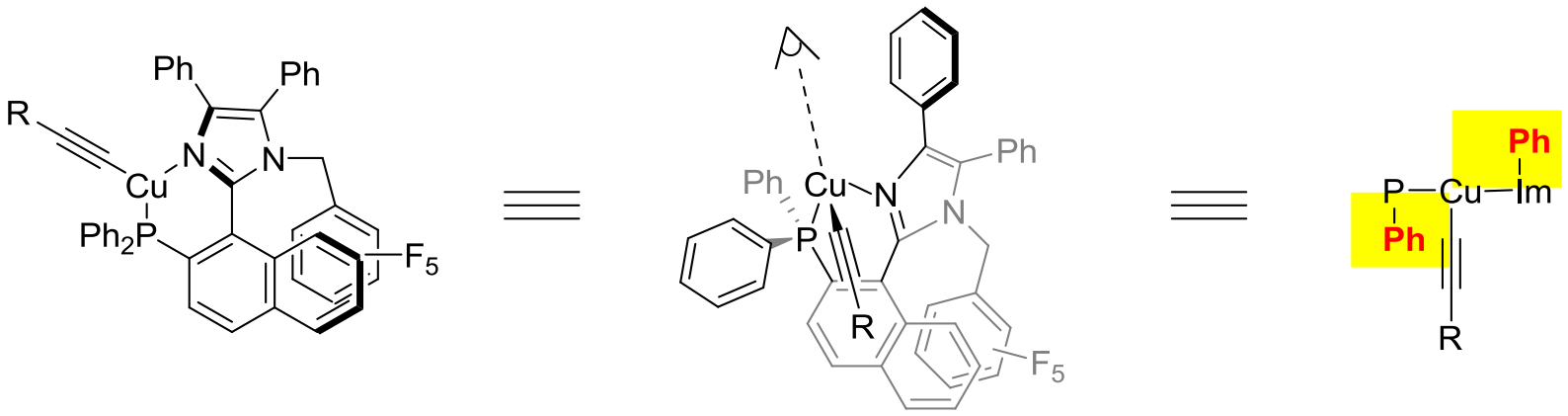


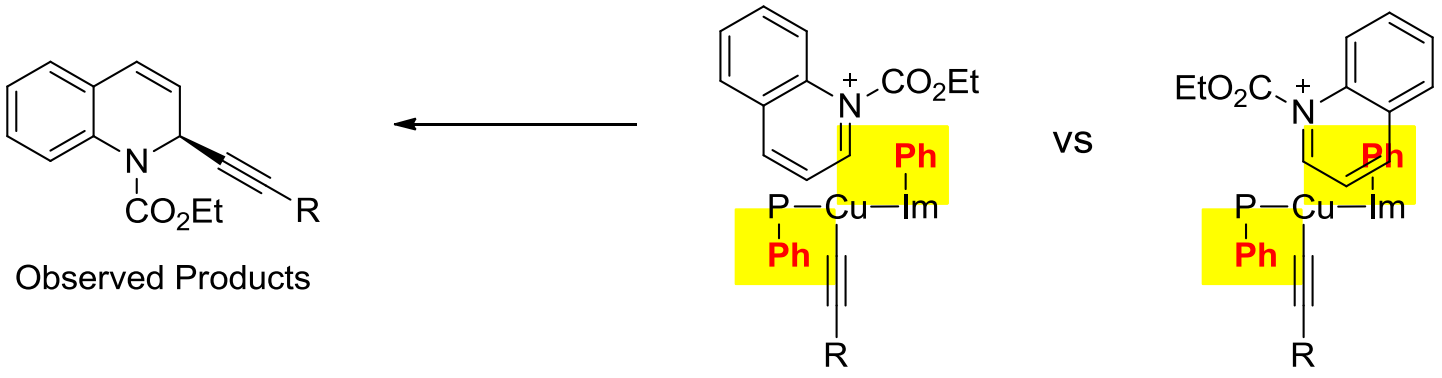
(+)-Galipinine
69% yield



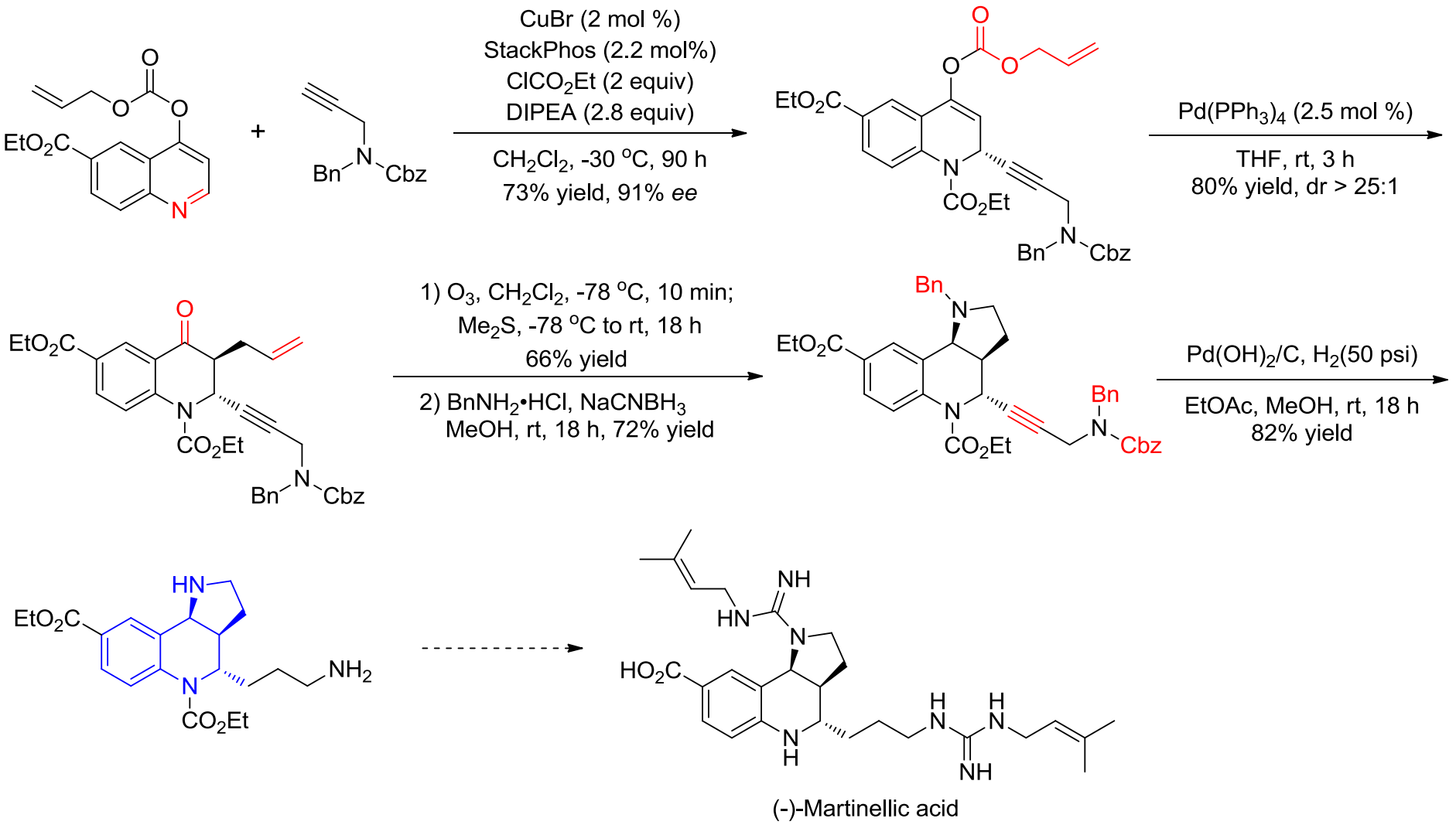
(+)-Angustureine
71% yield

Stereochemical Model





Total Synthesis of (-)-Martinellic Acid



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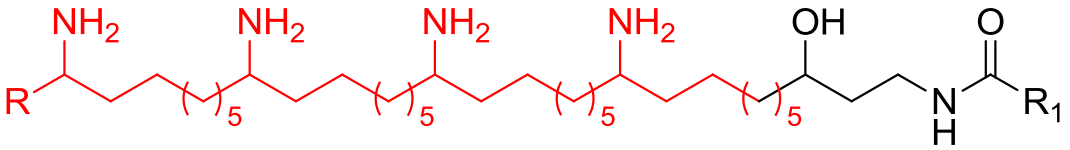
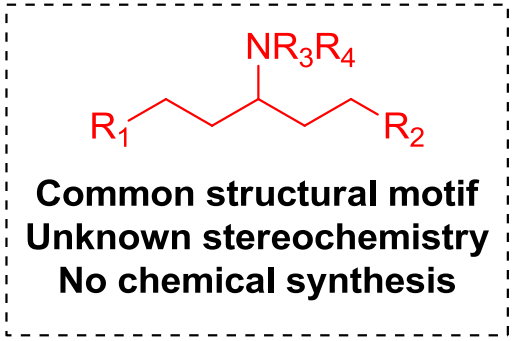
Linear Mono- and Polyamine Natural Products

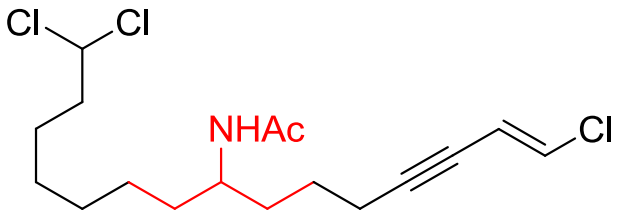


R = C_5H_{11} Zeamines
R = CH_3 Fabclavines

R_1 = peptides



Common structural motif
Unknown stereochemistry
No chemical synthesis

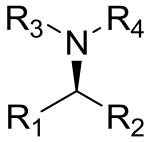


Taveuniamide F

Isolated from Microcoleus lyngbyaceus

Erickson, K. L. *et al. J. Nat. Prod.* **2001**, *64*, 572; Gerwick, W. H. *et al. Tetrahedron* **2004**, *60*, 7025; Tan, L. T. *et al. Phytochemistry* **2007**, *68*, 954; Simpson, T. J. *et al. Chem. Commun.* **2010**, *46*, 333; Bode, H. B. *et al. ChemBioChem* **2014**, *15*, 512.

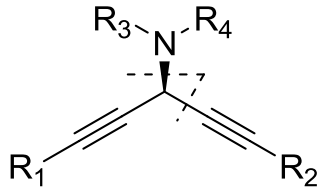
Preparation of Skipped Diyne Compounds



no electronical or sterical bias

R_1 similar to R_2

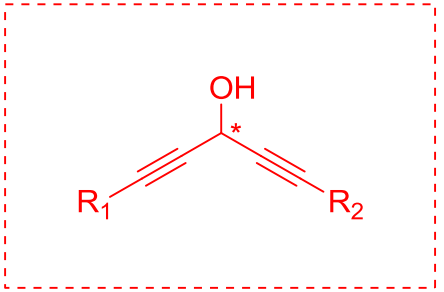
Extremely challenging

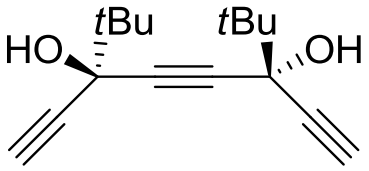


Enantioselective synthesis unknown

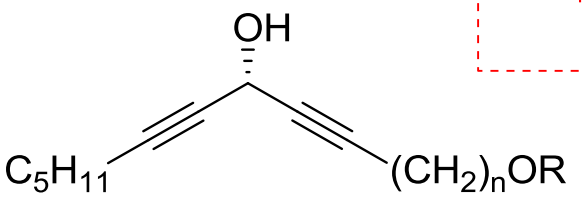
Asymmetric dialkynylcarbinols are “weakly chiral” compounds

- Chemical or enzymatical resolution





optically resolved *via* brucine

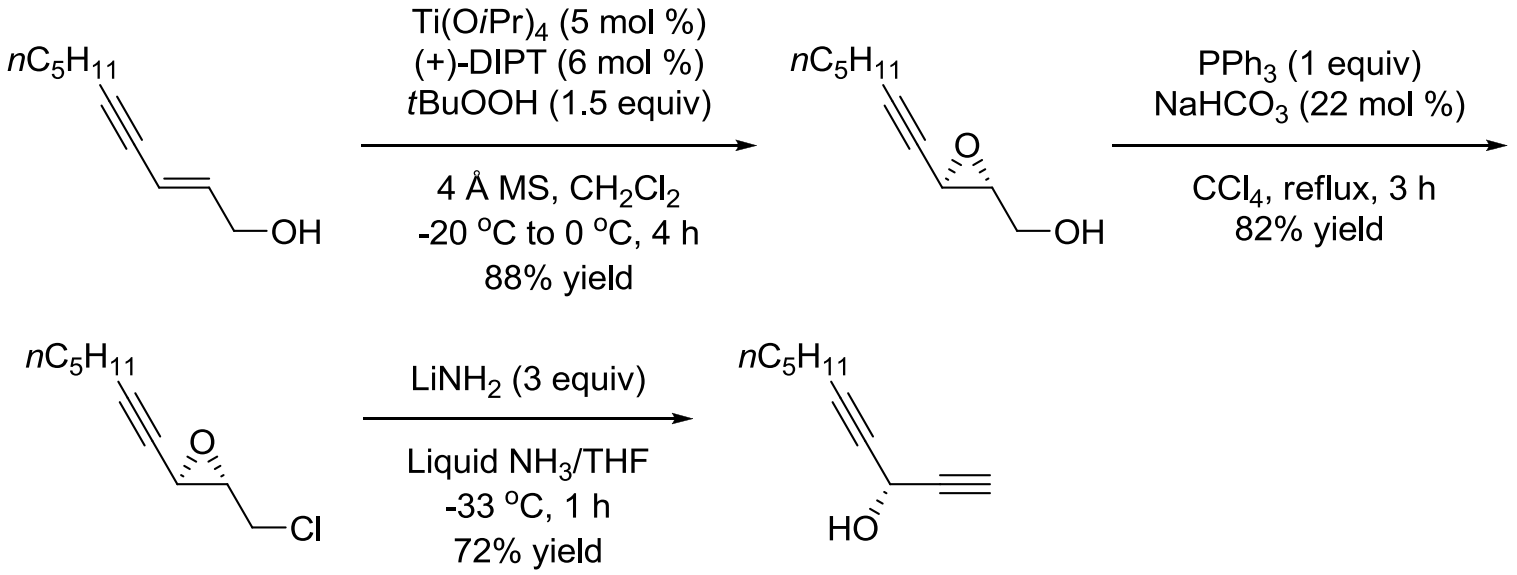


optically resolved *via* Lipase

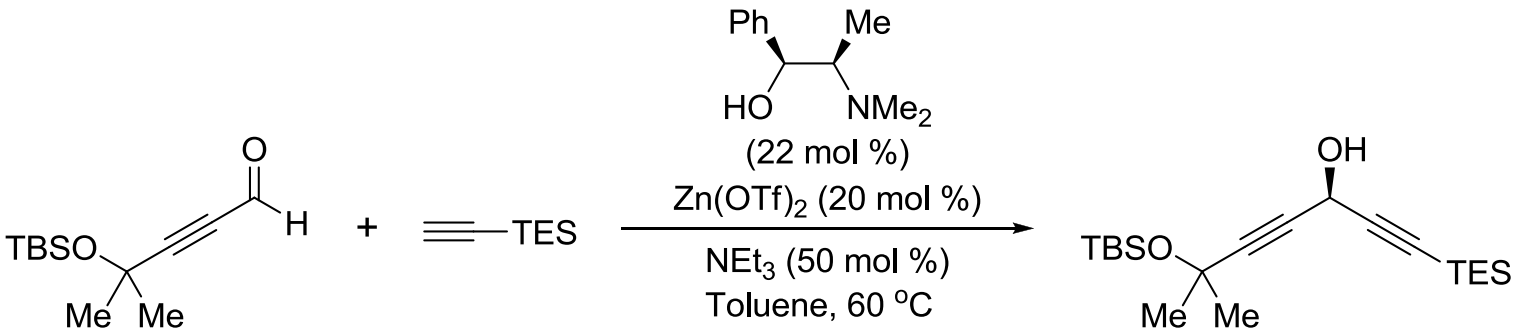
Toda, F. *et al. Angew. Chem. Int. Ed.* **1988**, *27*, 859; Chattopadhyay, S. *et al. J. Org. Chem.* **1998**, *63*, 6128; Yadav, J. S. *et al. Tetrahedron: Asymmetry* **2001**, *12*, 53.

Preparation of Skipped Diyne Compounds

- Enantioselective preparation of skipped diynes is scarce.

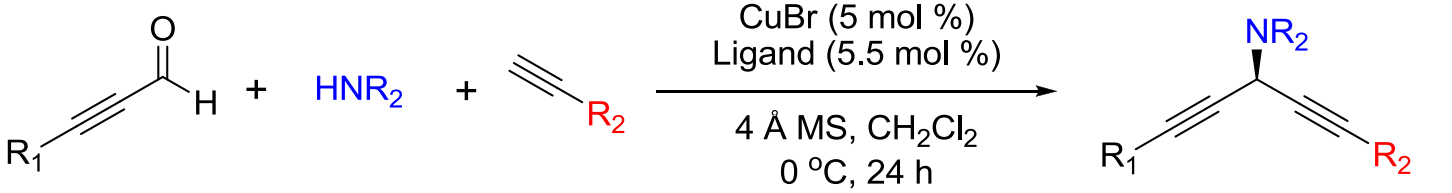


Yadav, J. S. *et al. Tetrahedron* **1990**, *46*, 7033.

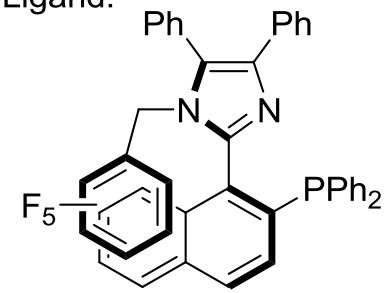


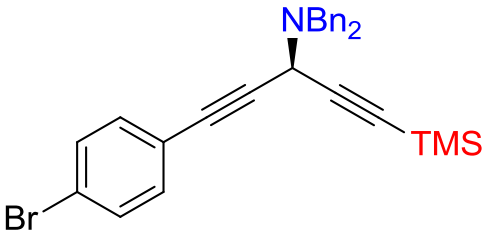
Carreira, E. M. *et al. J. Am. Chem. Soc.* **2001**, *123*, 9687.

Enantioselective Synthesis of Amino Skipped Diynes

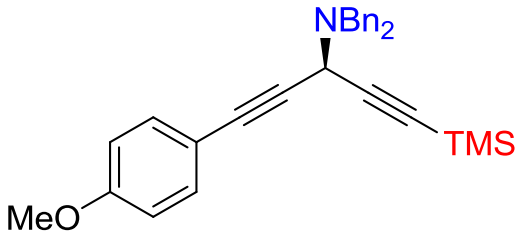


Ligand:

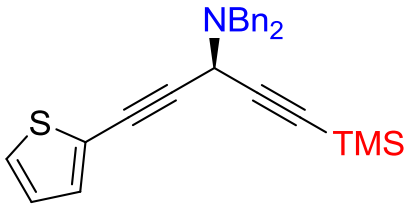




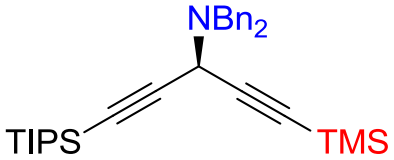
79% yield, 96% ee



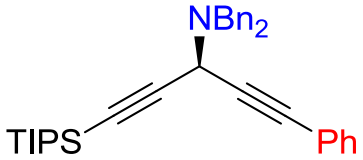
77% yield, 94% ee



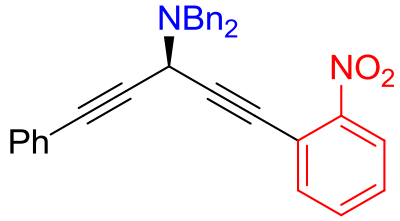
72% yield, 96% ee



72% yield, 96% ee



73% yield, 95% ee

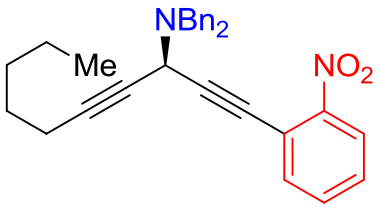


86% yield[a], 95% ee

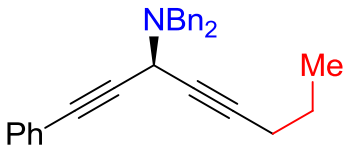
[a] Reaction time = 3 h.

Aponick, A. *et al. J. Am. Chem. Soc.* **2016**, *138*, 2150.

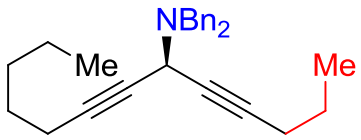
Enantioselective Synthesis of Amino Skipped Diynes



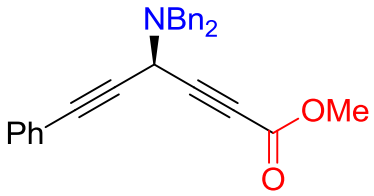
64% yield[a], 96% ee



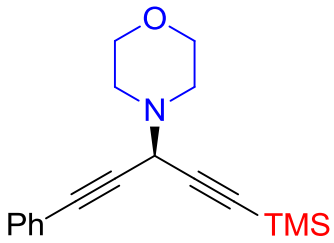
85% yield[a], 86% ee
65% yield[b, d], 89% ee



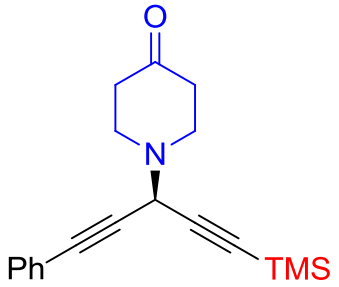
86% yield[a], 82% ee



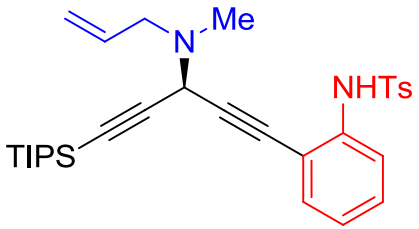
93% yield[c], 82% ee
96% yield[c, d], 86% ee



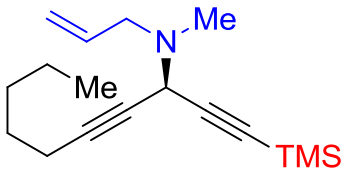
69% yield, 95% ee



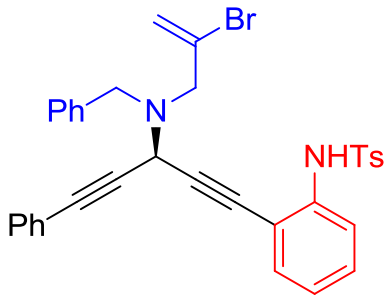
62% yield, 90% ee



63% yield[a], 90% ee



91% yield[a], 95% ee

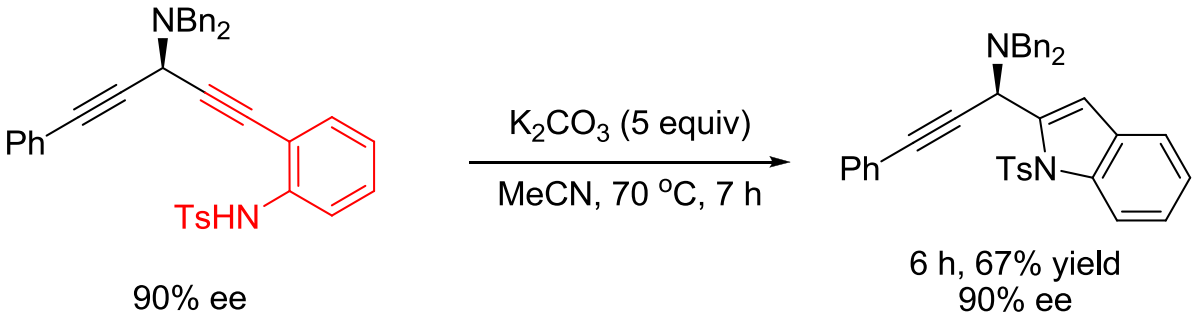


61% yield[a], 84% ee

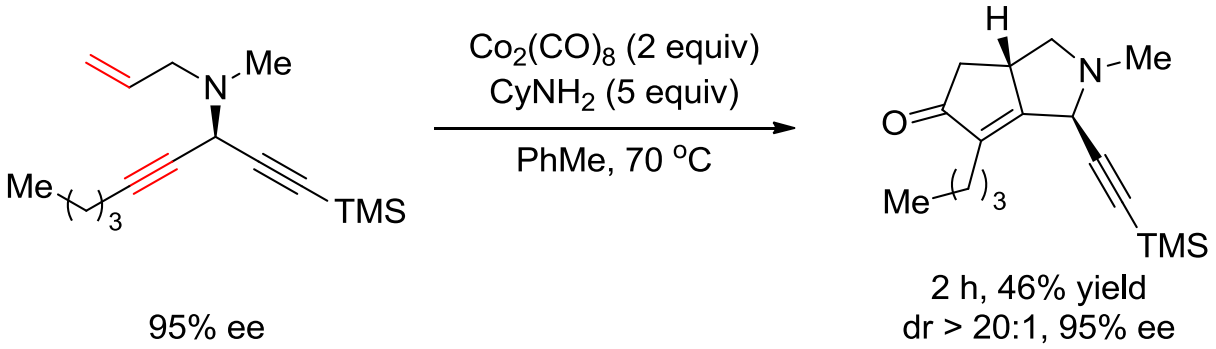
[a] Reaction time = 3 h. [b] Reaction time = 6 h. [c] Reaction time = 1 h. [d] Reaction temperature = -25 °C.

Versatility of 3-Amino Skipped Diynes

- Synthesis of 2-methanamine indole

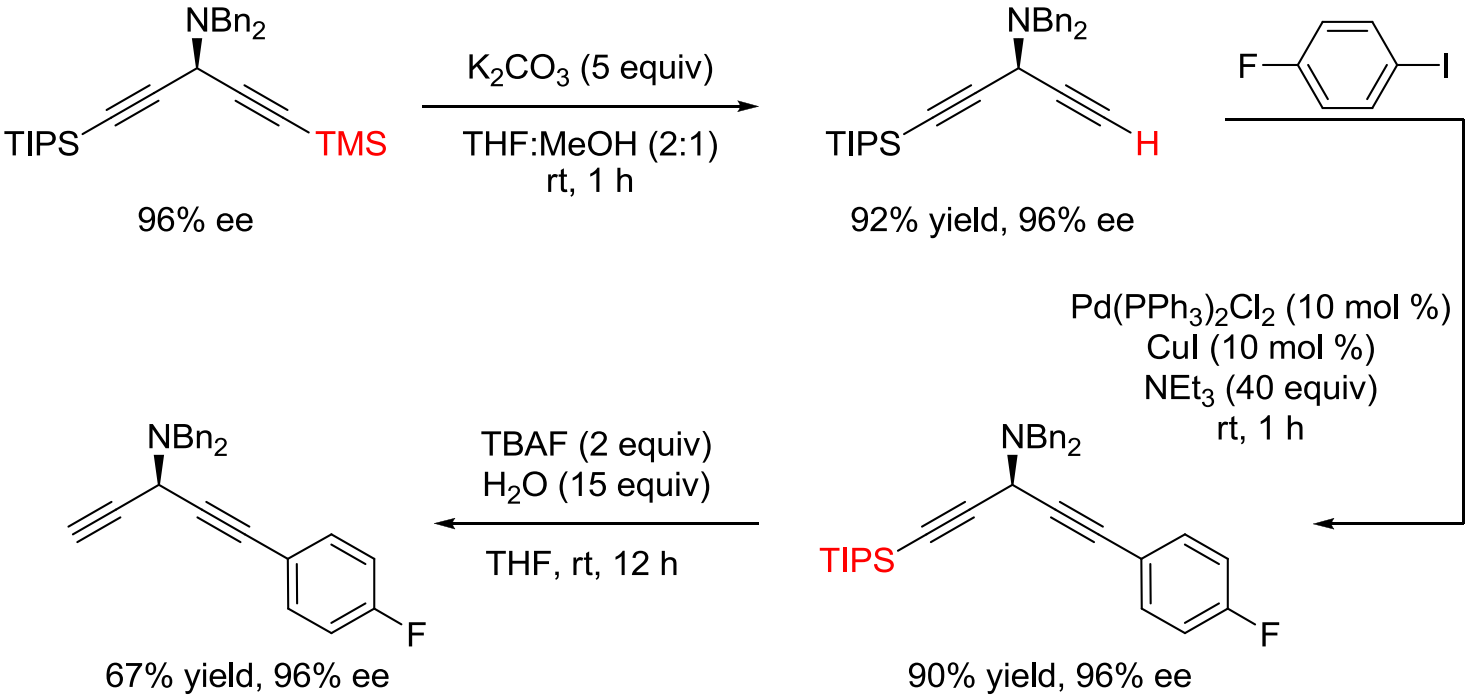


- Chemoselective Pauson-Khand reaction



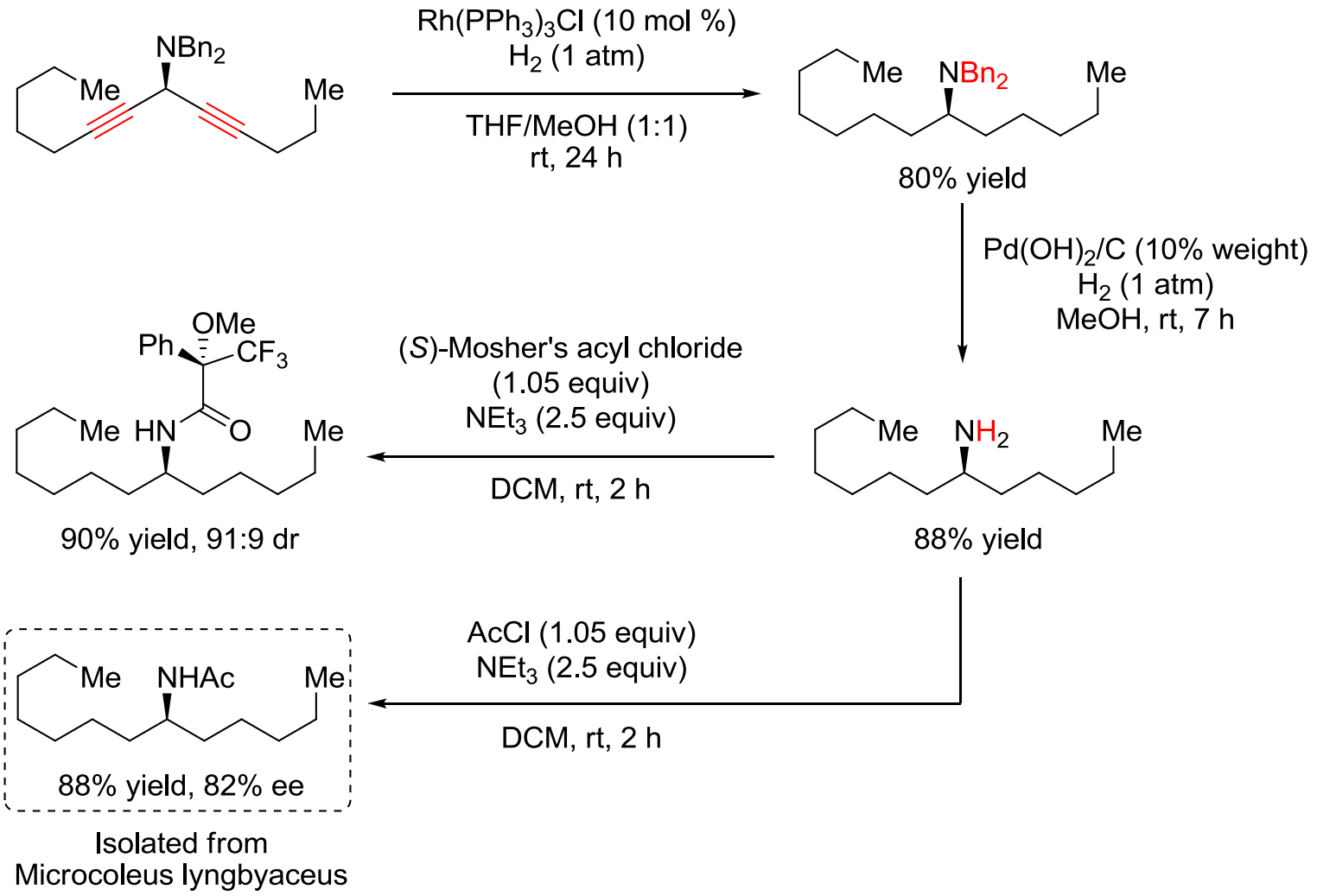
Versatility of 3-Amino Skipped Diynes

- Orthogonal diyne functionalization



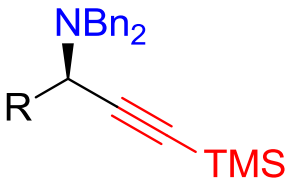
Versatility of 3-Amino Skipped Diynes

- Synthesis of chiral remote amines

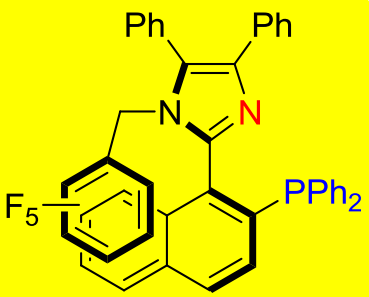


Summary

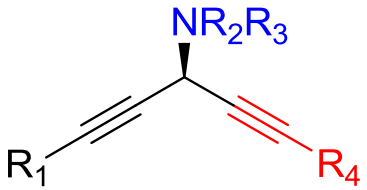
- The imidazole-based chiral biaryl P,N-ligand for asymmetric alkynylation



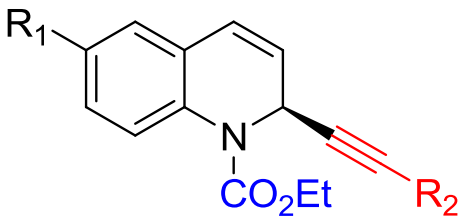
J. Am. Chem. Soc. **2013**, *135*, 14548.



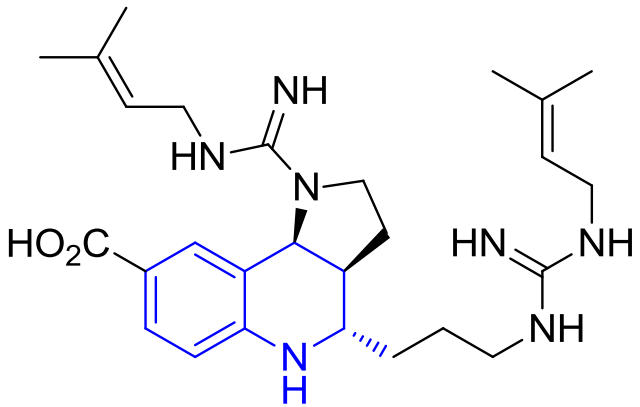
Aponick: StackPhos



J. Am. Chem. Soc. **2016**, *138*, 2150.



Angew. Chem. Int. Ed. **2015**, *54*, 15202.



(-)-Martinellic acid

Angew. Chem. Int. Ed. **2015**, *54*, 15827.

Natural products assembled by biosynthetic pathways involving hybrid polyketide synthase (PKS) and nonribosomal peptide synthetase (NRPS) machinery can possess interesting structures and exhibit potent biological activities. Utilizing a combination of the PKS/NRPS modules permits the direct fusion of polyketides and peptides and also facilitates the construction of heterocycles to yield important classes of compounds such as β-lactams (e.g., nocardicins) and oxazoles (e.g., rhizoxin) among many others. Recently, several linear mono- and polyamines exhibiting broad spectrum antibiotic activity have been isolated including the zeamines, fabclavines, and taveuniamides, but their stereochemistry remains unassigned.

In summary, we have disclosed the first enantioselective preparation of amino skipped diynes, a class of chiral molecules with minimal differences in two of the substituents rendering them chiral. Despite this challenging issue and potential reactivity issues, a Cu(I)-StackPhos-catalyzed C−C bond formation proved to be rapid and high yielding under very mild conditions while tolerating an exceptionally broad substrate scope. Due to the unique structural features of chiral 3-amino skipped diynes, we believe these building blocks will find application in a variety of areas, and to this end, we have demonstrated several preliminary applications. The method should enable the synthesis of more complex primary amine and polyamine natural products. These studies as well as detailed mechanistic investigations are ongoing in our laboratories and will be reported in due course.