Literature Report III

Asymmetric Synthesis of Chiral 1,4-Enynes through Organocatalytic Alkenylation of Propargyl Alcohols

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Checker: Xiao-Qing Wang
Date: 2019-07-15

Kano, T.; Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2019**, *58,* 8898.

CV of Prof. Taichi Kano

Education and Employment:

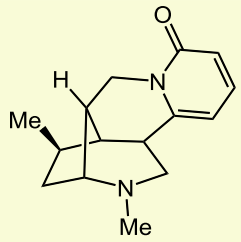
- **1992–1996** B.S., Nagoya University
- **1996–2001** Ph.D., Nagoya University (with Prof. H. Yamamoto)
- **2001–2002** Postdoc, Caltech (with Prof. B. M. Stoltz)
- **2003–2006** Assistant Professor, Kyoto University
- **2006–2015** Lecturer, Kyoto University
- **2015–Now** Associate Professor, Kyoto University

Research Interests:

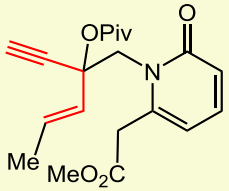
- Design of Chiral Phase Transfer Catalysts for Practical Amino Acid Synthesis
- Design of Chiral Organocatalysts for Practical Asymmetric Synthesis
- Development of Bidentate Lewis Acid Chemistry and Application to Selective Organic Synthesis

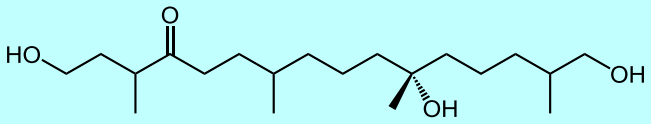
Contents

Introduction

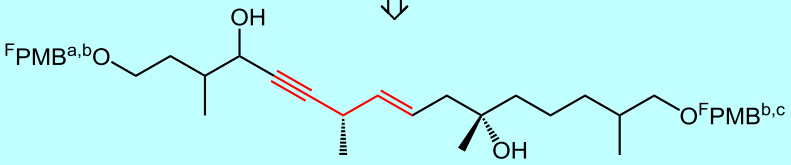


(-)-Hosieine A



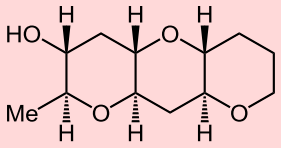


Hormone α1

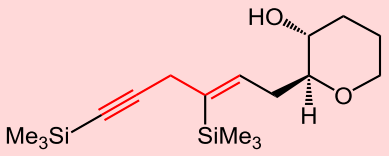


^{F}PMB on O1 encodes C3
3*S*, tag a, -$CH_2C_6H_6$-4-O$(CH_2)_3CF_3$
3*R*, tag b, -$CH_2C_6H_6$-4-O$(CH_2)_3C_4F_9$

^{F}PMB on O16 encodes C15
15*R*, tag b, -$CH_2C_6H_6$-4-O$(CH_2)_3C_4F_9$
15*S*, tag c, -$CH_2C_6H_6$-4-O$(CH_2)_3C_6F_{13}$



Ladder Polyether



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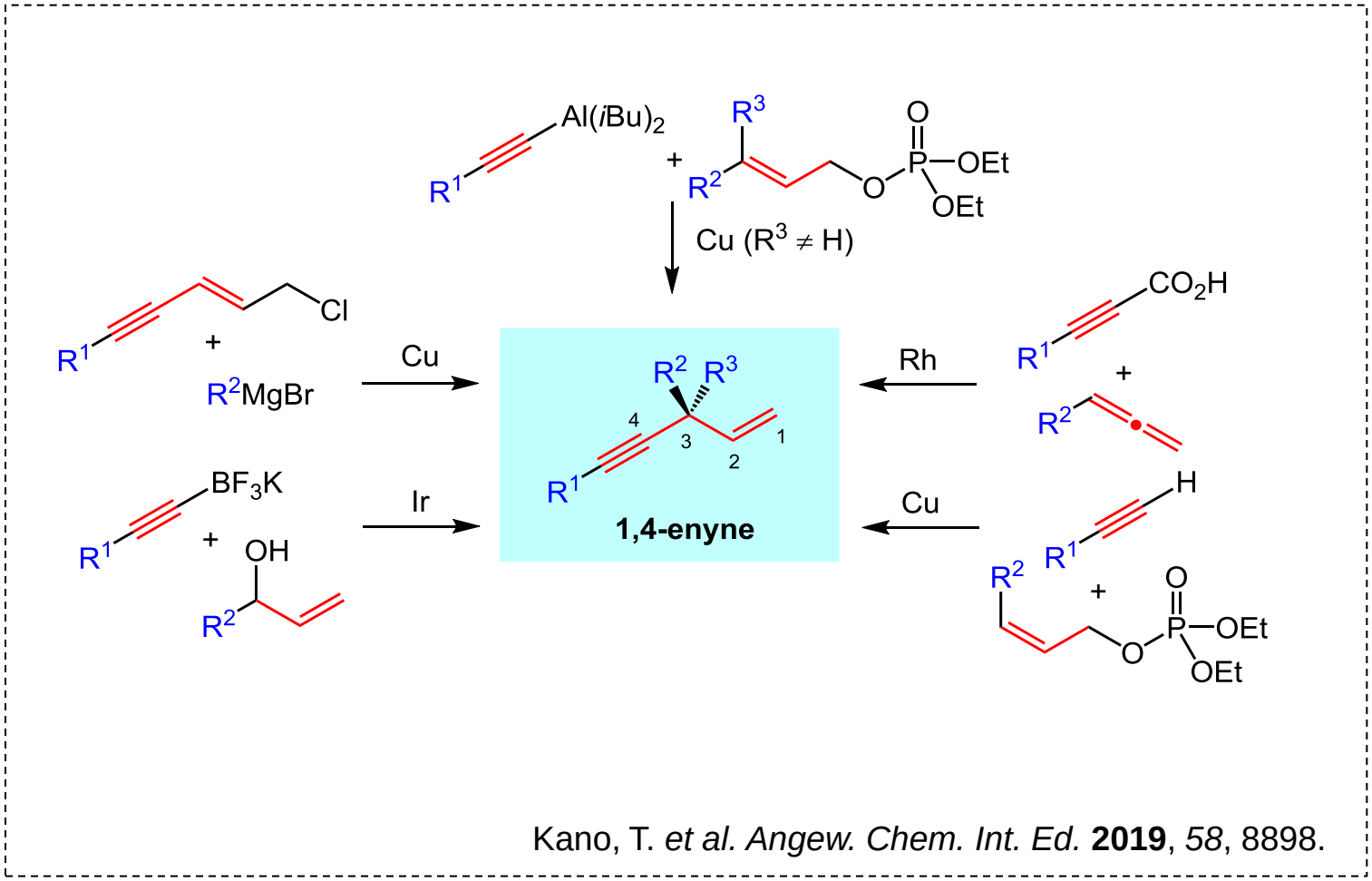
Curran, D. P. *et al. J. Am. Chem. Soc.* **2011**, *133*, 20435.
Jamison, T. F. *et al. Org. Lett.* **2003**, *5*, 2339.

Asymmetric synthesis of 1,4-enynes



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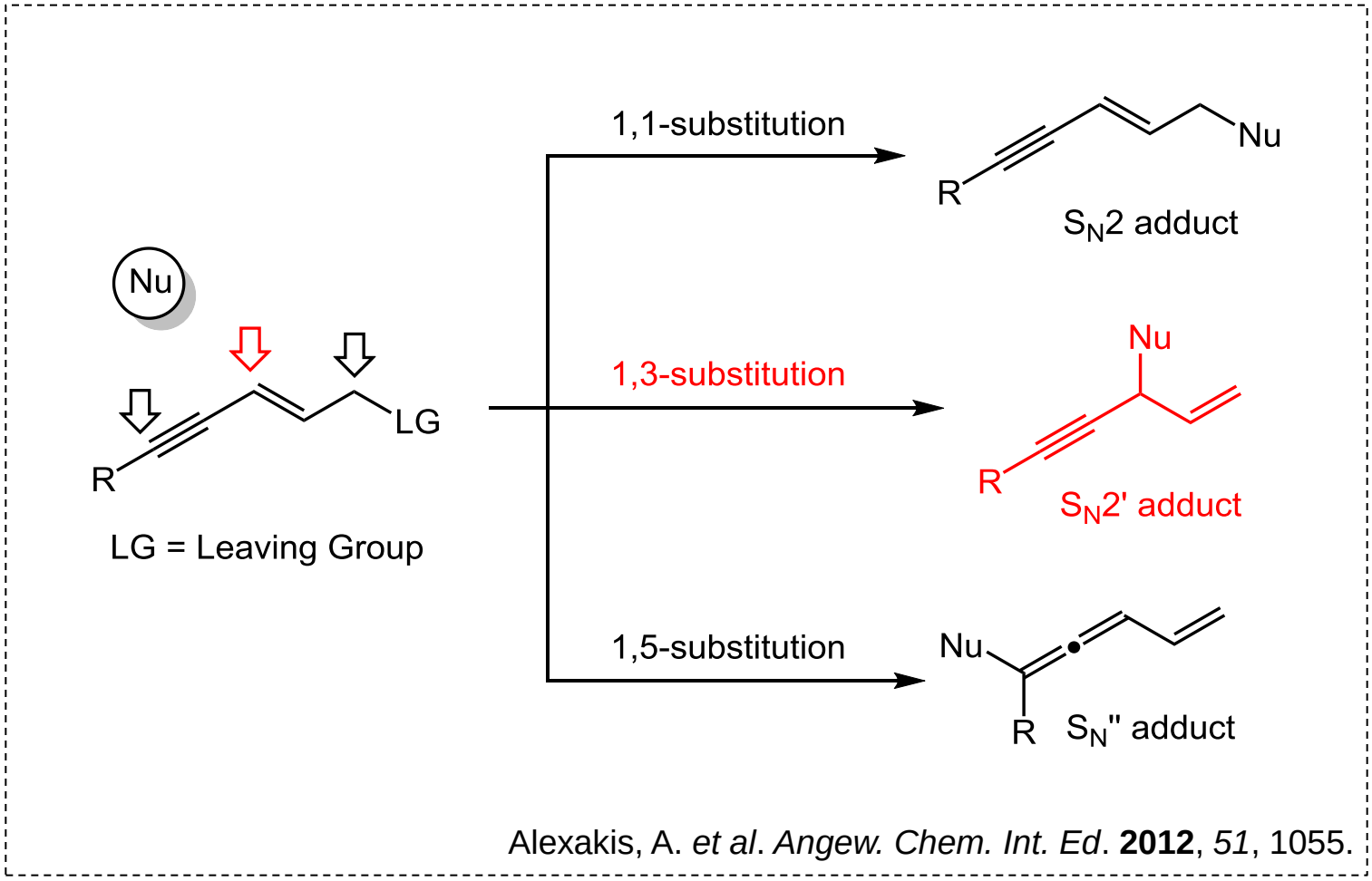
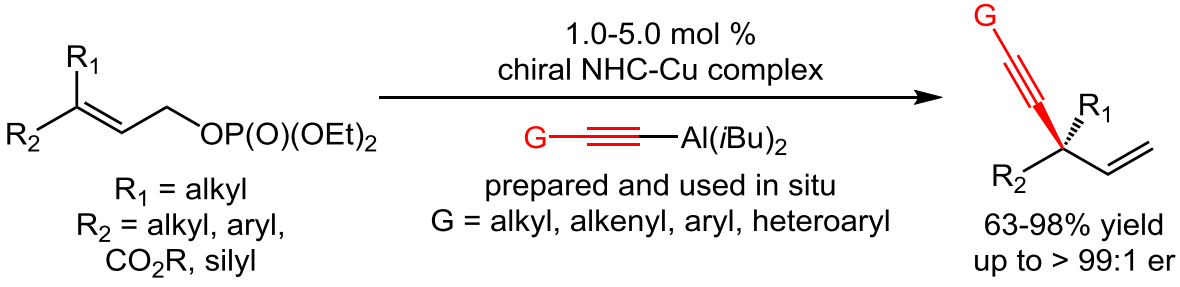
Possible products by substitution reaction

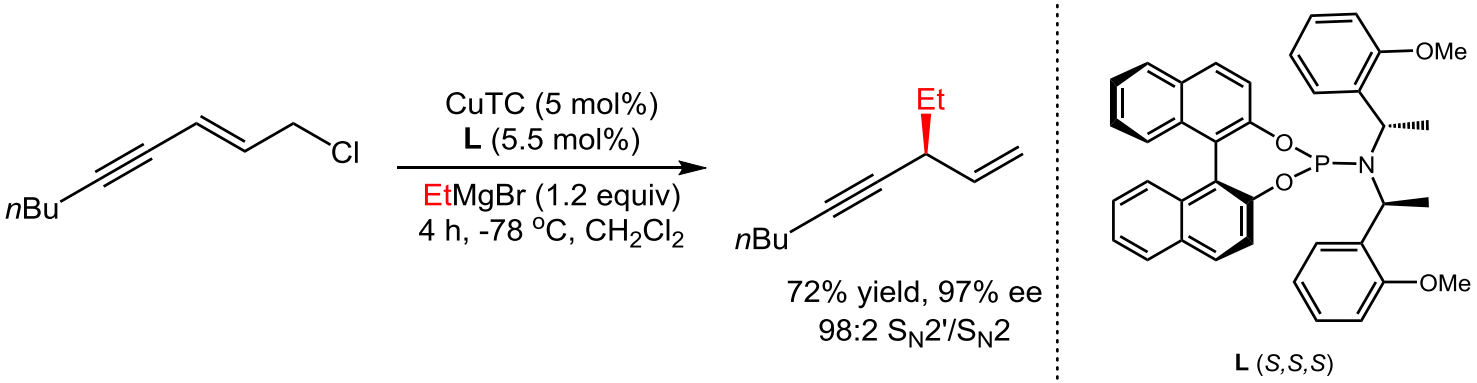


Alexakis, A. *et al*. *Angew. Chem. Int. Ed*. **2012**, *51*, 1055.

Asymmetric synthesis of 1,4-enynes

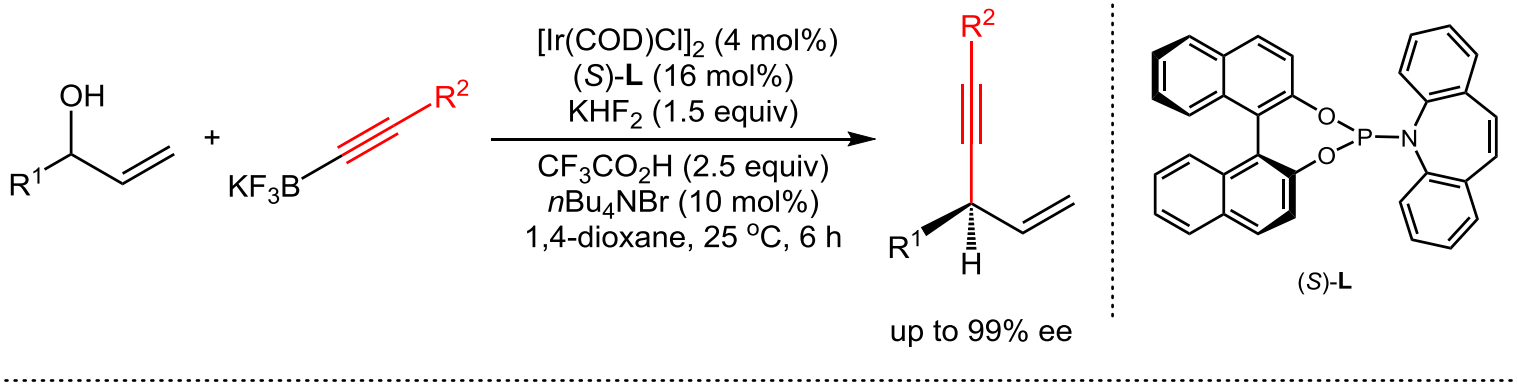


Hoveyda, A. H. *et al. J. Am. Chem. Soc.* **2011**, *133*, 4778.

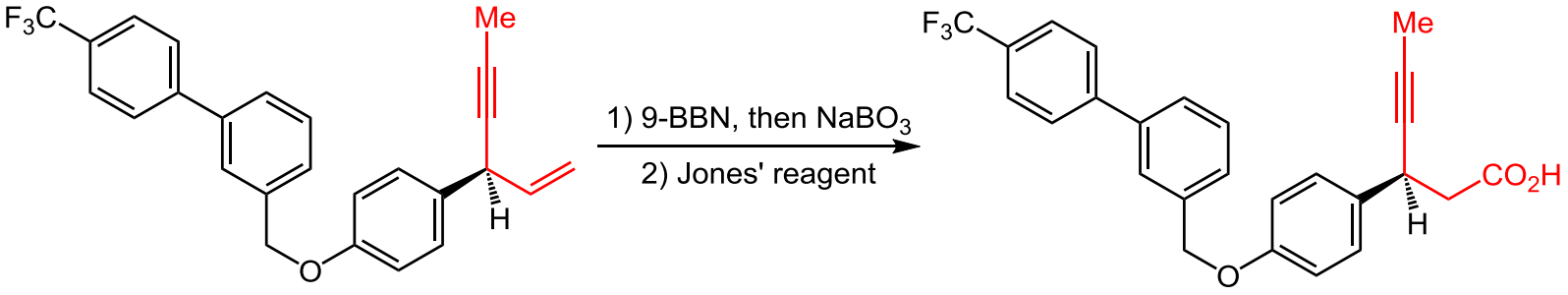


Alexakis, A. *et al*. *Angew. Chem. Int. Ed*. **2012**, *51*, 1055.

Asymmetric synthesis of 1,4-enynes



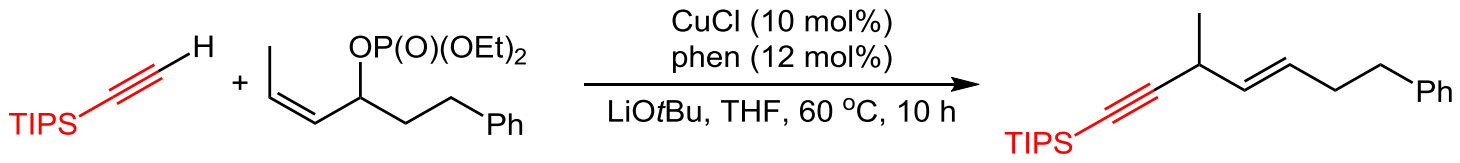
up to 99% ee



AMG 837 [*GPR40 agonist*]
74% yield, > 99% ee

Carreira, E. M. *et al. Angew. Chem. Int. Ed*. **2013**, *52*, 7532.

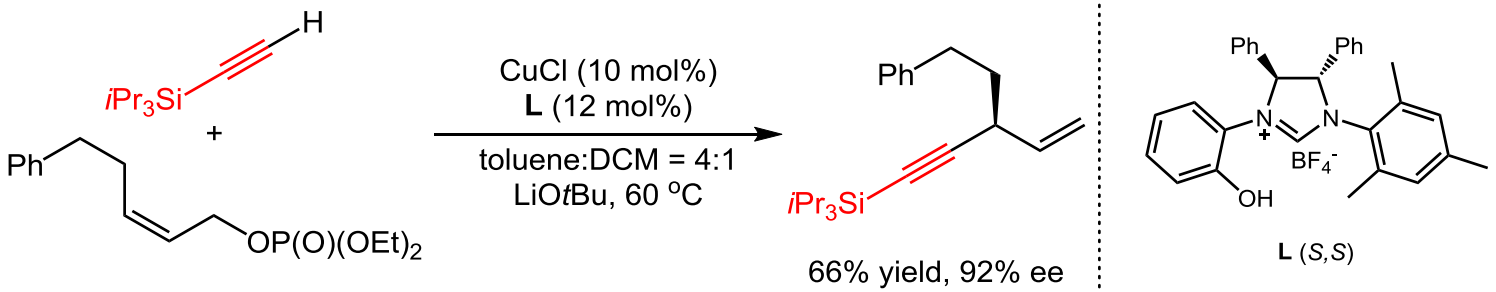
Asymmetric synthesis of 1,4-enynes



SM1 **SM2** **TM**

γ/α > 99:1; *E/Z* > 99:1

Sawamura, M. *et al. Angew. Chem. Int. Ed*. **2013**, *52*, 5350.

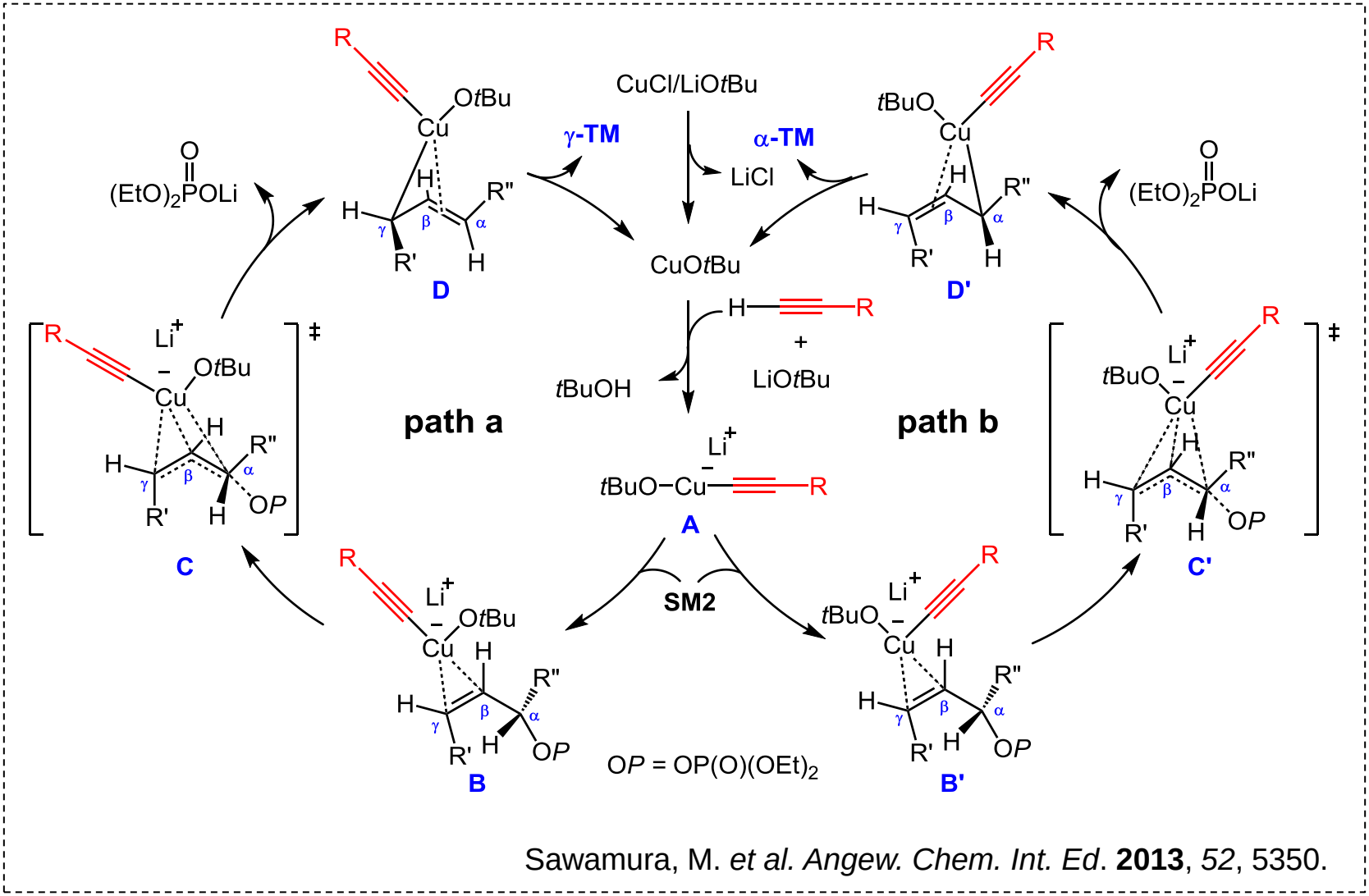


66% yield, 92% ee

L (*S,S*)

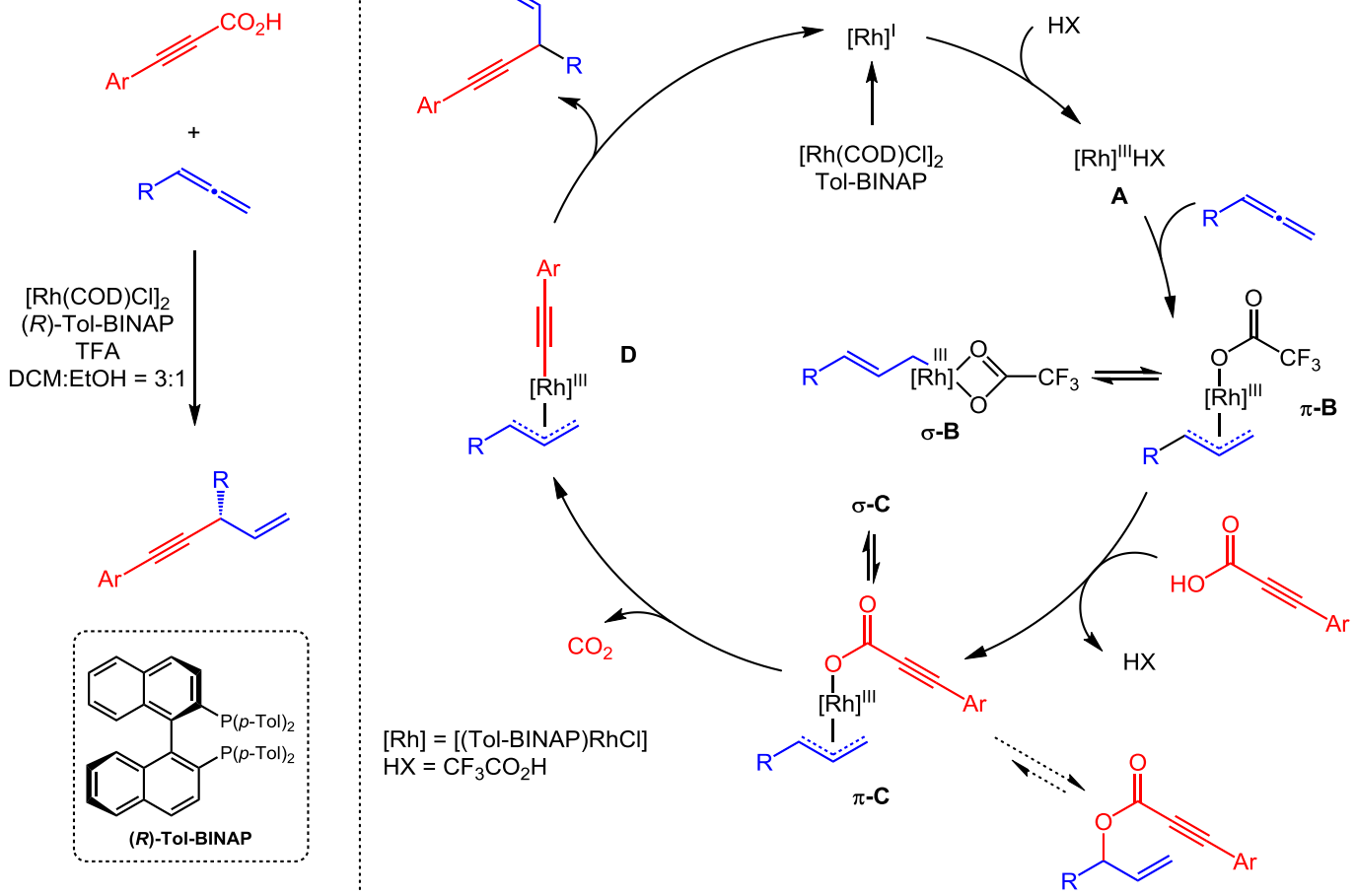
Sawamura, M. *et al. J. Am. Chem. Soc.* **2014**, *136*, 13932.

Proposed mechanism



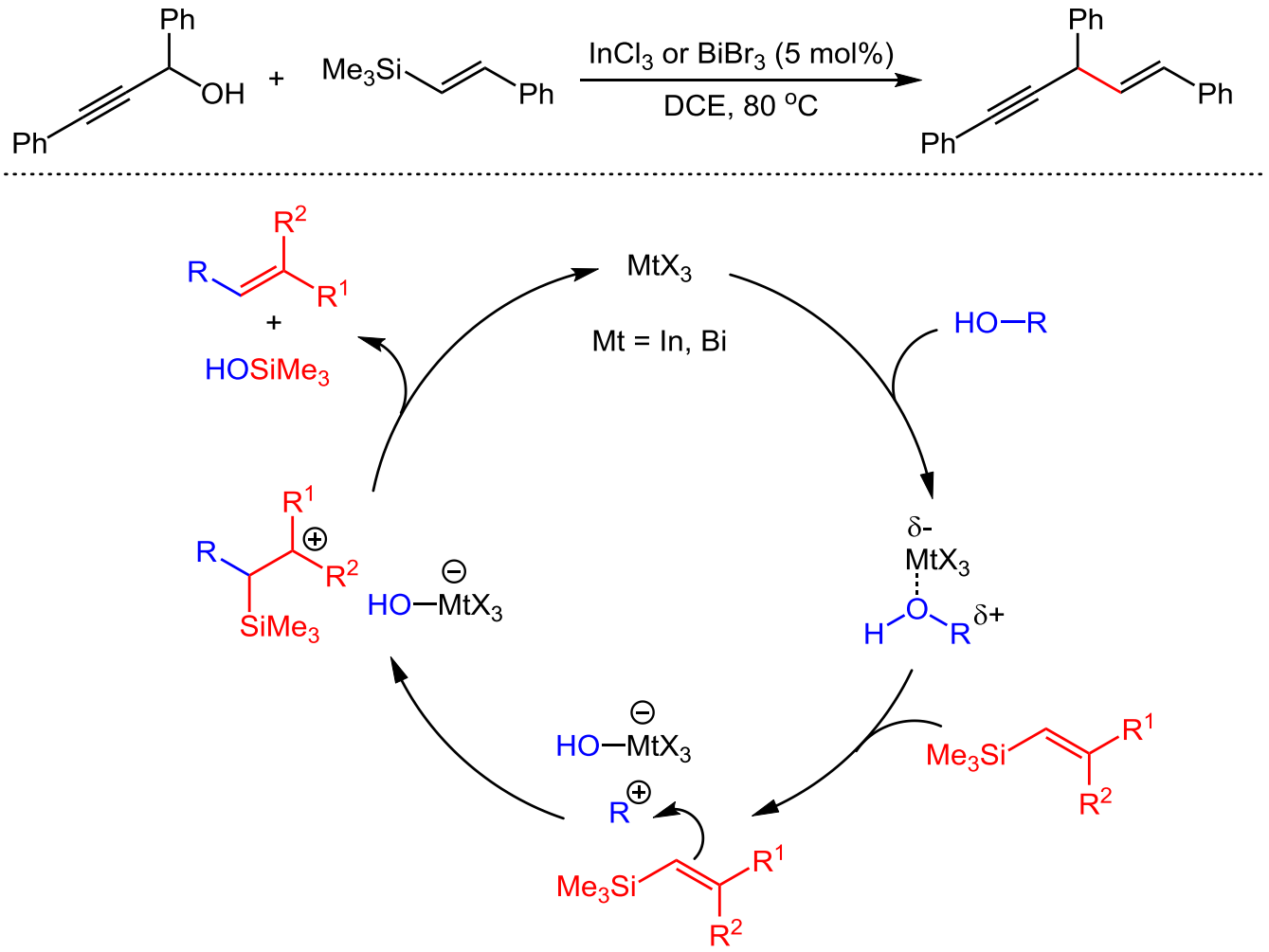
Sawamura, M. *et al. Angew. Chem. Int. Ed*. **2013**, *52*, 5350.

Asymmetric synthesis of 1,4-enynes



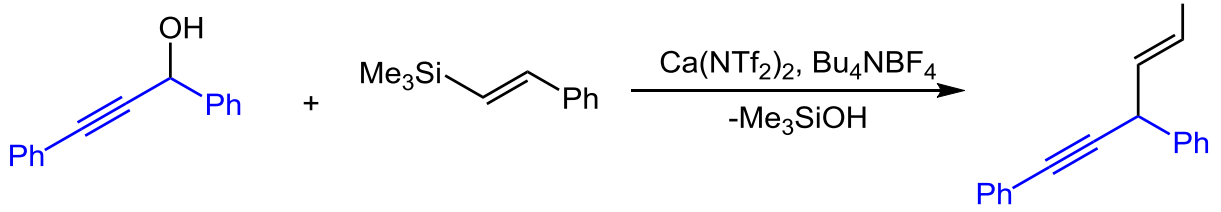
Breit, B. *et al. Org. Lett.* **2018**, *20*, 1066.

Synthesis of 1,4-enynes

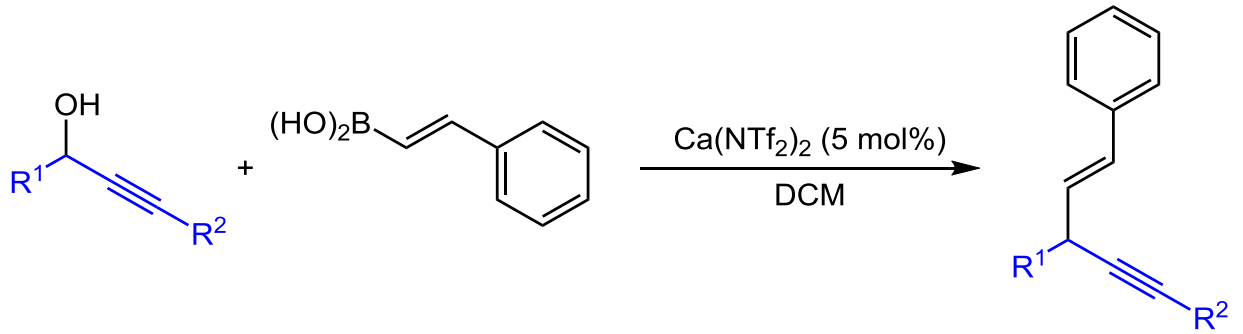


Baba, A. *et al. Chem. Commun.* **2008**, 6396.

Synthesis of 1,4-enynes

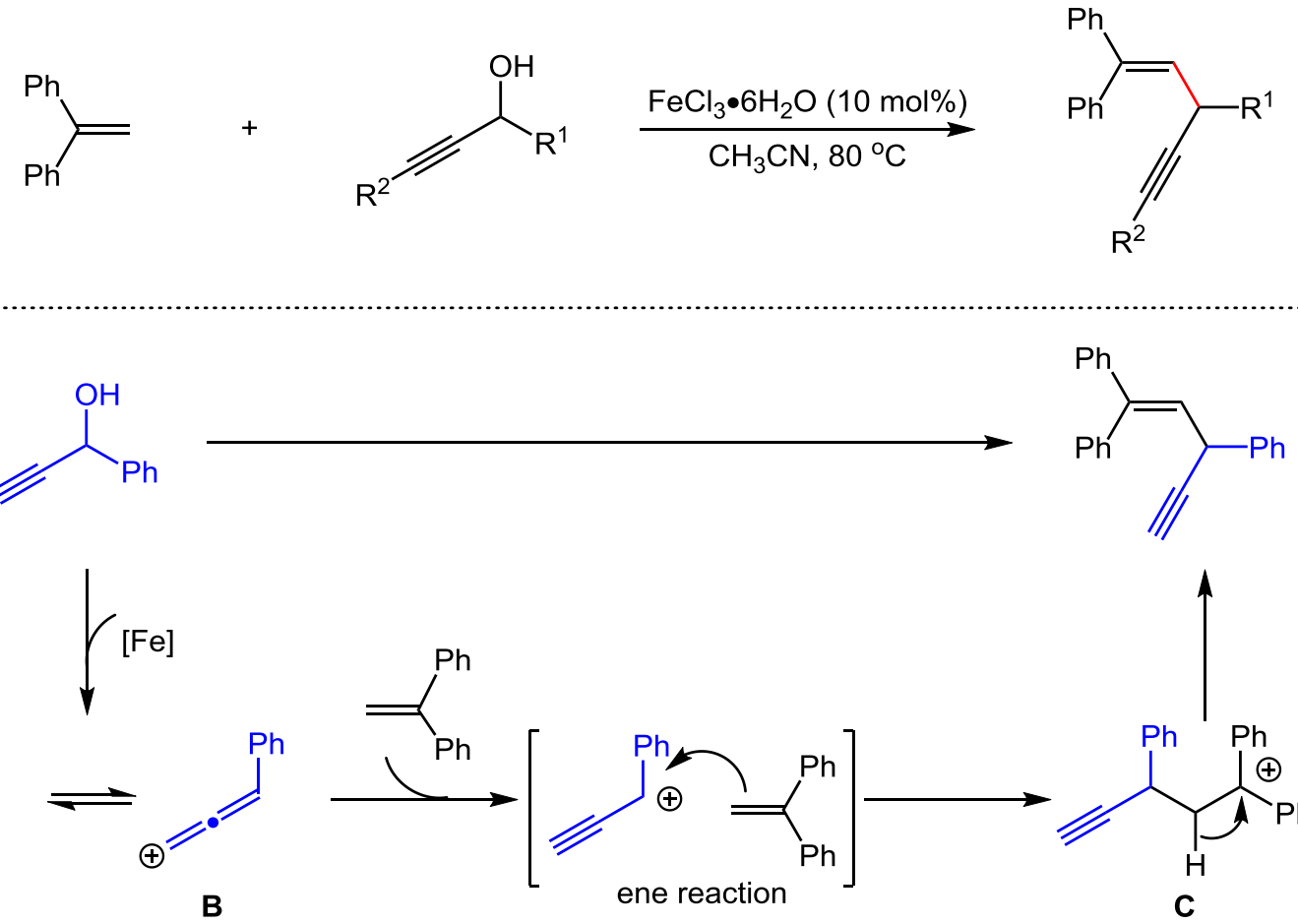


Niggemann, M. *et al. Eur. J. Org. Chem.* **2011**, 3671.



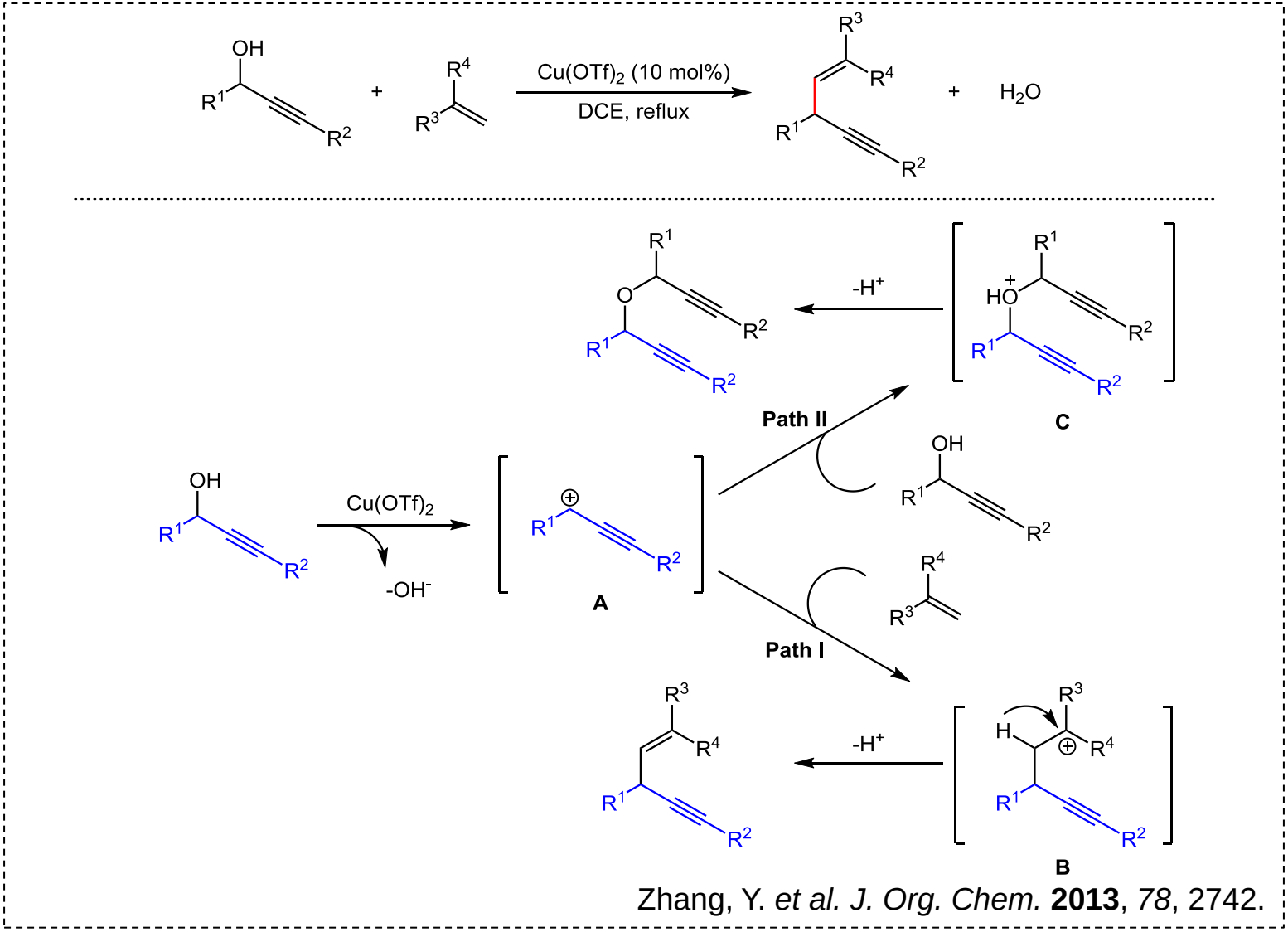
Gandon, V. *et al. Chem. Eur. J.* **2015**, *21*, 11001.

Synthesis of 1,4-enynes



Wang, J. *et al. Org. Biomol. Chem.* **2012**, *10*, 225.

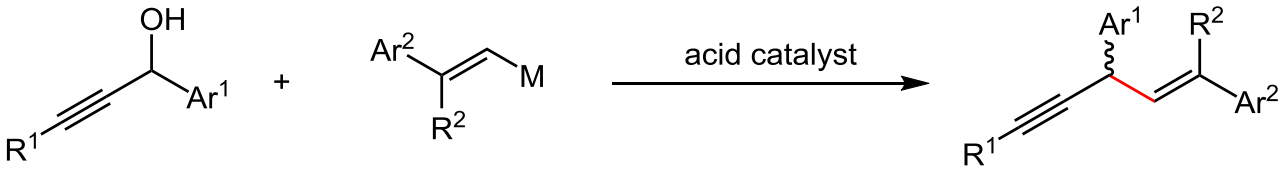
Synthesis of 1,4-enynes



Zhang, Y. *et al. J. Org. Chem.* **2013**, *78*, 2742.

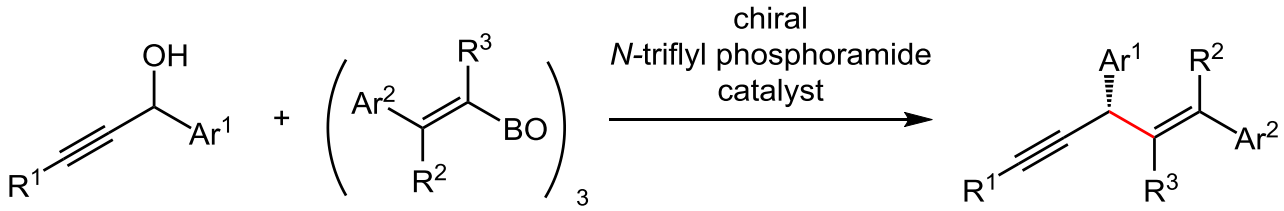
Asymmetric synthesis of 1,4-enynes

Previous work



M = $B(OH)_2$, $SiMe_3$, H

This work



Ar^1 = 4-AcNH-C_6H_4
4-HO-C_6H_4

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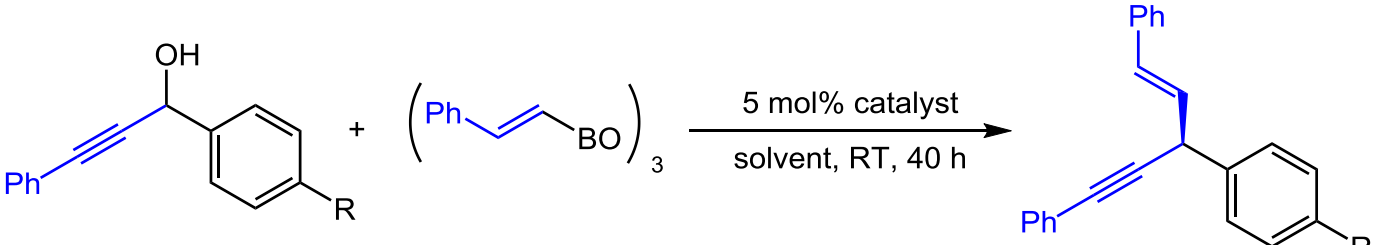
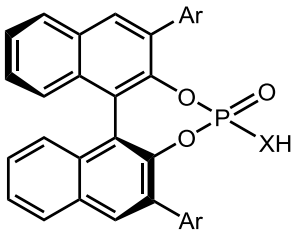
Optimization of the reaction conditions



1a (R = H)
1b (R = AcNH)

2a

3a (R = H)
3b (R = AcNH)



(*S*)-**4a** (Ar = 4-*t*Bu-2,6-(*i*Pr)$_2$-C$_6$H$_2$, X = NTf)
(*S*)-**4b** (Ar = 4-(1-Ad)-2,6-(*i*Pr)$_2$-C$_6$H$_2$, X = NTf)
(*S*)-**4c** (Ar = 2,4,6-(*c*Pent)$_3$-C$_6$H$_2$, X = NTf)
(*S*)-**4d** (Ar = 2,4,6-(*c*Hex)$_3$-C$_6$H$_2$, X = NTf)
(*S*)-**4e** (Ar = 2,4,6-(*i*Pr)$_3$-C$_6$H$_2$, X = NTf)
(*S*)-**5** (Ar = 2,4,6-(*i*Pr)$_3$-C$_6$H$_2$, X = O)

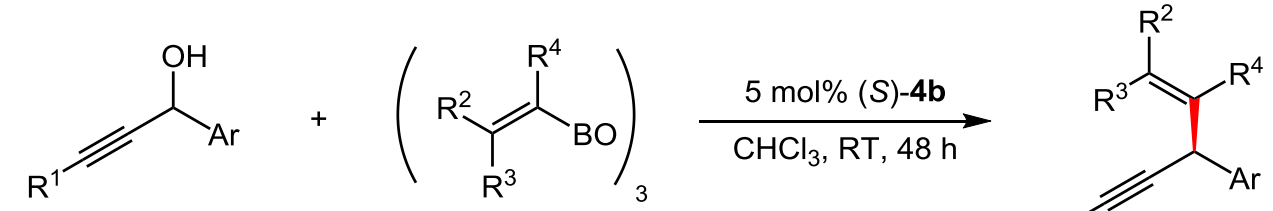
Entry[a]	**1**	Catalyst	Solvent	Yield [%][b]	Ee [%][c]
1[d]	**1a**	(*S*)-**4a**	CH_2Cl_2	76	28
2	**1b**	(*S*)-**4a**	CH_2Cl_2	76	85
3	**1b**	(*S*)-**4b**	CH_2Cl_2	80	88
4	**1b**	(*S*)-**4c**	CH_2Cl_2	64	85
5	**1b**	(*S*)-**4d**	CH_2Cl_2	70	87
6	**1b**	(*S*)-**4e**	CH_2Cl_2	77	81
7	**1b**	(*S*)-**5**	CH_2Cl_2	8	-24

Optimization of the reaction conditions

Entry[a]	**1**	Catalyst	Solvent	Yield [%][b]	Ee [%][c]
8[e]	**1b**	(*S*)-**4b**	CH_2Cl_2	92	87
9[e]	**1b**	(*S*)-**4b**	$CHCl_3$	88	89
10[e]	**1b**	(*S*)-**4b**	$ClCH_2CH_2Cl$	85	82
11[e]	**1b**	(*S*)-**4b**	THF	53	4
12[e]	**1b**	(*S*)-**4b**	1,4-dioxane	49	5
13[e,f]	**1b**	(*S*)-**4b**	$CHCl_3$	84	64
14[g,h]	**1b**	(*S*)-**4b**	$CHCl_3$	72	91
15[g,h,i]	**1b**	(*S*)-**4b**	$CHCl_3$	57	87
16[g,h,j]	**1b**	(*S*)-**4b**	$CHCl_3$	61	73
17[g,h,k]	**1b**	(*S*)-**4b**	$CHCl_3$	n.d.	-

[a] Use of **1** (0.06 mmol), **2a** (0.02 mmol), a catalyst (0.003 mmol) and a solvent (2 mL). [b] Determined by ^{1}H-NMR with 1,2-dichloroethane as internal standard. [c] Determined by chiral HPLC methods. [d] Performed for 24 h. [e] Use of **1b** (0.072 mmol). The yield is based on **2a**. [f] Use of $CHCl_3$ (0.6 mL). [g] Performed for 48 h. [h] Use of $CHCl_3$ (3 mL). [i] Use of molecular sieve 5Å (50 mg). [j] Use of (*E*)-styryl-B(O*i*Pr)$_2$ instead of **2a**. [k] Use of (*E*)-styryl-B(pin) instead of **2a**. pin = pinacolato. n.d.= not detected. Ad = adamantyl.

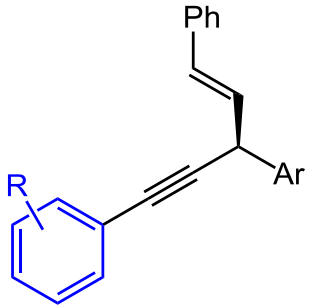
Substrate scope



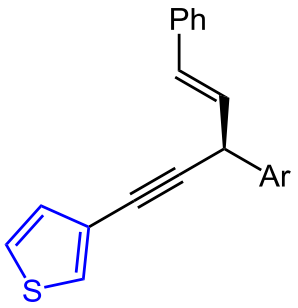
1
Ar = 4-AcNH-C_6H_4

2

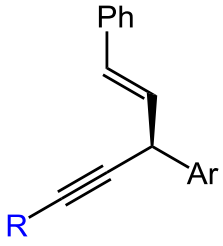
3



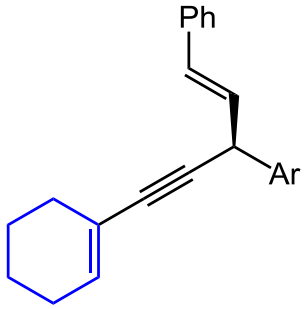
3b	R = H	70%, 91% ee
3c	R = 4-MeO	67%, 93% ee
3d	R = 4-Me	77%, 90% ee
3e	R = 4-Br	83%, 90% ee
3f	R = 3-MeO	77%, 91% ee
3g	R = 3-Cl	70%, 90% ee
3h	R = 2-MeO	60%, 92% ee
3i	R = 2-Cl	79%, 90% ee



3j 65%, 91% ee

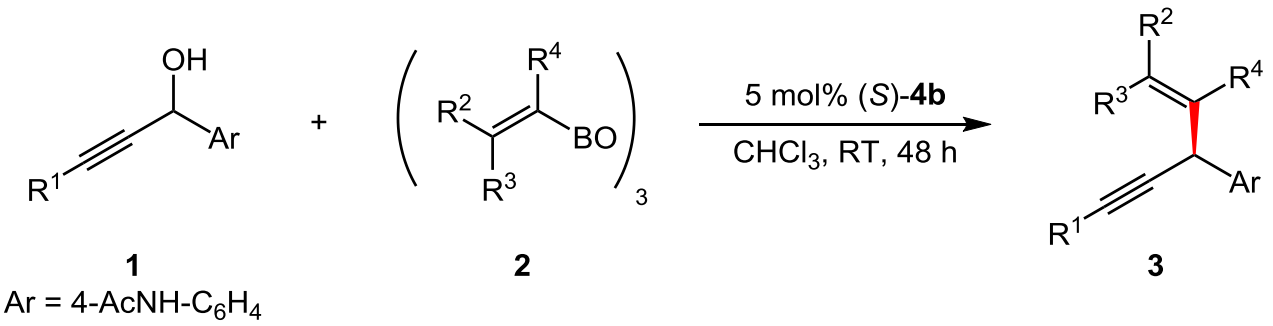


3l	R = Bn	68%, 90% ee
3m	R = Pr	74%, 92% ee
3n	R = *c*Pr	77%, 90% ee
3o	R = *t*Bu	66%, 92% ee
3p	R = Me_3Si	78%, 92% ee



3k 67%, 90% ee

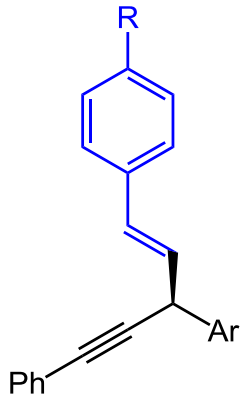
Substrate scope



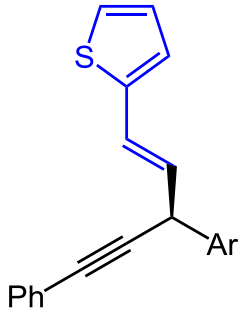
1
Ar = 4-AcNH-C_6H_4

2

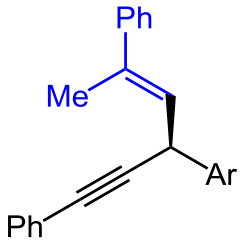
3



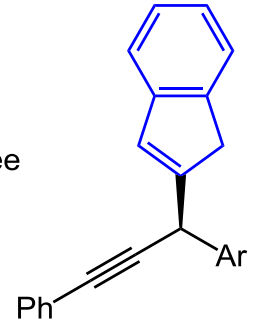
3q R = Me 83%, 91% ee
3r R = Br 63%, 90% ee



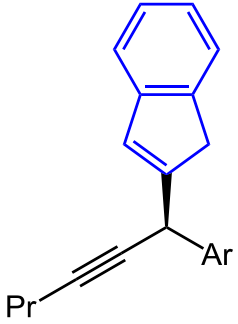
3s 85%, 89% ee



3t 86%, 84% ee



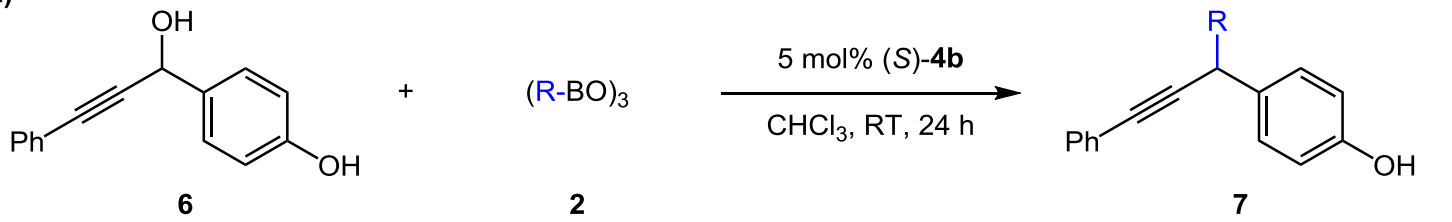
3u 86%, 96% ee



3v 89%, 98% ee

Alkenylation of propargyl alcohols

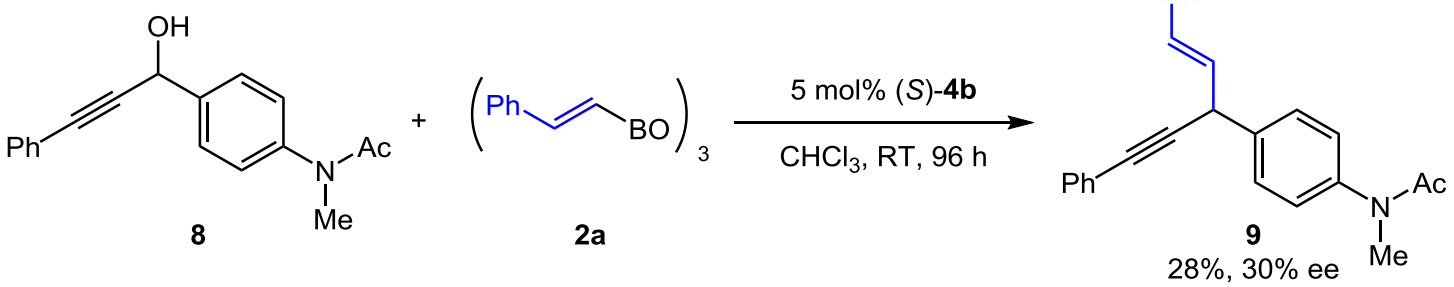
a)



6 + **2** → **7**

7a (R = (*E*)-styryl) 55%, 87% ee
7b (R = 2-indenyl) 80%, 94% ee

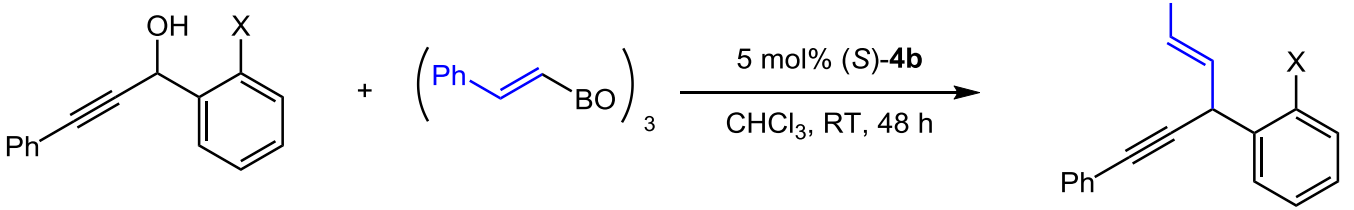
b)



8 + **2a** → **9**

28%, 30% ee

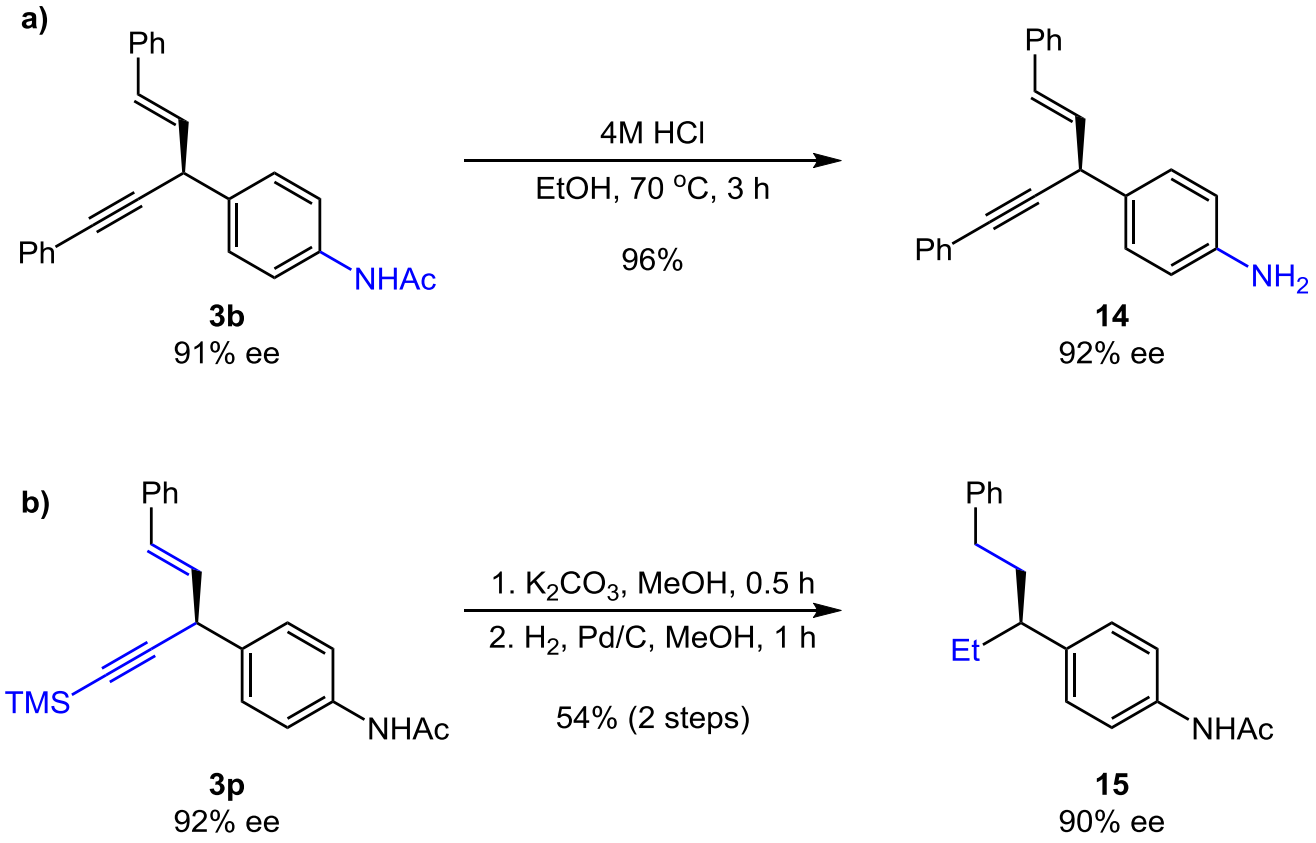
c)



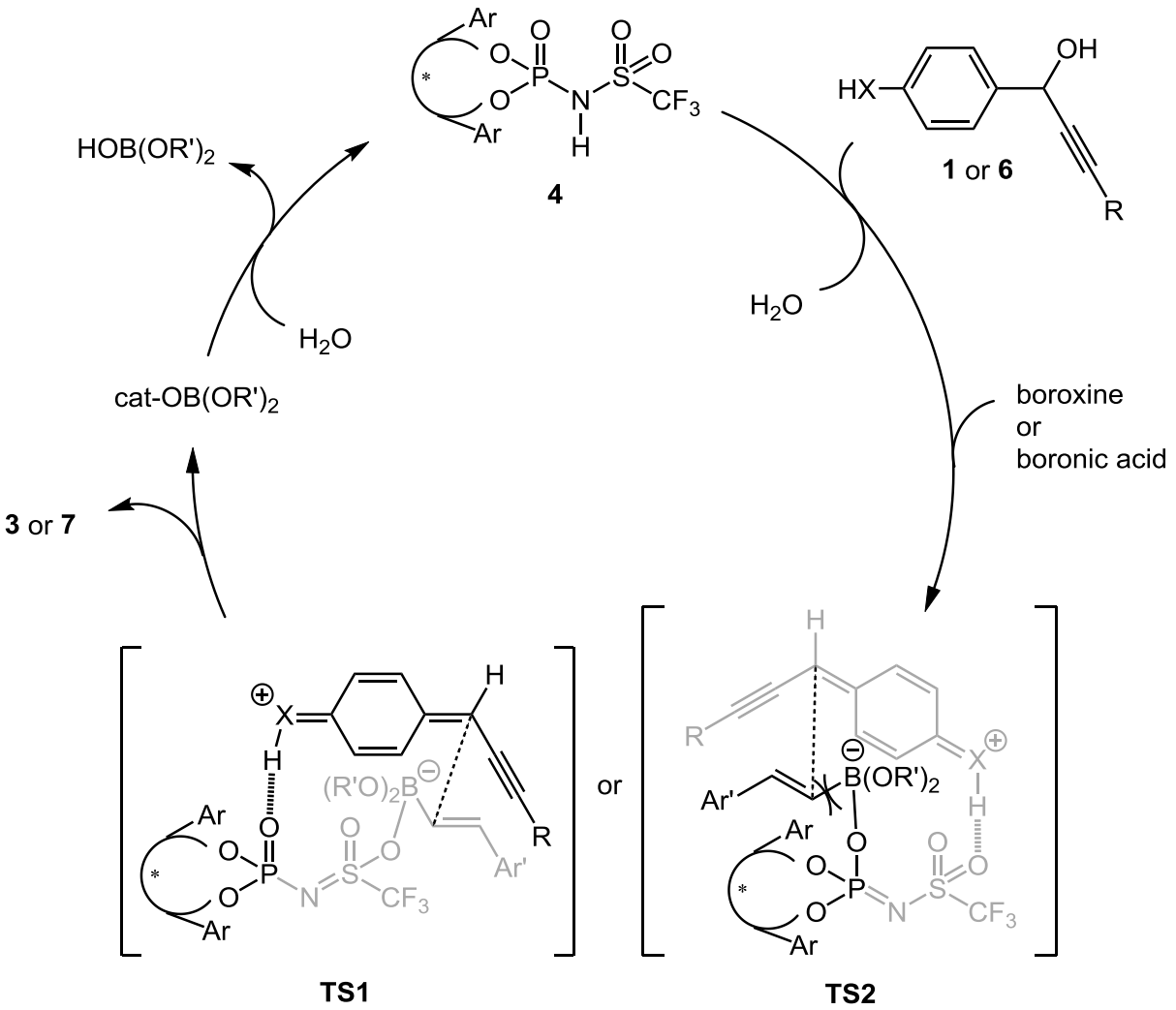
10 (X = NHAc)
12 (X = OH)

2a → **11** (X = NH_2) 48%, 2% ee
13 (X = OH) 52%, 1% ee

Transformation of alkenylation products

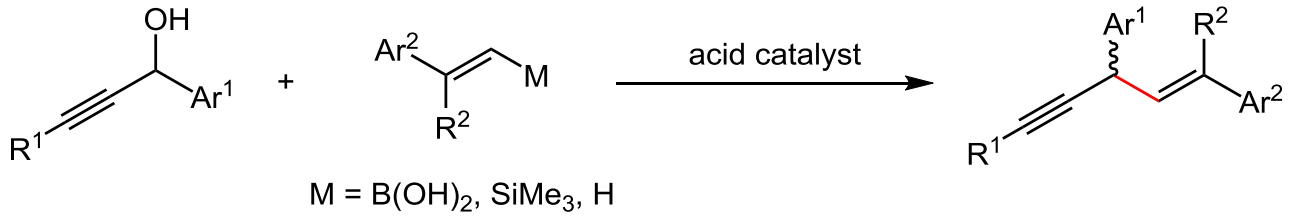


Proposed catalytic cycle

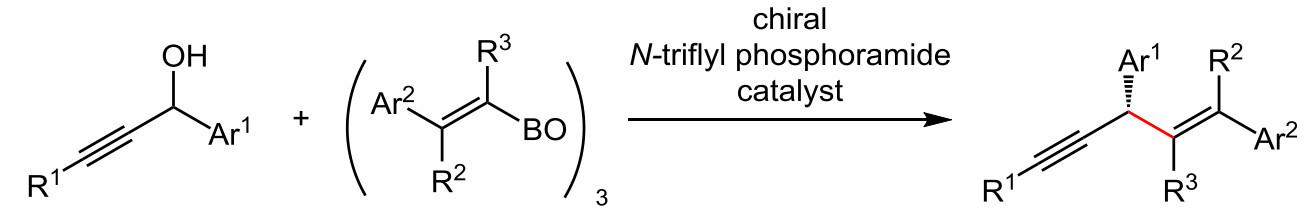


Summary

Synthesis of 1,4-enynes by alkenylation of propargyl alcohols



M = $B(OH)_2$, $SiMe_3$, H



Ar^1 = 4-AcNH-C_6H_4
4-HO-C_6H_4

The first paragraph

Chiral 1,4-enynes are important and versatile synthetic intermediates. Both alkenyl and alkynyl groups on the chiral center at the 3-position can serve as handles for further elaboration. Various synthetic approaches to 1,4-enynes have been developed thus far. Asymmetric synthesis of chiral 1,4-enynes has also been achieved through transition-metal-catalyzed enantioselective allylic substitution. In recent years, the development of effective and environmentally benign methods using non-metal catalysts has attracted much attention. In this context, alkenylation of propargyl alcohols is an alternative promising approach to 1,4-enynes, in which the carbocation intermediate is generated by acid-mediated elimination of the hydroxy group.

The first paragraph

To the best of our knowledge, however, the catalytic asymmetric variant has not been developed, probably due to the difficulty in enantioface selection of the carbocation intermediate by the chiral acid catalyst. Thus, we became interested in a chiral Brønsted acid catalyzed synthesis of chiral 1,4-enynes. Herein we report an organocatalytic enantioselective alkenylation of propargyl alcohols with trialkenylboroxines.

The last paragraph

In summary, an organocatalytic asymmetric synthesis of 1,4-enynes has been realized. In this process, readily available propargyl alcohols bearing a hydrogen bond donor and trialkenylboroxines can be employed and a highly acidic chiral N-triflyl phosphoramide was found to be the optimal Brønsted acid catalyst. This asymmetric alkenylation of propargyl alcohols with trialkenylboroxines offers an alternative approach to the asymmetric synthesis of 1,4-enynes, and will probably find application in the synthesis of a range of chiral compounds with alkynyl, alkenyl or alkyl carbon chains.

Thanks
for your attention