Literature Report

Enantioselective Copper Catalyzed Alkyne−Azide Cycloaddition by Dynamic Kinetic Resolution

Reporter: Mu-Wang Chen
Checker: Xiao-Qing Wang
Date: 2019-05-06

Liu, E.-C.; Topczewski, J. J.
J. Am. Chem. Soc. **2019**, *141*, 5135-5138.

CV of Prof. Topczewski, J. J.

Research:

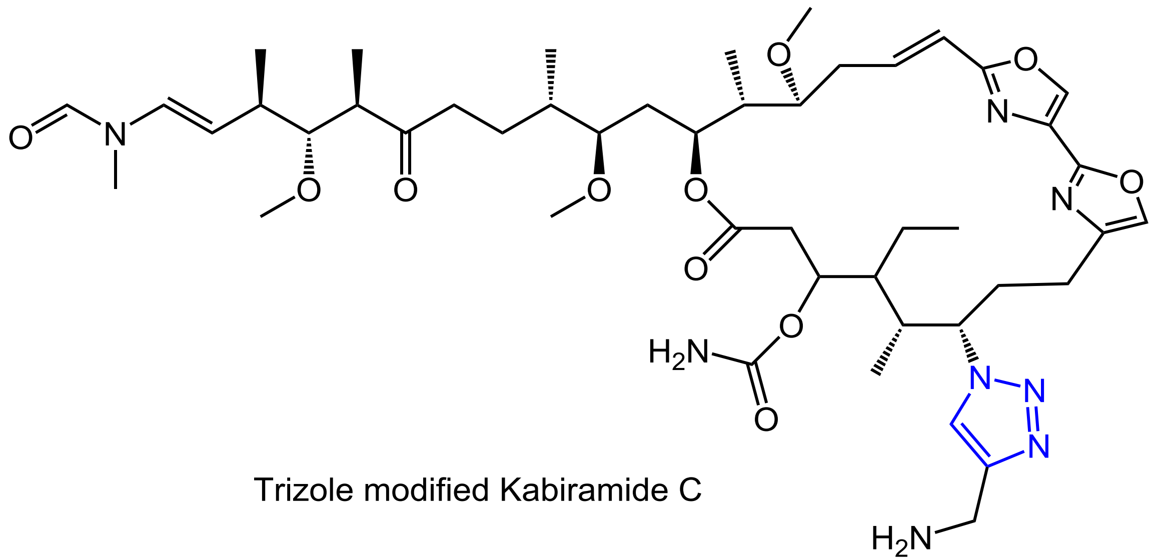
- Developing new and efficient methods of chemical synthesis.
- Developing highly selective reactions and on reactions that exploit dynamic systems.

Background:

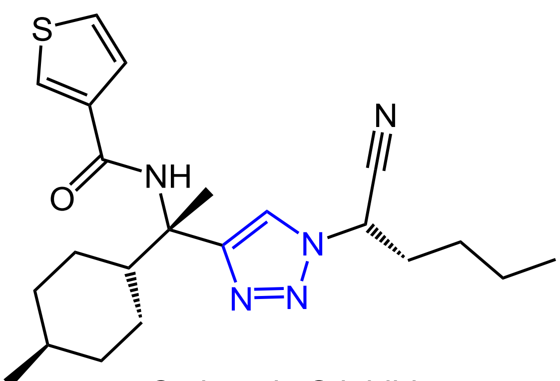
- **2003-2007** B.S., University of Wisconsin at Parkside
- **2007-2011** Ph.D., University of Iowa, David Wiemer
- **2011-2013** Post Doctorate, University of Iowa, Hien Nguyen & Daniel Quinn
- **2013-2015** Post Doctorate, University of Michigan, Melanie Sanford
- **2015-now** Assistant Professor, University of Minnesota Twin Cities

Contents

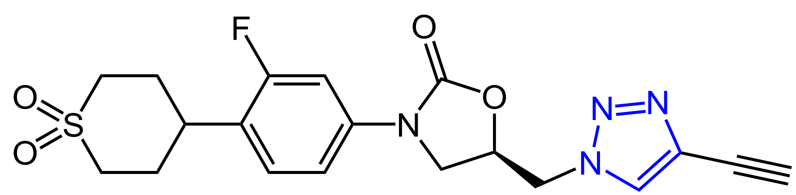
Introduction



Trizole modified Kabiramide C

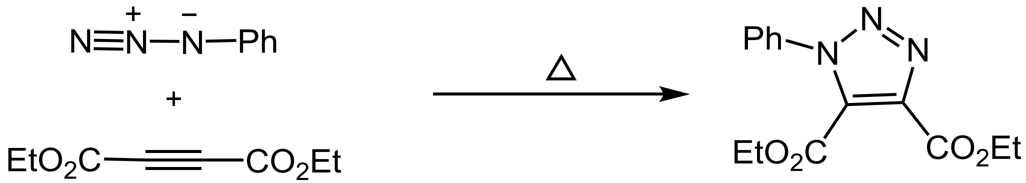


Cathepsin S inhibitor

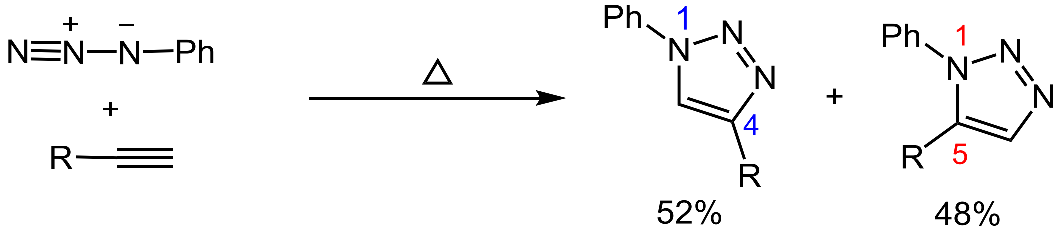


Antibacterial Agent

Introduction

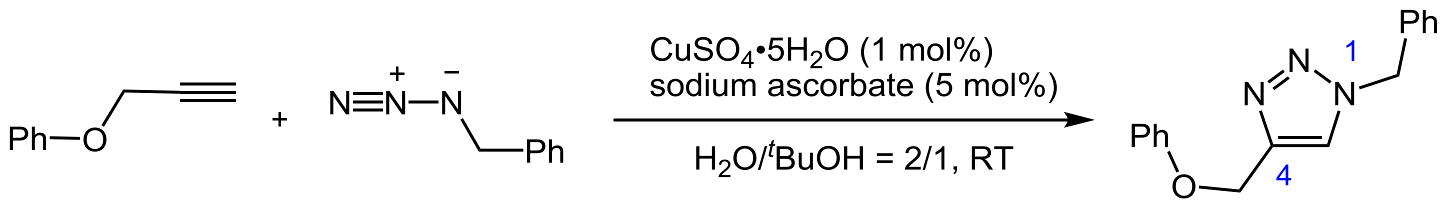


Michael, A. *J. Prakt. Chem*. **1893**, *48*, 94.



Huisgen, R. *Angew. Chem. Int. Ed*. **1963**, *2*, 565.

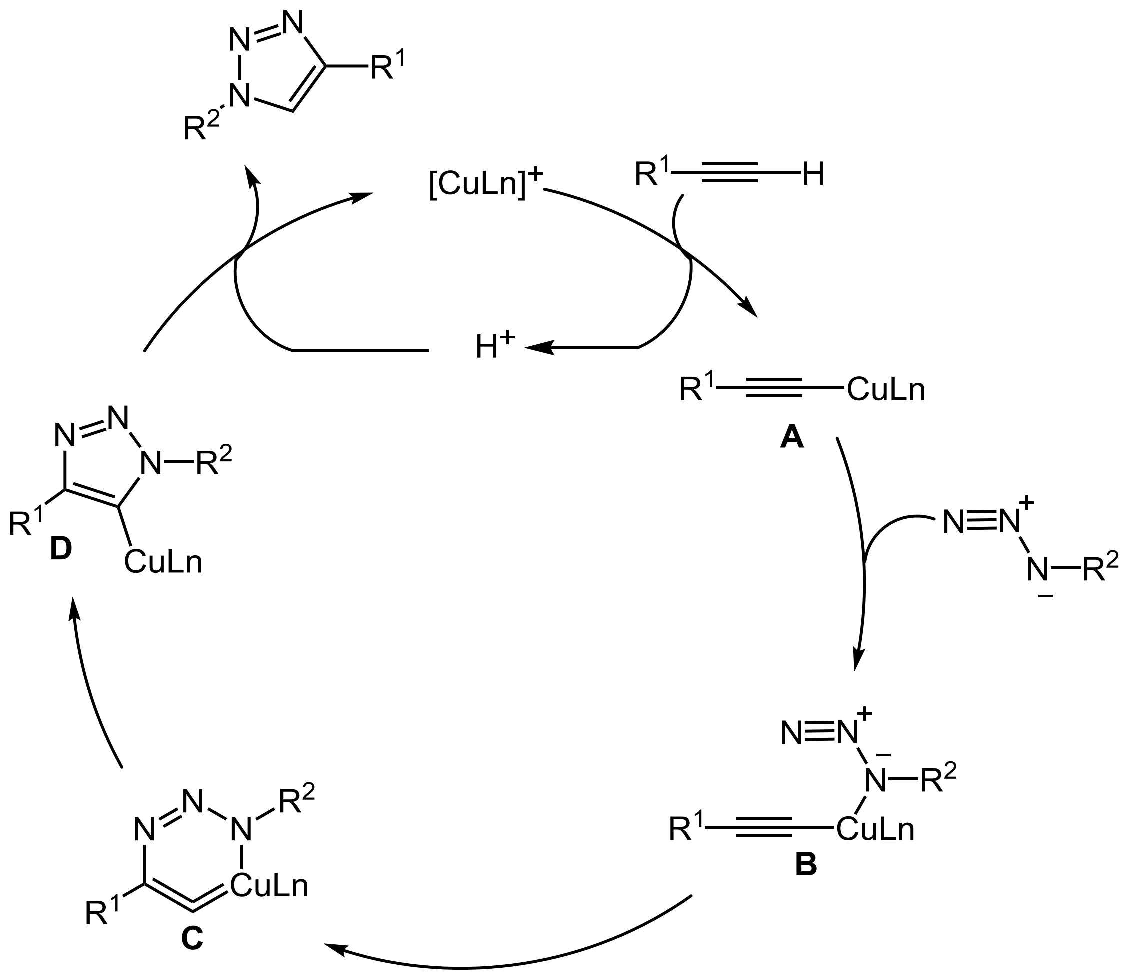
Introduction



Sharpless, K. B. *et al. Angew. Chem. Int. Ed*. **2002**, *41*, 2596.

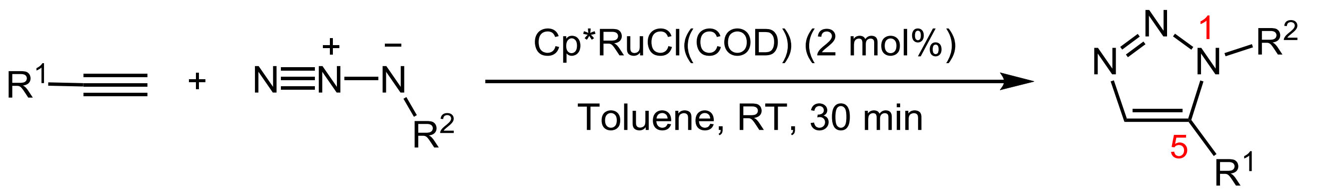
- **High efficient**
- **Atom economy**
- **Selectivity**
- **Great functionality tolerance**
- **Simple reaction conditions**
- **Simple product isolation**

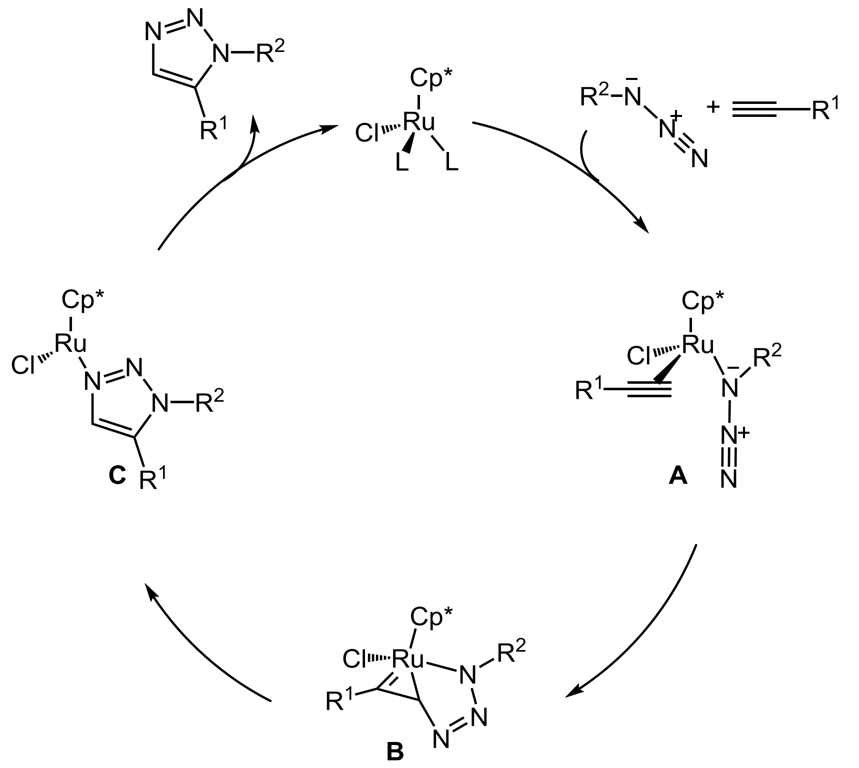
Introduction



Astruc, D. *et al. Coord. Chem. Rev.* **2016**, *316*, 1.

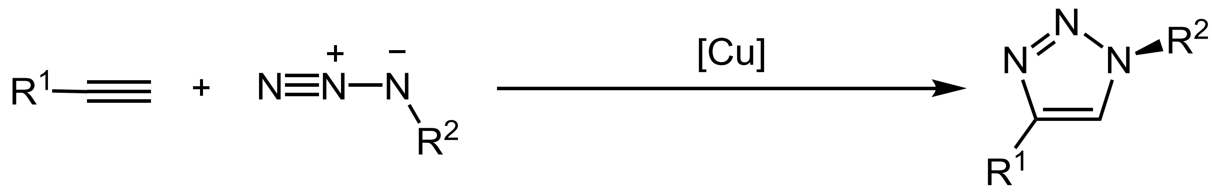
Introduction





Fokin, V. V. *et al. J. Am. Chem. Soc*. **2008**, *130*, 8923.

Enantioselective CuAAC



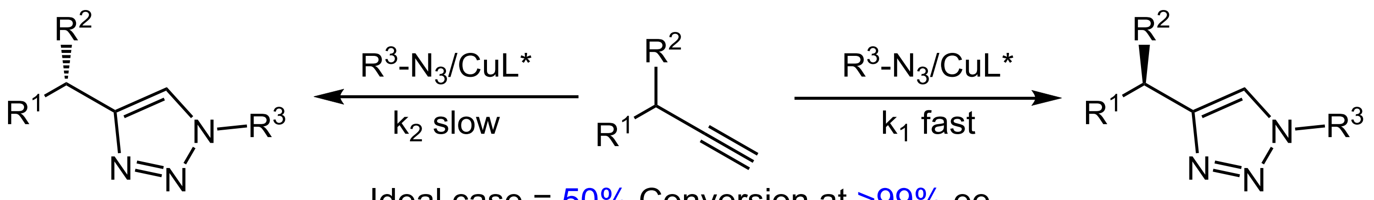
Challenges:

First: Alkynes and azides have a **linear geometry** and the resulting triazole is a **sp^2 hybridized heterocycle**. No new stereogenic centers are formed in most CuAAC reactions. **E-CuAAC requires the transmission of stereochemical information beyond the forming triazole**.

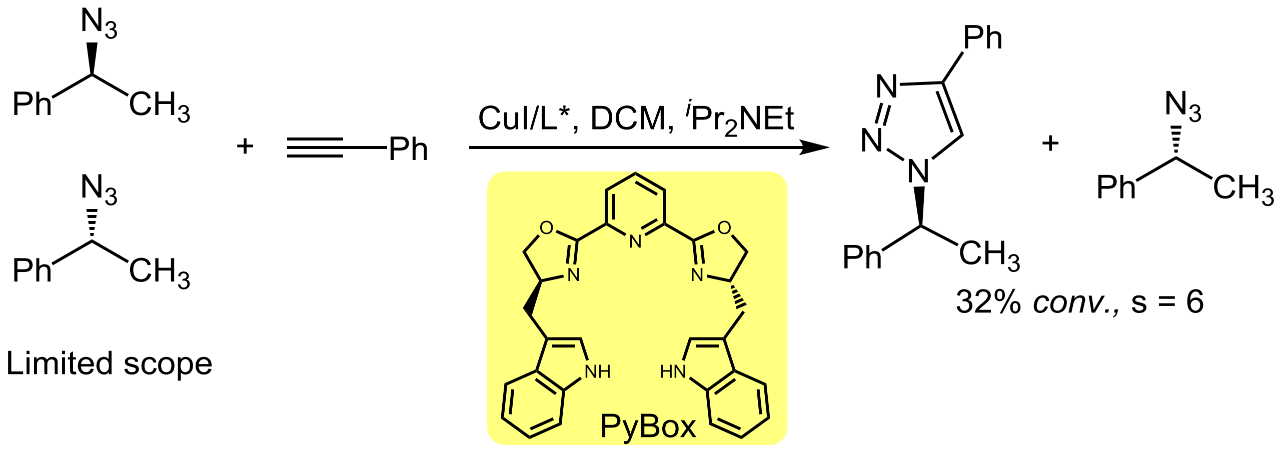
Second: Need to outcompete the facile **background CuAAC reaction**.

Kinetic resolution by CuAAC

Kinetic resolution is a key approach to the formation and recovery of enantioenriched materials



Ideal case = 50% Conversion at >99% ee

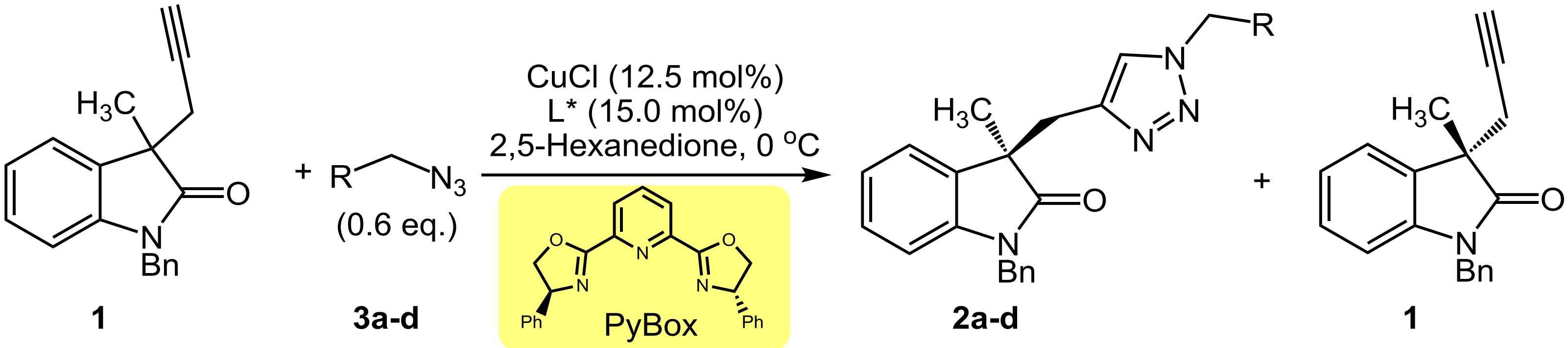


Limited scope

32% *conv.*, s = 6

Meng, J.-C.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett*. **2005**, *46*, 4543.

Kinetic resolution by CuAAC

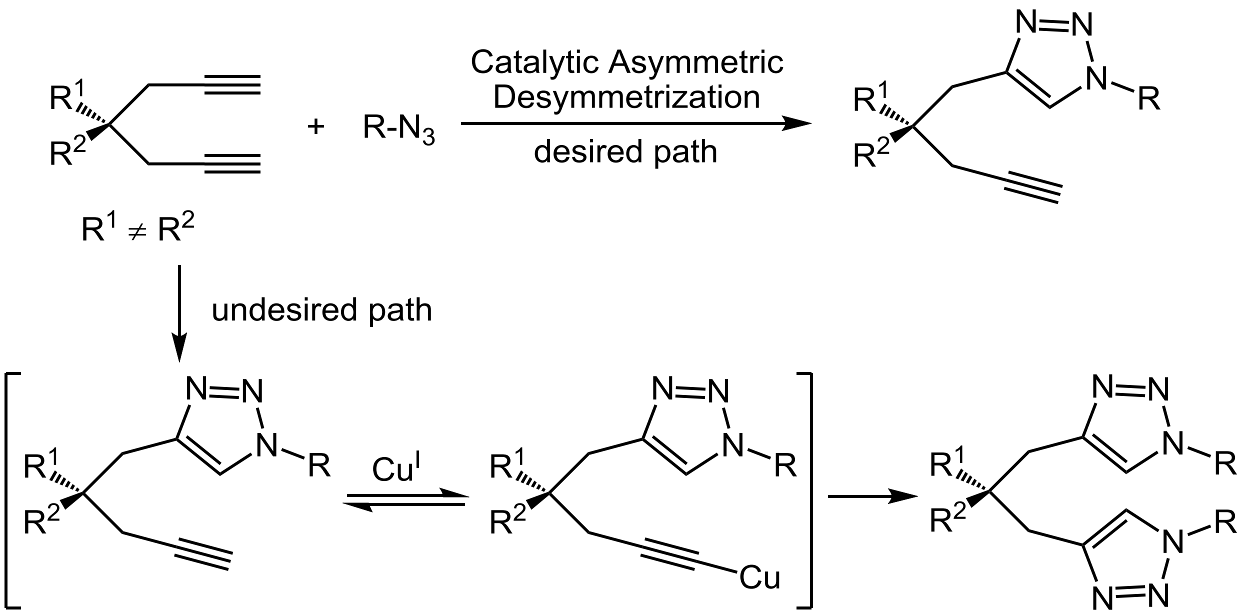


Entry	R	Conv. (%) [a]	Ee SM (%) [b]	*s* [c]
1	C_6H_5 (**2a**)	46	72	22.1
2	2-PhC_6H_4 (**2b**)	45	67	17.5
3	4-MeC_6H_4 (**2c**)	46	65	13.1
4	3,5-$(CF_3)_2C_6H_3$ (**2d**)	39	51	11.1

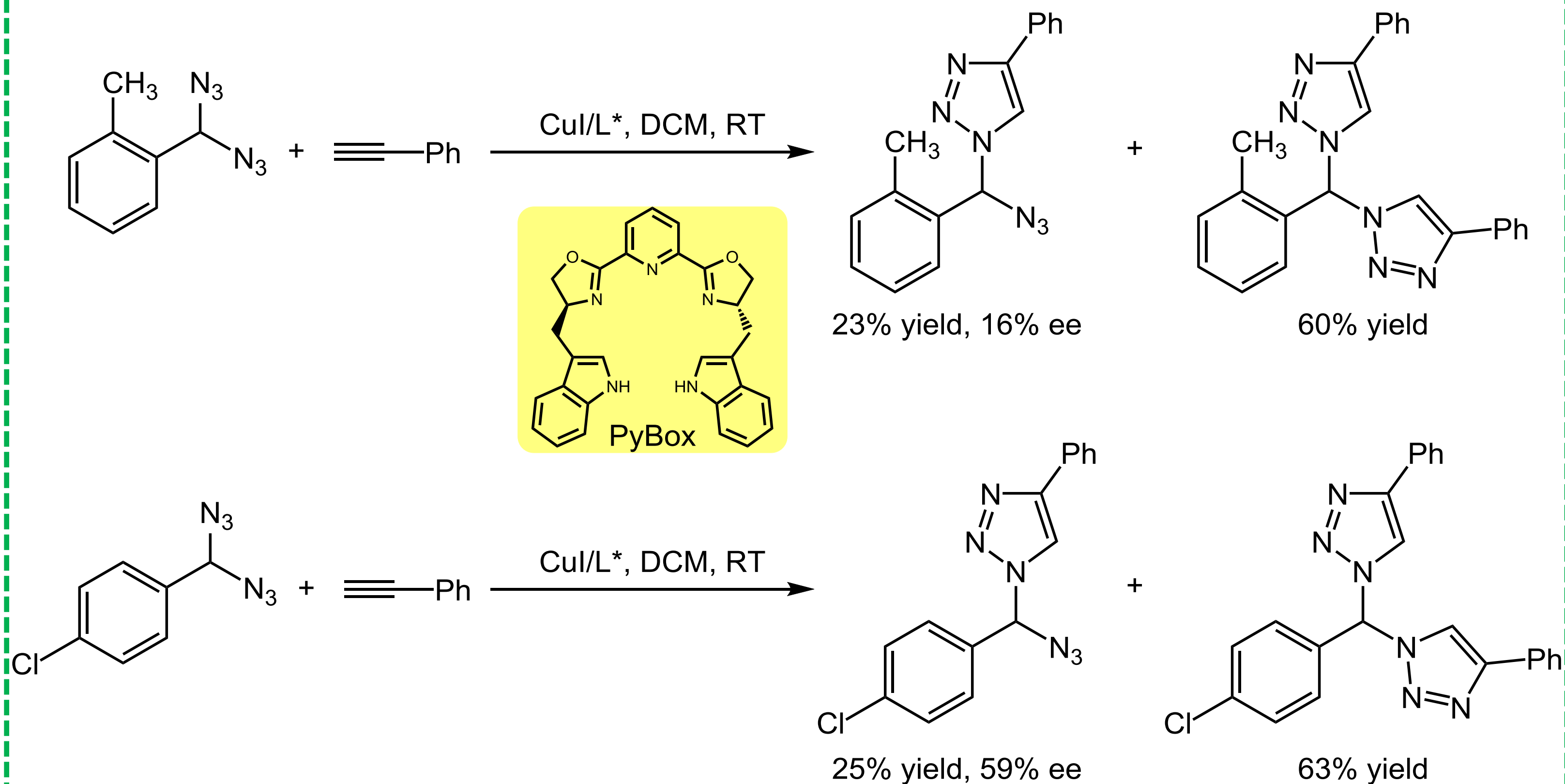
[a] Conversion determined by inspection of ^{1}H NMR spectra (see ESI). [b] Ee of recovered starting material (HPLC). [c] *s* = ln[(1-c)(1-Ee)]/ln[(1-c)(1+Ee)].

Brittain, W. D. G.; Buckley, B. R.; Fossey, J. S. *Chem. Commun*. **2015**, *51*, 17217.

Desymmetrization of dialkynes by CuAAC

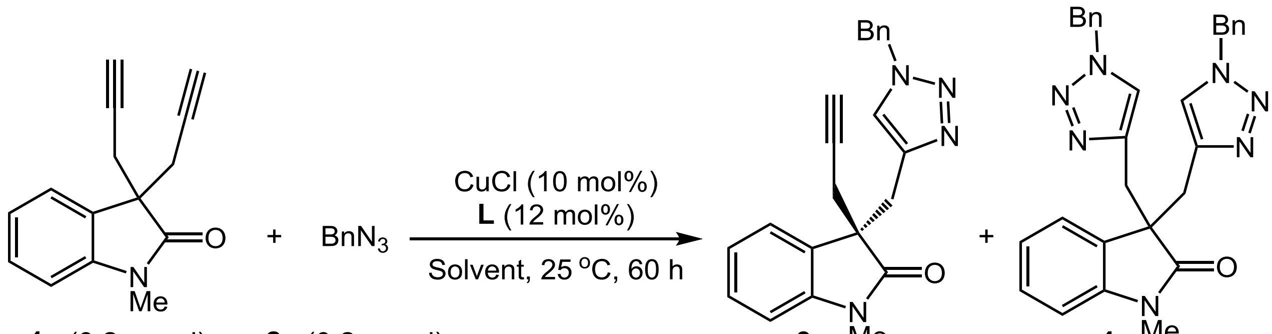


Desymmetrization of dialkynes by CuAAC



Meng, J. C.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett*. **2005**, *46*, 4543.

Asymmetric CuAAC to quaternary oxindoles

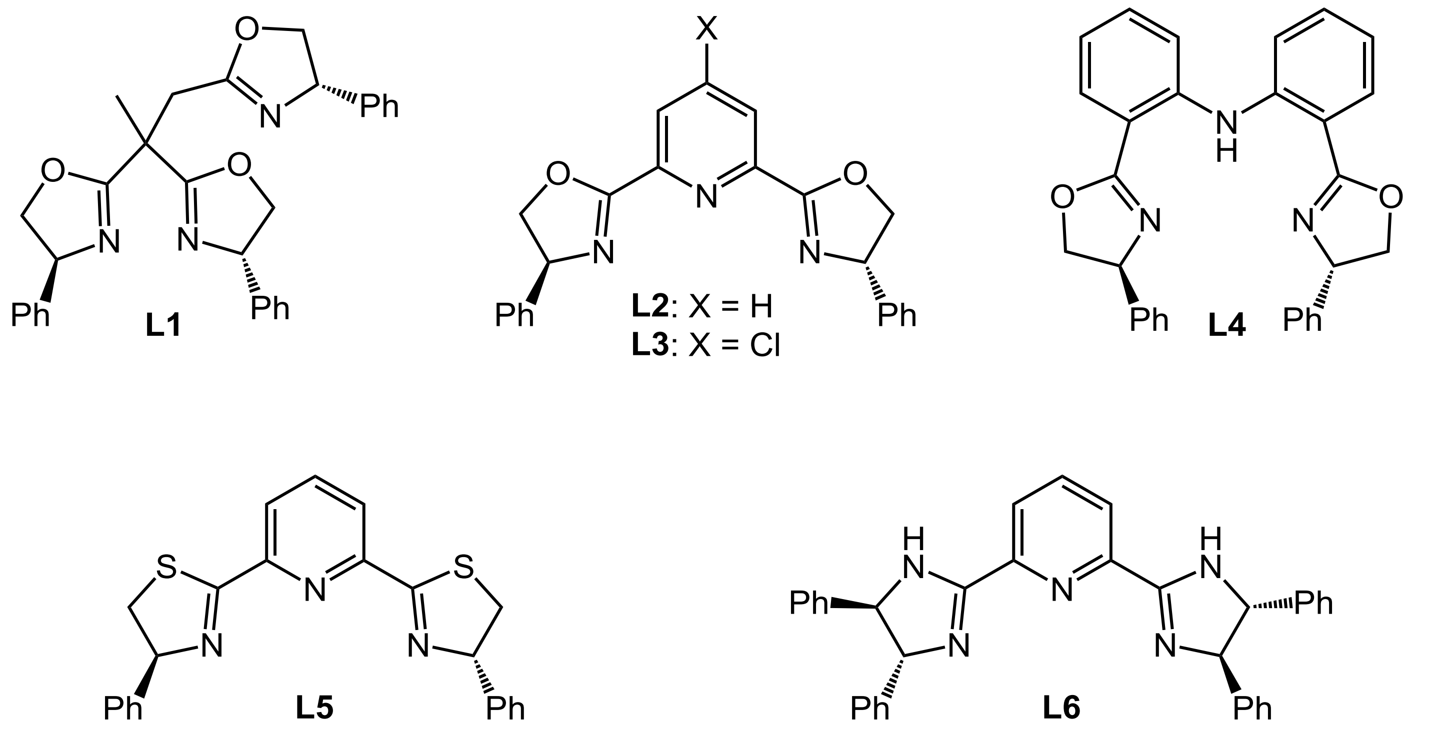


1a (0.2 mmol) **2a** (0.2 mmol) **3a** **4a**

Entry	L	Solvent	Yield of 3a (%) [a]	Ee of 3a [b]	3a:4a [a]
1	-	CH_2Cl_2	10	-	1:3
2	**L1**	CH_2Cl_2	17	-6	1:1
3	**L2**	CH_2Cl_2	11	67	1:4
4	**L3**	CH_2Cl_2	11	64	1:4
5	**L4**	CH_2Cl_2	5	2	1:9
6	**L5**	CH_2Cl_2	6	23	1:9
7	**L6**	CH_2Cl_2	8	0	1:5
8	**L2**	acetone	20	75	1:2

Zhou, F.; Tan, C.; Tang, J. Zhou, J. *J. Am. Chem. Soc*. **2013**, *135*, 10994.

PYBOX-type ligands

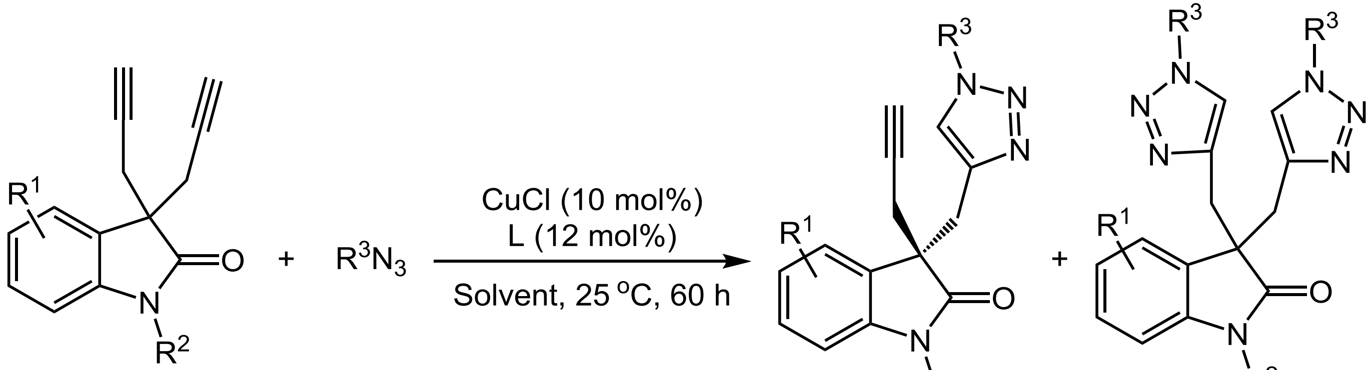


Asymmetric CuAAC to quaternary oxindoles

Entry	L	Solvent	Yield of 3a (%) [a]	Ee of 3a [b]	3a:4a [a]
9	**L2**	2-butanone	21	77	1:2
10	**L2**	2-pentanone	22	75	1:2
11	**L2**	3-pentanone	21	84	1:2
12	**L2**	cyclopentanone	24	60	1:2
13	**L2**	2,5-hexanedione	32 [c]	90	1:1
14 [d]	**L2**	2,5-hexanedione	50 [c]	85	2:1
15 [e]	**L2**	**2,5-hexanedione**	**77 [c]**	**90**	**7:1**

[a] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] Determined by HPLC analysis. [c] Isolated yield. [d] 0.24 mmol of **1a** was used. [e] 0.24 mmol of **1a**, 15 mol% CuCl, and 18 mol% **L2** were used at 0 °C for 96 h.

Substrate scope of the asymmetric CuAAC



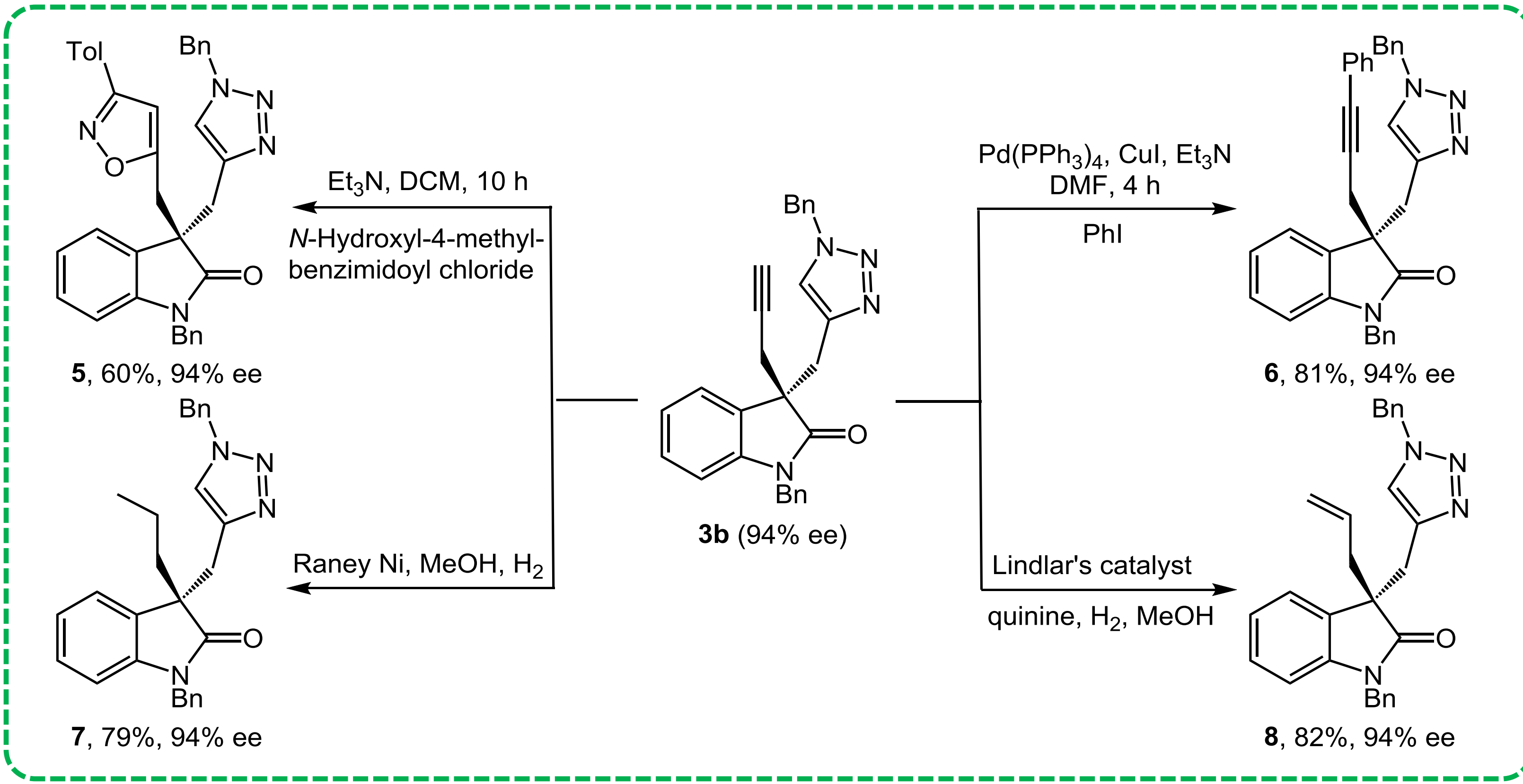
1 (0.24 mmol) + **2** (0.2 mmol) → **3** + **4**

up to 98% ee, **3**:**4** = 12:1

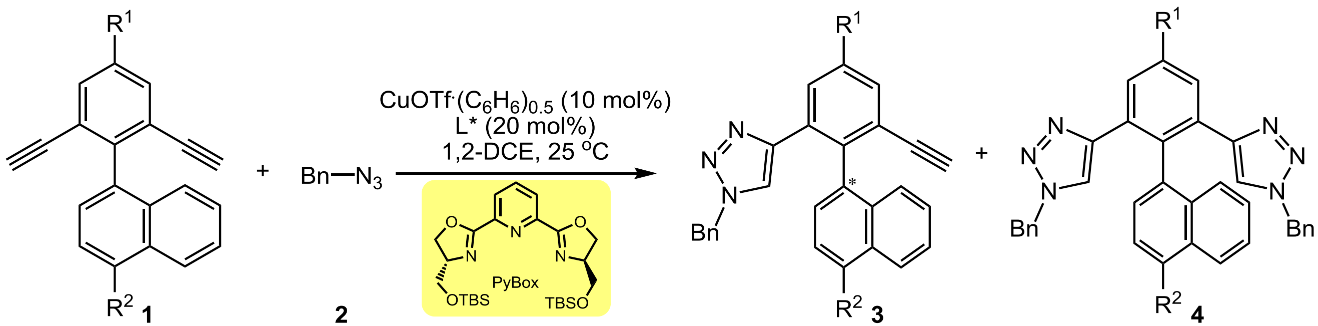
1a: R^1 = H, R^2 = Me
1b: R^1 = H, R^2 = Bn
1c: R^1 = H, R^2 = ^{i}Pr
1d: R^1 = H, R^2 = Ac
1e: R^1 = 5-F, R^2 = Bn
1f: R^1 = 7-Me, R^2 = Bn
1g: R^1 = 5-OMe, R^2 = Bn
1h: R^1 = 6-OMe, R^2 = Bn
1i: R^1 = 6-Cl-7-Me, R^2 = Bn
1j: R^1 = 7-Cl, R^2 = Bn
1k: R^1 = 5-Br, R^2 = Bn

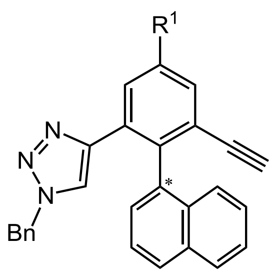
2a: R^3 = Bn
2b: R^3 = 2-$FC_6H_4CH_2$
2c: R^3 = 3-$FC_6H_4CH_2$
2d: R^3 = 4-$ClC_6H_4CH_2$
2e: R^3 = 2-$MeC_6H_4CH_2$
2f: R^3 = 3-$MeC_6H_4CH_2$
2g: R^3 = 4-$MeC_6H_4CH_2$
2h: R^3 = 2-$OHC_6H_4CH_2$
2i: R^3 = 4-$OHC_6H_4CH_2$
2g: R^3 =CH_2CO_2Bn
2k: R^3 = Ph
2l: R^3 = *c*-hexyl

Synthetic elaboration of 3b



Construction of chiral biaryl derivative by CuAAC





3

3a: R^1 = H, 64%, 91% ee; **4a**: 32%

3b: R^1 = OMe, 56%, 78% ee; **4b**: 40%

3c: R^1 = OPh, 63%, 92% ee; **4c**: 36%

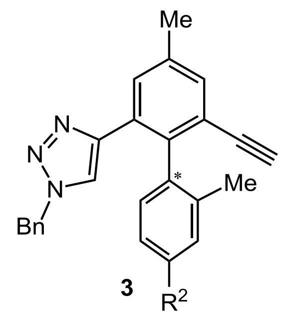
3d: R^1 = Me, 62%, 93% ee; **4d**: 38%

3e: R^1 = ^{t}Bu, 66%, 78% ee; **4e**: 25%

3f: R^1 = Bn, 57%, 91% ee; **4f**: 37%

3g: R^1 = Cl, 68%, 91% ee; **4g**: 30%

3h: R^1 = NO_2, 54%, 87% ee; **4h**: 37%



3

3i: R^2 = H, 70%, 98% ee; **4i**: 28%

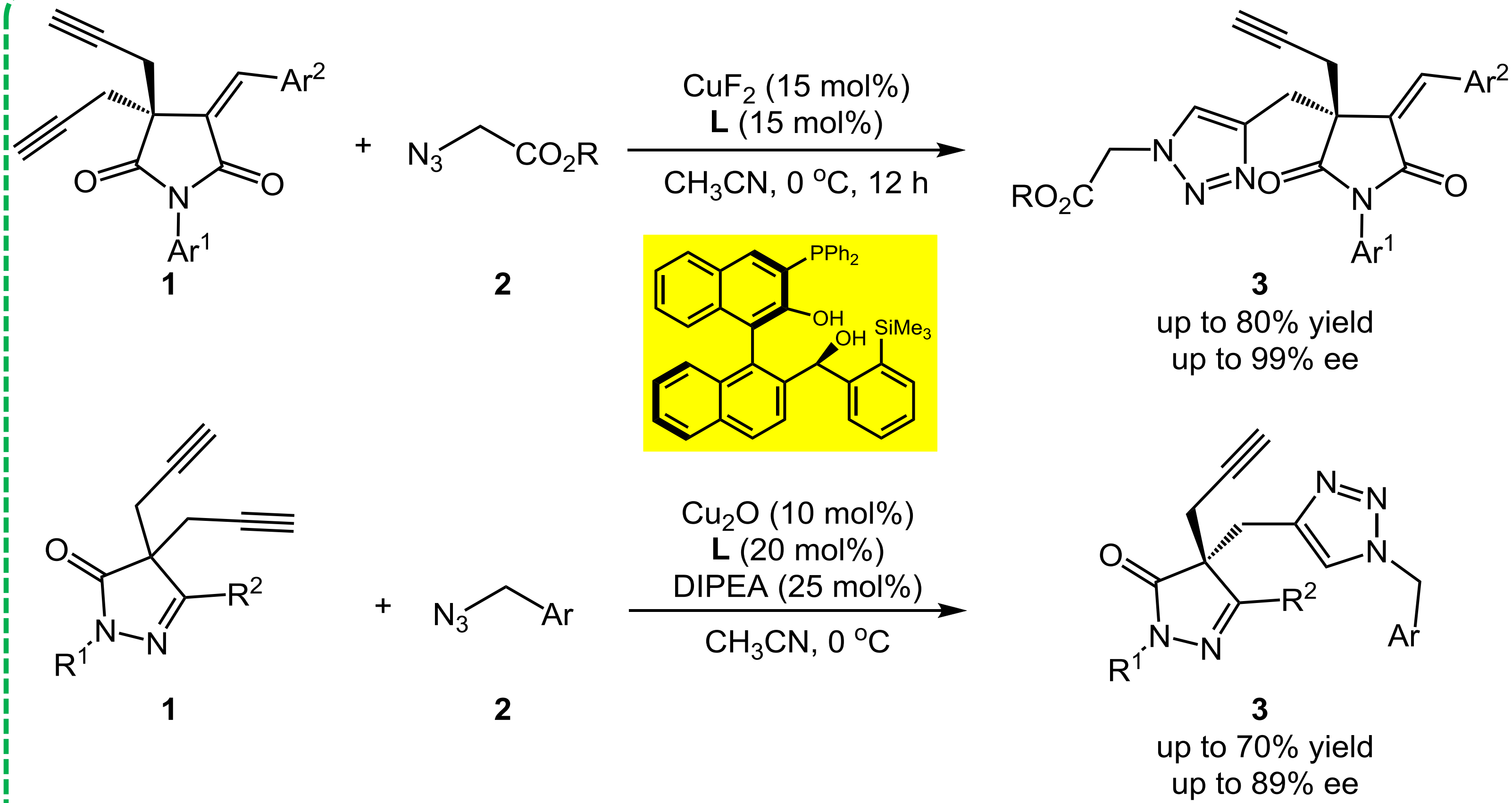
3j: R^2 = OMe, 63%, 99% ee; **4j**: 32%

3k: R^2 = Me, 76%, 97% ee; **4k**: 20%

3l: R^2 = F, 64%, 99% ee; **4d**: 33%

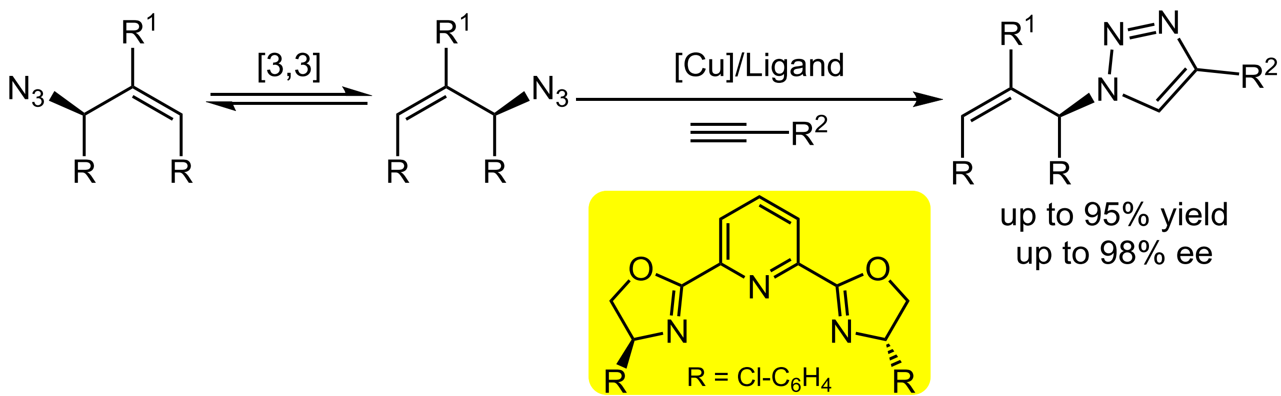
Osako, T.; Uozumi, Y. *Org. Lett*. **2014**, *16*, 5866.

Desymmetrization of dialkynes by CuAAC



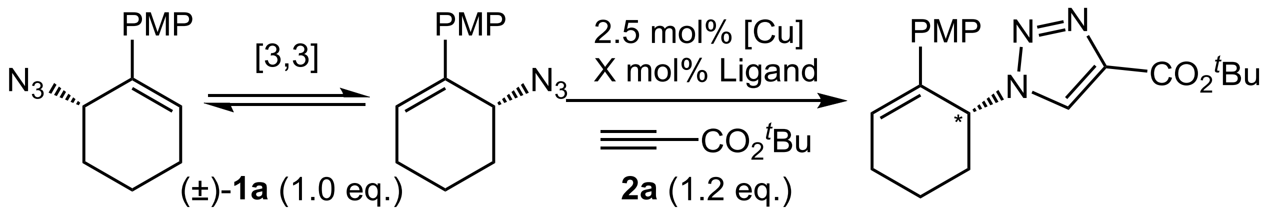
Song, T.; Li, L.; Zhou, W.; Xu, L.-W. *et al. Chem. Eur. J.* **2015**, *21*, 554.
Chen, M.-Y.; Xu, Z.; Chen, L.; Xu, L.-W. *et al. ChemCatChem*. **2018**, *10*, 280.

E-CuAAC by dynamic kinetic resolution



Liu, E.-C.; Topczewski, J. J. *J. Am. Chem. Soc.* **2019**, *141*, 5135.

Optimization of E-CuAAC by DKR



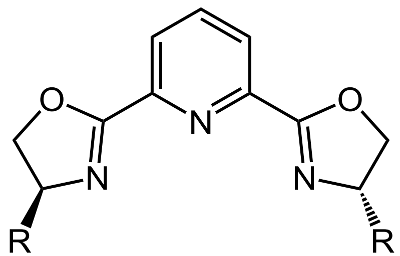
Entry [a]	[Cu] source	Ligand (X mol%)	Yield (%) [b]	Ee (%) [c]
1	CuI	**L1** (2.5%)	80	14
2	$(CuOTf)_2PhMe$	**L1** (2.5%)	>98	20
3	$(CuOTf)_2PhMe$	**L2** (2.5%)	95	6
4	**$(CuOTf)_2PhMe$**	**L3 (2.5%)**	**93**	**72**
5	**$(CuOTf)_2PhMe$**	**L4 (2.5%)**	**80**	**52**
6	$(CuOTf)_2PhMe$	**L5** (2.5%)	58	2
7	$(CuOTf)_2PhMe$	**L6** (2.5%)	87	4
8	$(CuOTf)_2PhMe$	**L7** (2.5%)	65	4

Optimization of E-CuAAC by DKR

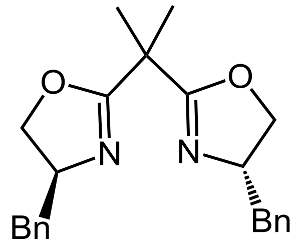
Entry [a]	[Cu] source	Ligand	Yield (%) [b]	Ee (%) [c]
9	$(CuOTf)_2PhMe$	**L8** (2.5%)	>98	4
10	$(CuOTf)_2PhMe$	**L4** (5.0%)	83	76
11 [d]	**$(CuOTf)_2PhMe$**	**L4 (5.0%)**	**>98**	**98**
12 [d]	$Cu(MeCN)_4PF_6$	**L4** (5.0%)	73	80
13 [d]	$Cu(MeCN)_4BF_4$	**L4** (5.0%)	82	82

[a] Reactions conducted with allylic azide **1a** (0.10 mmol), alkyne **2a** (0.12 mmol), in dimethoxyethane (0.2 M), with 2.5% [Cu] and either 2.5 mol% or 5.0 mol% ligand, RT. [b] Yield based on ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Chiral HPLC was used to determine Ee. [d] 40 ^{o}C.

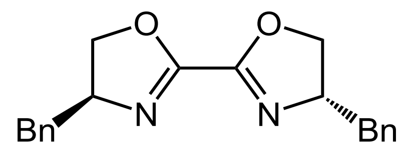
Ligands



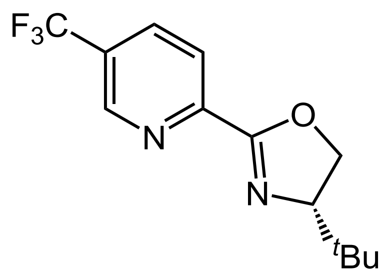
L1: R = ^{i}Pr
L2: R = ^{t}Bu
L3: R = Ph
L4: R = 4-Cl-Ph



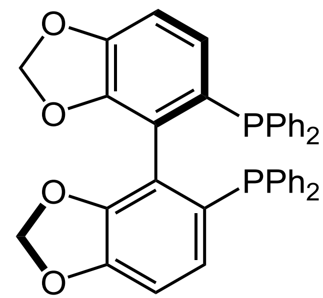
L5



L6

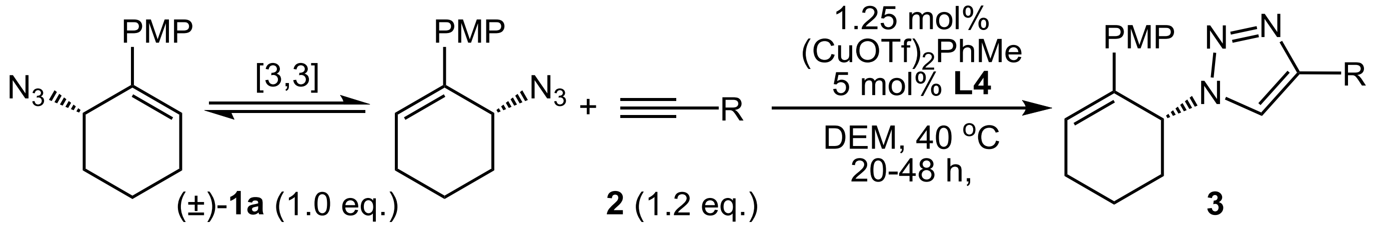


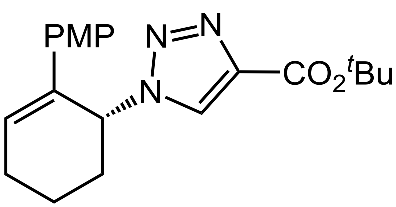
L7



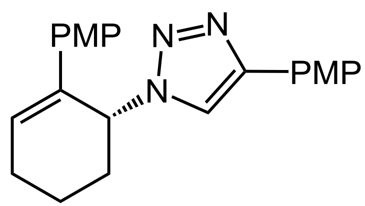
L8

Scope of DKR E-CuAAC with respect to alkyne 2

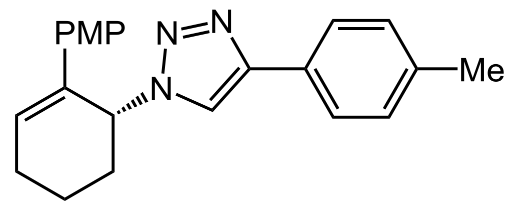




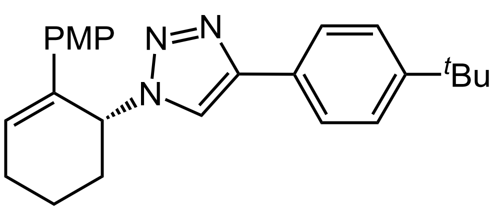
3a 95%, 98% ee



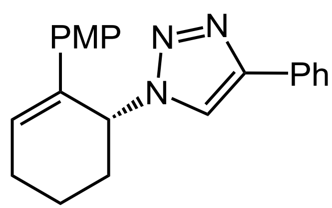
3b 89%, 86% ee



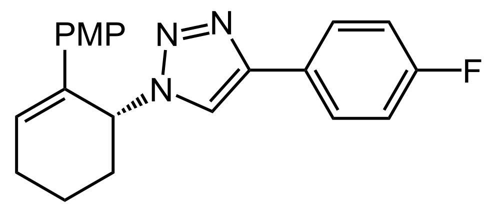
3c 91%, 86% ee



3d 96%, 84% ee

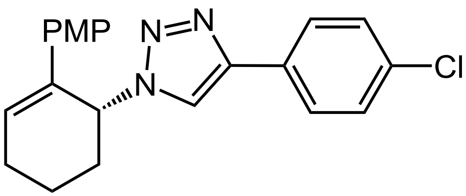


3e 85%, 92% ee

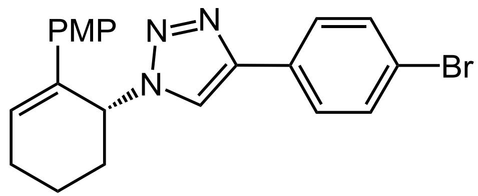


3f 90%, 86% ee

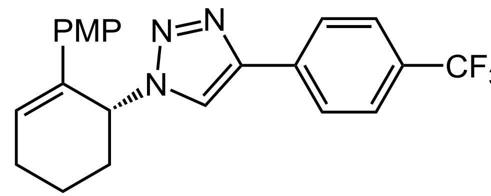
Scope of DKR E-CuAAC with respect to alkyne 2



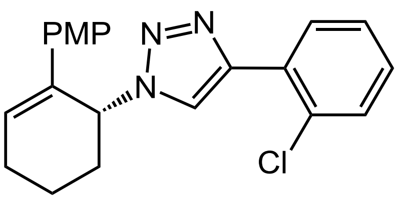
3g 91%, 84% ee



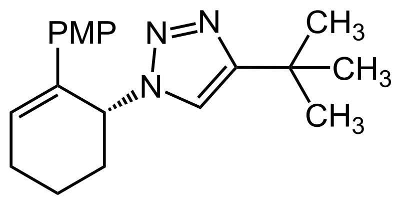
3h 86%, 90% ee



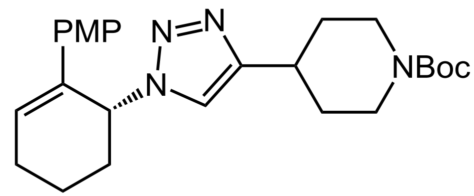
3i 92%, 80% ee



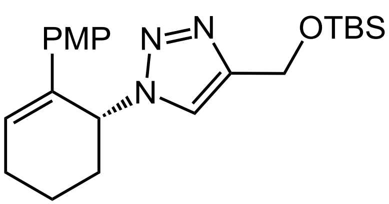
3j 80%, 90% ee



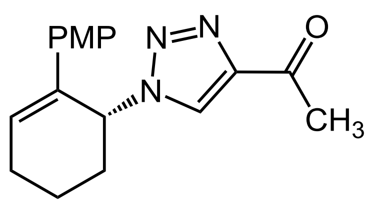
3k 71%, 84% ee



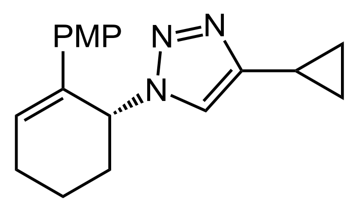
3l 96%, 86% ee



3m 95%, 88% ee

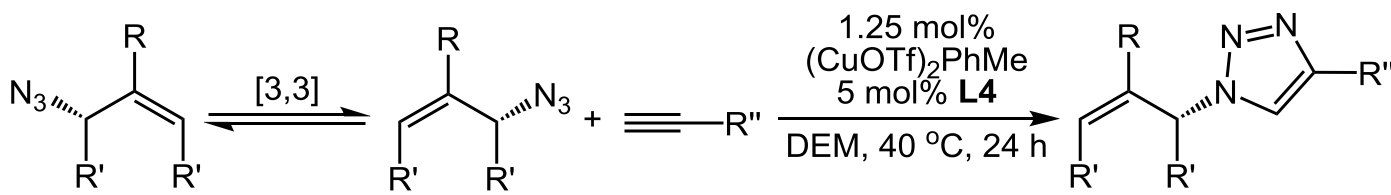


3n 96%, 84% ee

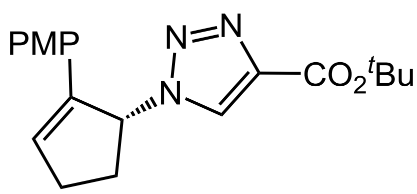


3o 80%, 94% ee

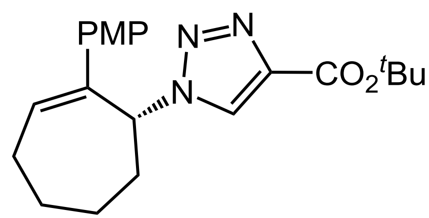
Scope of DKR E-CuAAC with respect to azide 1



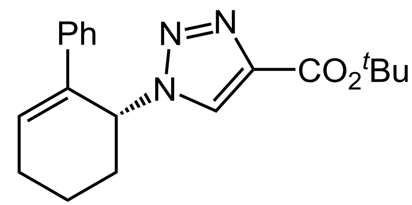
(±)-**1** (1.0 eq.) **2** (1.2 eq.) **3**



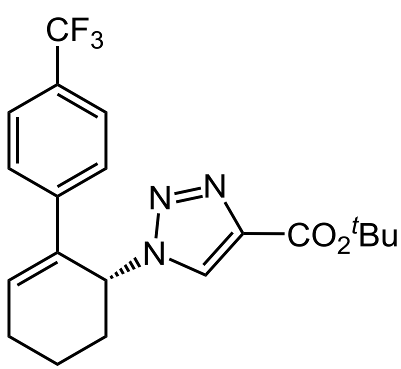
3p 79%, 88% ee



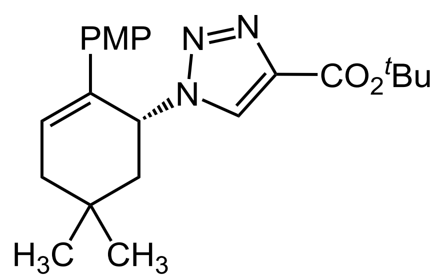
3q 99%, 80% ee



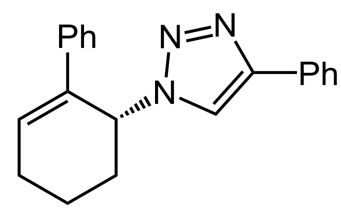
3r 96%, 90% ee



3s 96%, 88% ee

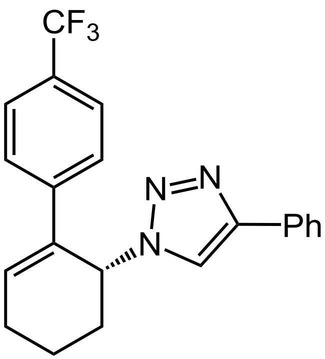


3t 85%, 88% ee

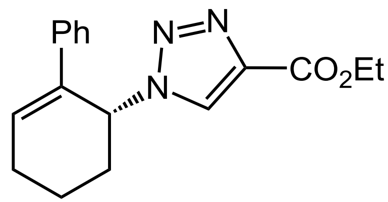


3u 85%, 92% ee

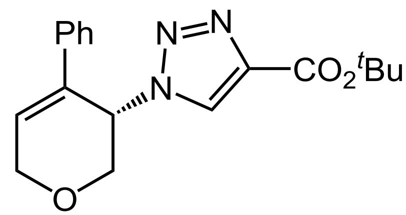
Scope of DKR E-CuAAC with respect to azide 1



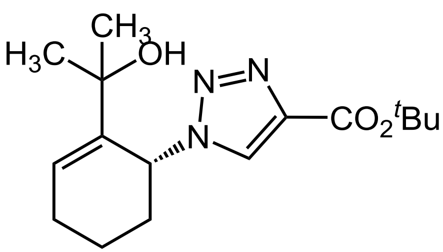
3v 82%, 86% ee



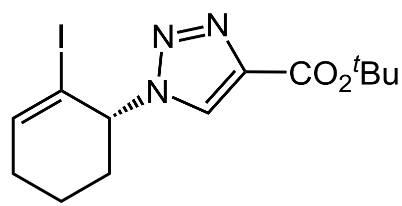
3w 85%, 92% ee



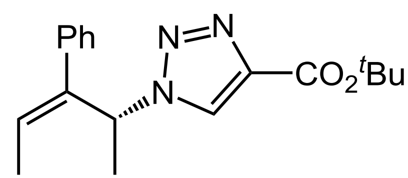
3x 90%, 70% ee



3y 96%, 80% ee

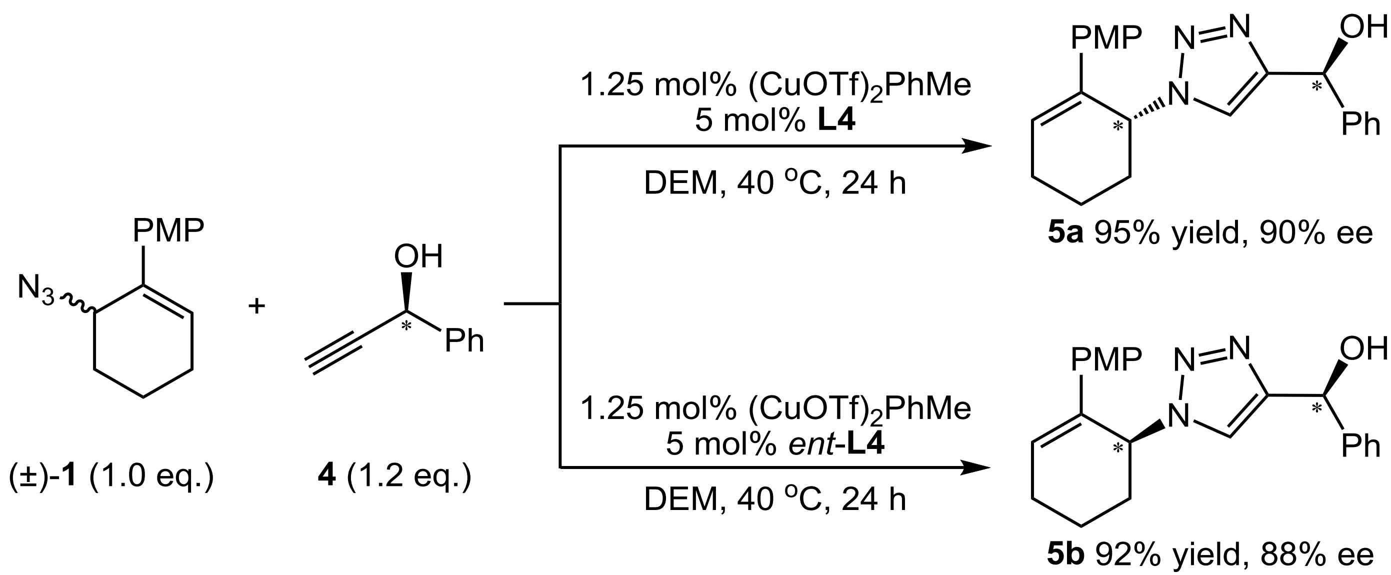


3z 85%, 74% ee

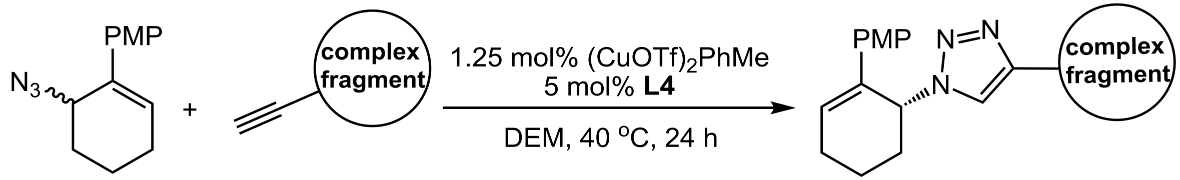


3aa 92%, 72% ee
93:7 *E:Z*

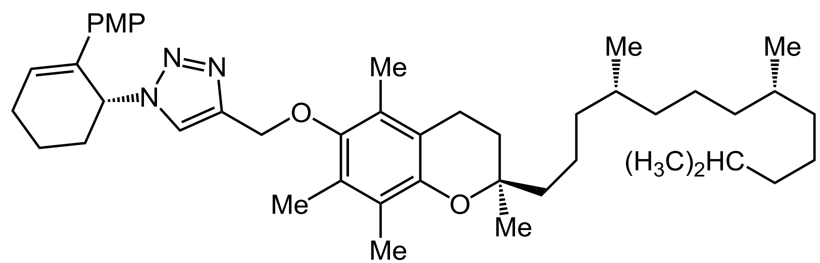
Test for matched/mismatched behavior



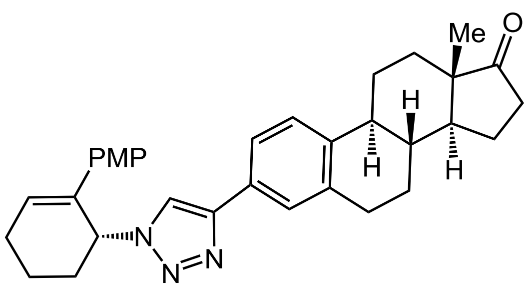
DKR E-CuAAC in complex molecular setting



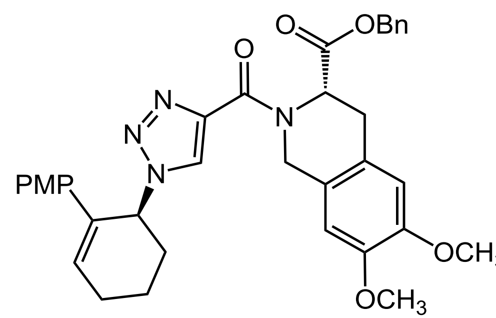
(±)-**1** (1.0 eq.) **2** (1.2 eq.) **6**



6a 92%, 97:3 dr



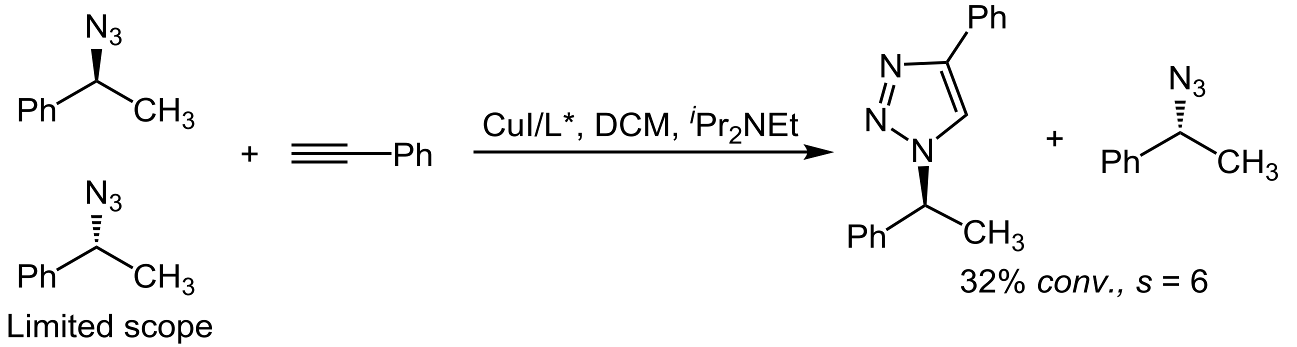
6b 99%, 86:14 dr



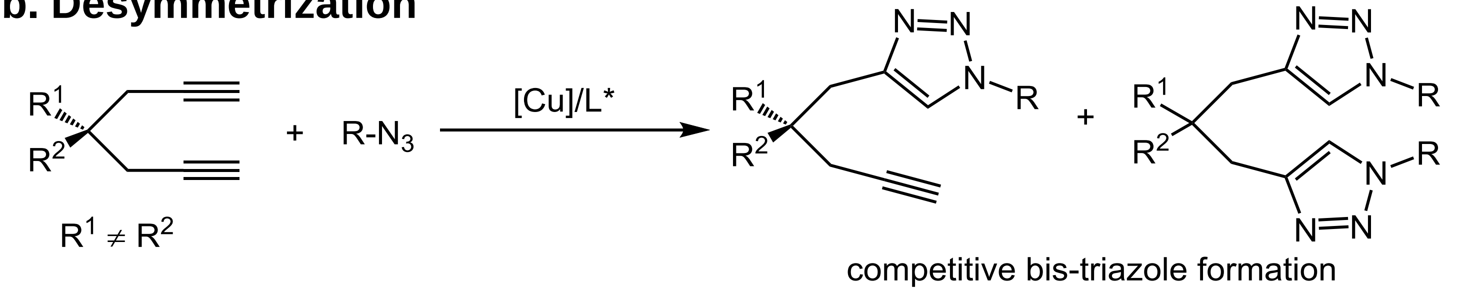
6c 99%, 97:3 dr

Summary

a. Kinetic resolution

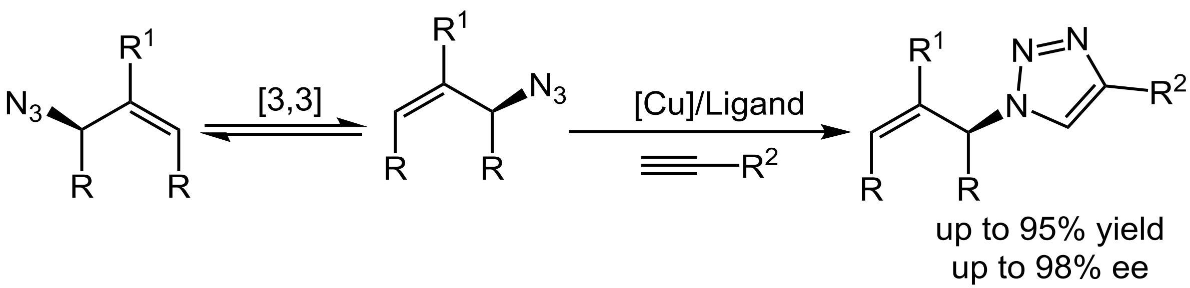


b. Desymmetrization



Summary

c. Dynamic kinetic resolution



The first paragraph

The copper(I) catalyzed alkyne−azide cycloaddition (CuAAC) has transformed many aspects of modern chemical synthesis since it was first reported contemporaneously by Meldal, Sharpless, and co-workers. The CuAAC reaction is robust, mild, high yielding, and chemo-orthogonal. Applications for CuAAC have permeated and transformed numerous fields including chemical biology, material science, polymer chemistry, and medicinal chemistry. Triazoles, formed by CuAAC, are now common peptidomimetics and pharmaceutical building blocks. With the tremendous utility of CuAAC, a versatile catalyst that could impart enantioselectivity to the process would likely find numerous applications, especially as examples of *α*-chiral triazoles are emerging in active biological agents.

The last paragraph

We report an effective system for the enantioselective copper(I) catalyzed alkyne−azide cycloaddition (E-CuAAC) “click” reaction that is enabled by the dynamic kinetic resolution of allylic azides. A negative nonlinear effect was observed in this system. The reaction proceeds in high yield and high selectivity.The scope of this process is broad and the reaction can proceed in a complex molecular environment.