Literature Report III

Enantioselective Synthesis of Allylic Sulfones *via* Rhodium Catalyzed Direct Hydrosulfonylation of Allenes and Alkynes

Reporter: Yan-Xin Sun
Checker: Kai Xue
Date: 2024-07-15

Chang, C.-Y.; Aponick, A.* *J. Am. Chem. Soc.* **2024**, *146*, 16996

CV of Prof. Aaron Aponick

Background:

- **1998** B.S., Lebanon Valley College
- **1999-2003** Ph.D., University of Michigan
- **2003-2006** Postdoctoral Work, Stanford University
- **2006-2013** Assistant Professor, University of Florida
- **2013-2020** Associate Professor, University of Florida
- **2020-now** Full Professor, University of Florida

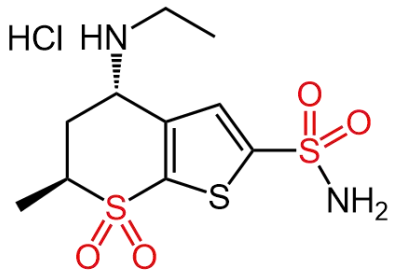
Research:

- **Ligand Development**
- **New Synthetic Methodologies**
- **Gold Catalysis**

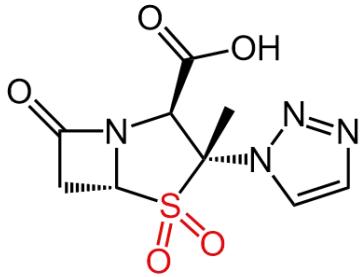
Contents

Introduction

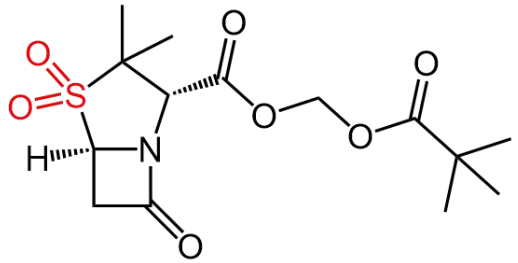
Sulfone Moiety and Bioactive Compounds with a Sulfone Chiral Center



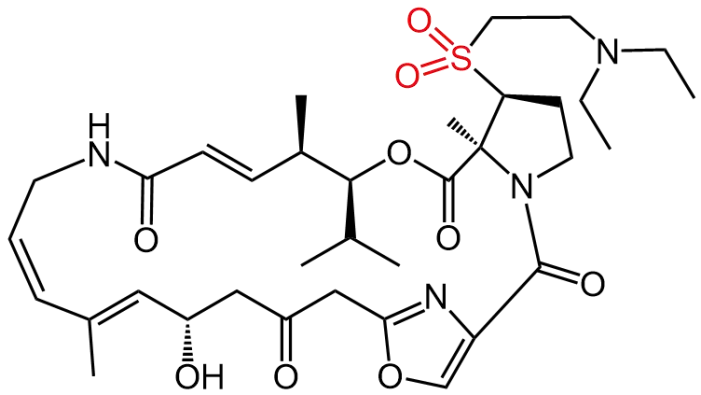
dorzolamide-HCl
treat glaucoma



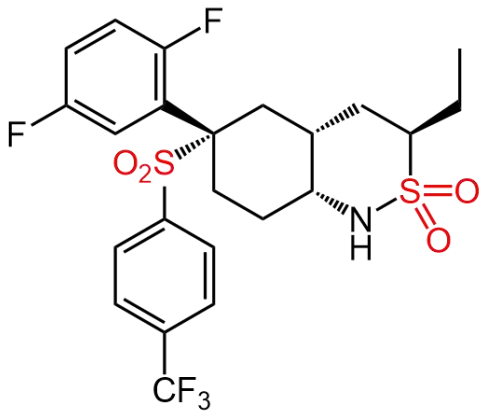
tazobactam
antibacterial activity



sulbactam
treat meningitis



dalfopristin
anti-infective

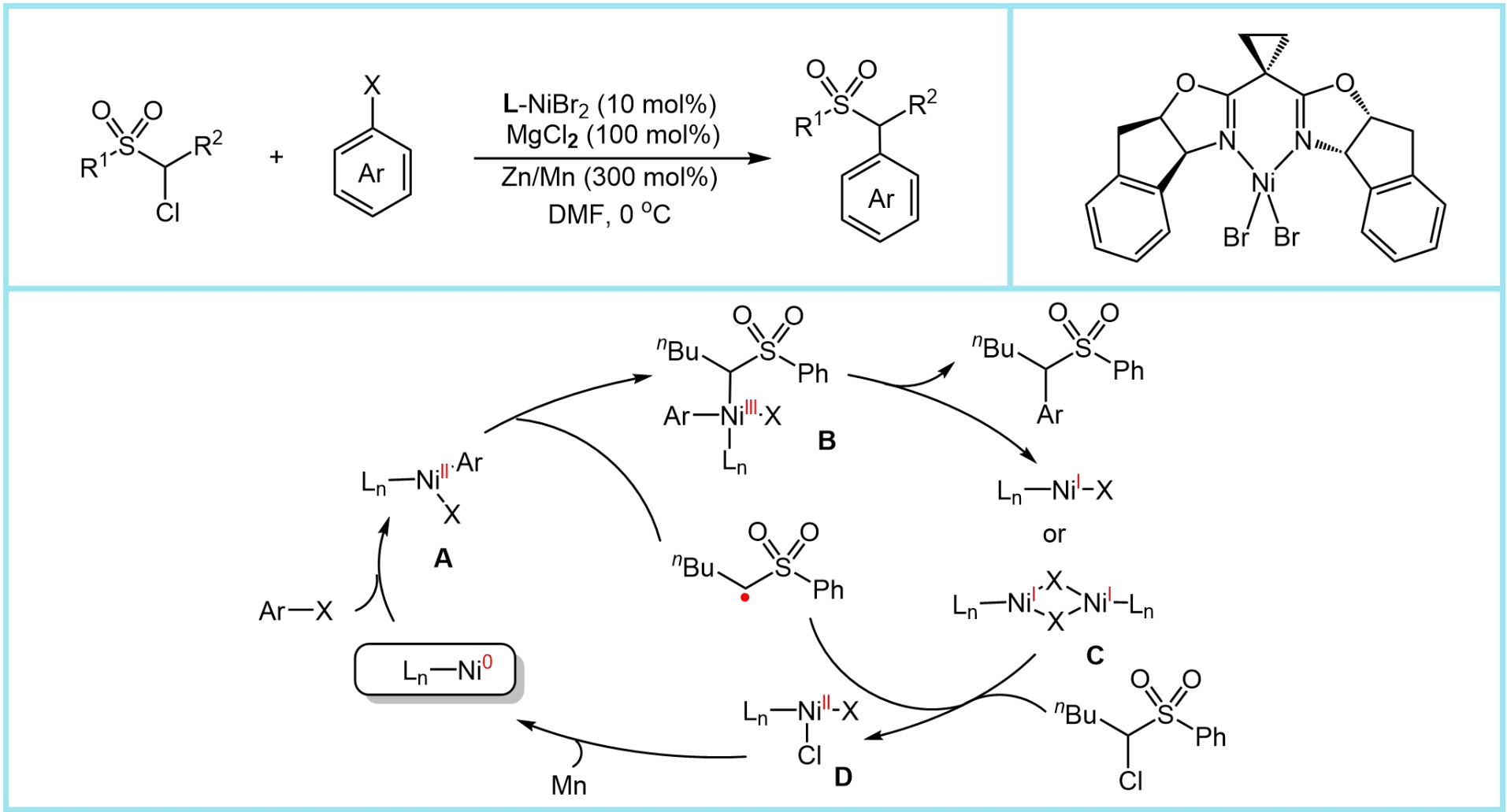


?-secretase inhibitor

Zhu, C.*; Cai, Y.; Jiang, H.* *Org. Chem. Front.* **2021**, *8*, 5574

Introduction

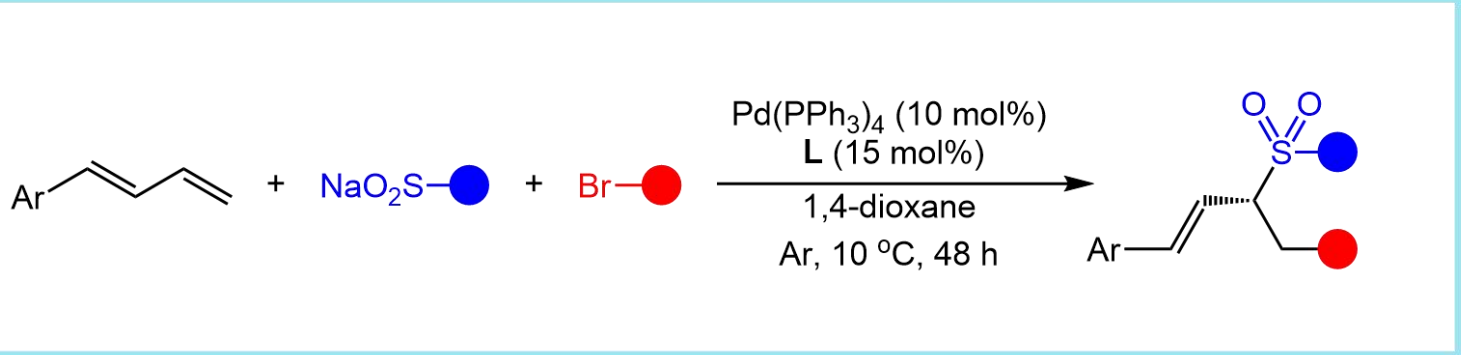
Asymmetric Reductive Arylation of α-Chlorosulfones with Aryl Halides

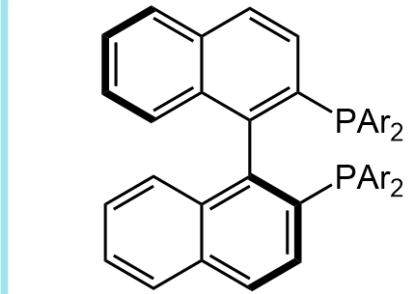


Sun, D.; Ma, G.; Zhao, X.; Lei, C.*; Gong, H.* *Chem. Sci.* **2021**, *12*, 5253

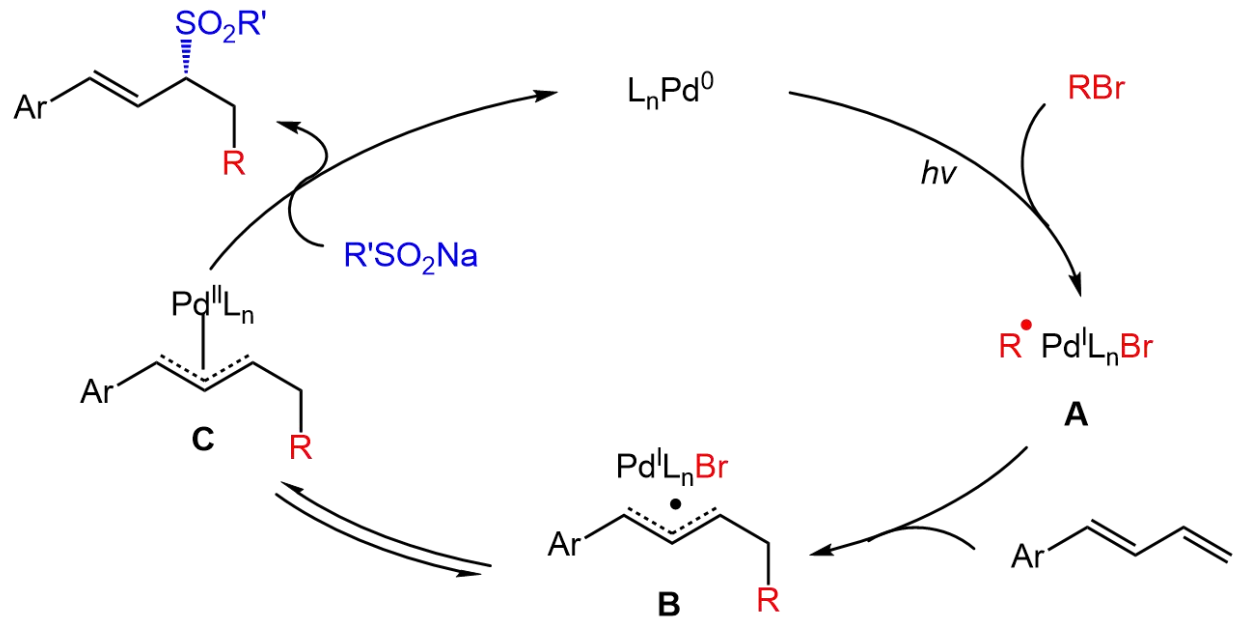
Introduction

Enantioselective 1,2-Alkylsulfonylation of 1,3-Dienes





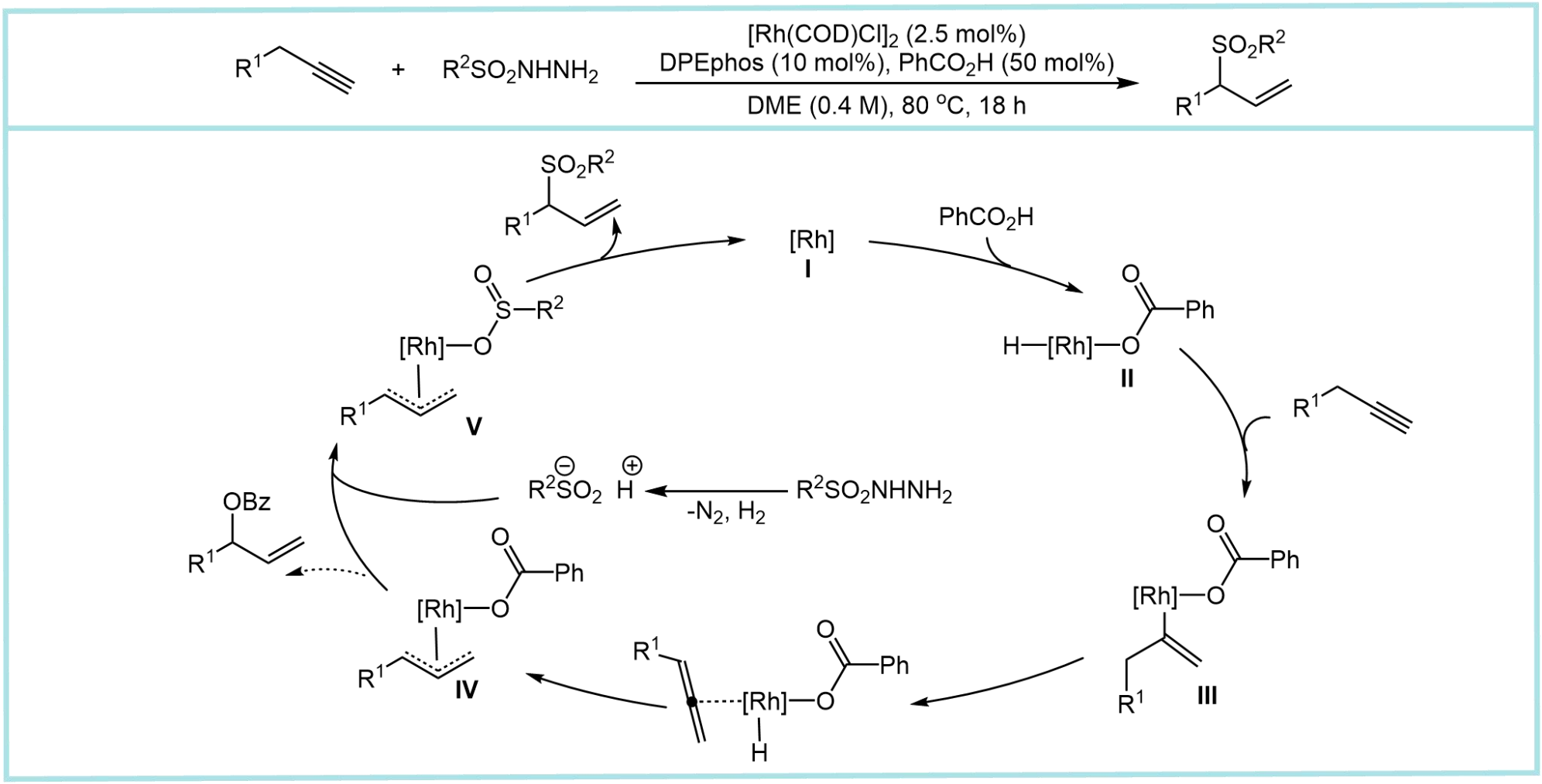
L: Ar = 4-*tol*



Liu, Z.-L.; Ye, Z.-P.; Liao, Z.-H.; Lu, Chen, K.; Chen, X.-Q.; Xiang, H.-Y.*; Yang, H.* *ACS Catal.* **2024**, *14*, 3725

Introduction

Direct Transformation of Terminal Alkynes to Allylic Sulfones

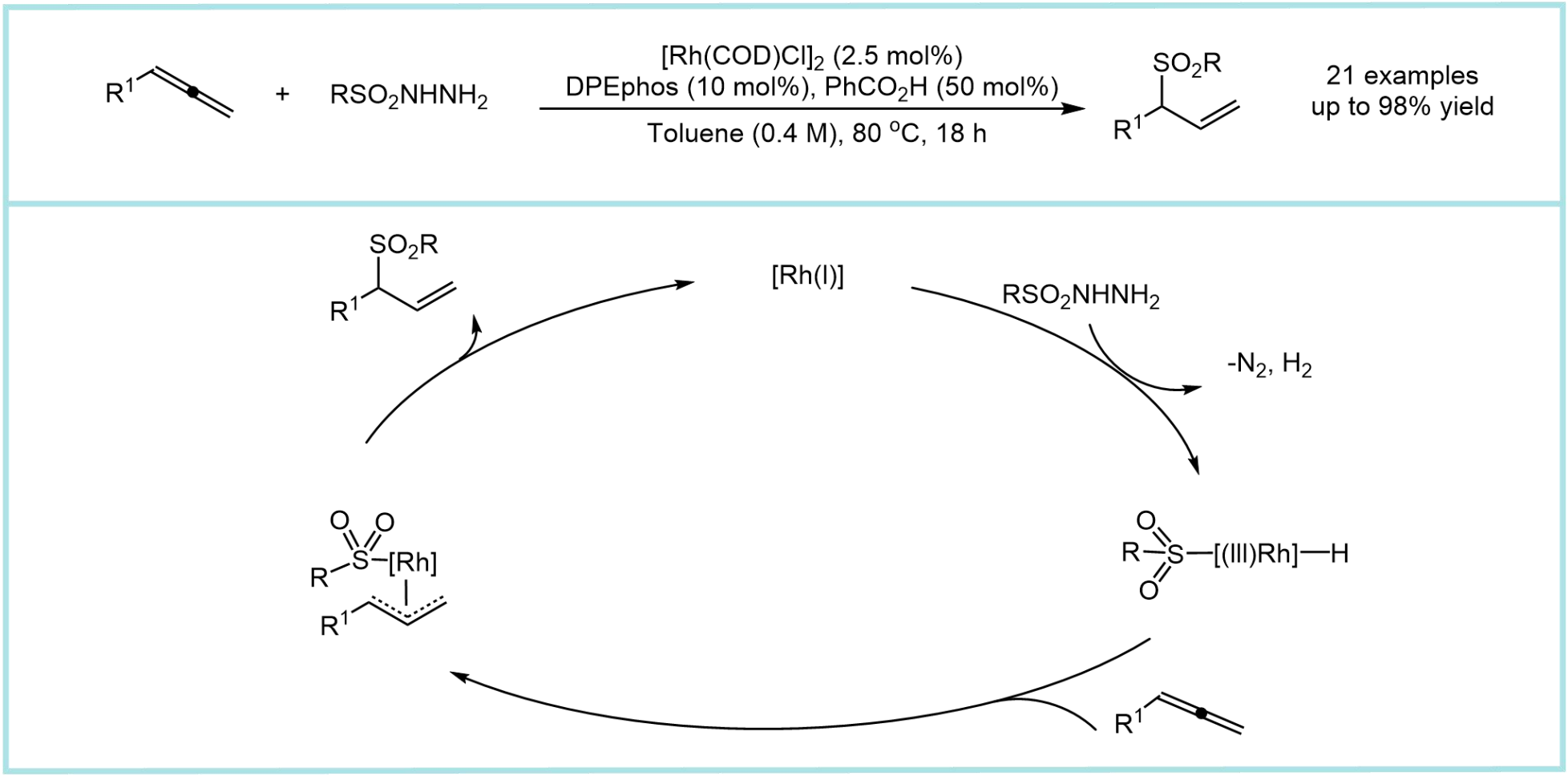


Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B.* *J. Am. Chem. Soc.* **2014**, *136*, 16124

Gellrich, U.; Meißner, A.; Steffani, A.; Kahny, M.; Plattner, D. A.; Breit, B.* *J. Am. Chem. Soc.* **2014**, *136*, 1097

Introduction

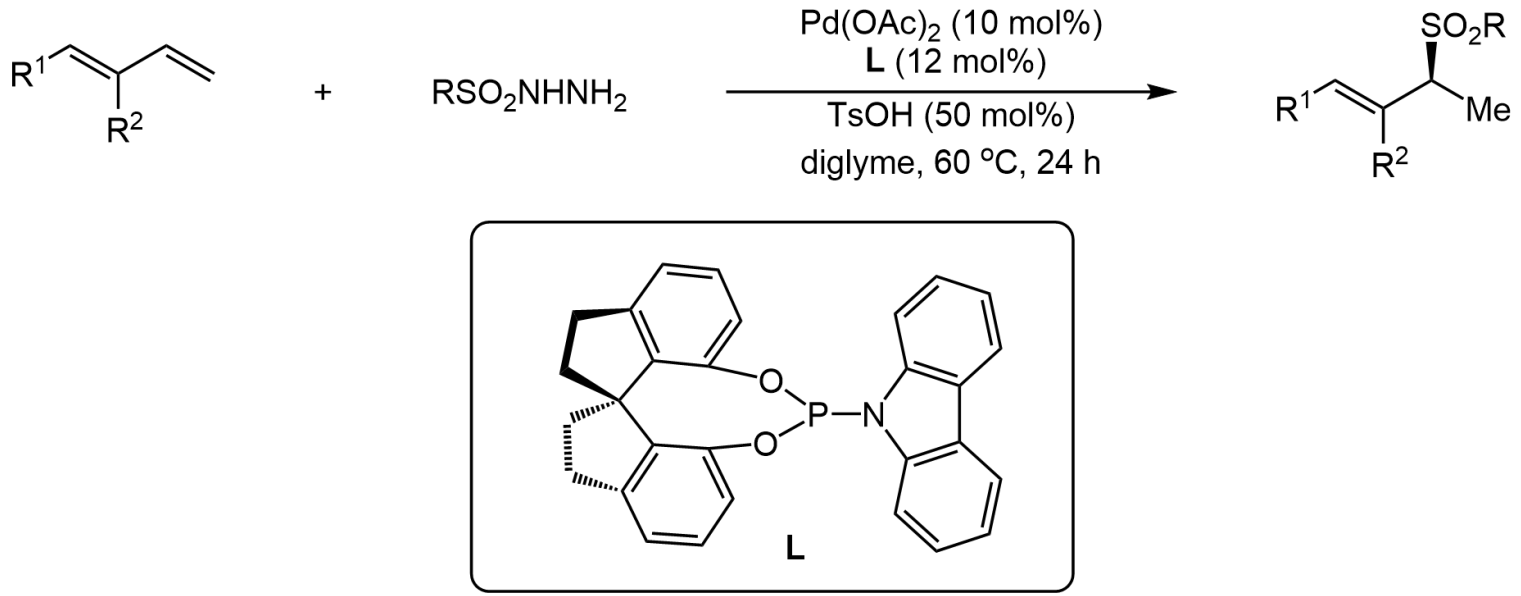
Addition of Sulfonyl Hydrazides to Allenes



Khakyzadeh, V.; Wang,Y.-H.; Breit, B.* *Chem. Commun.* **2017**, *53*, 4966

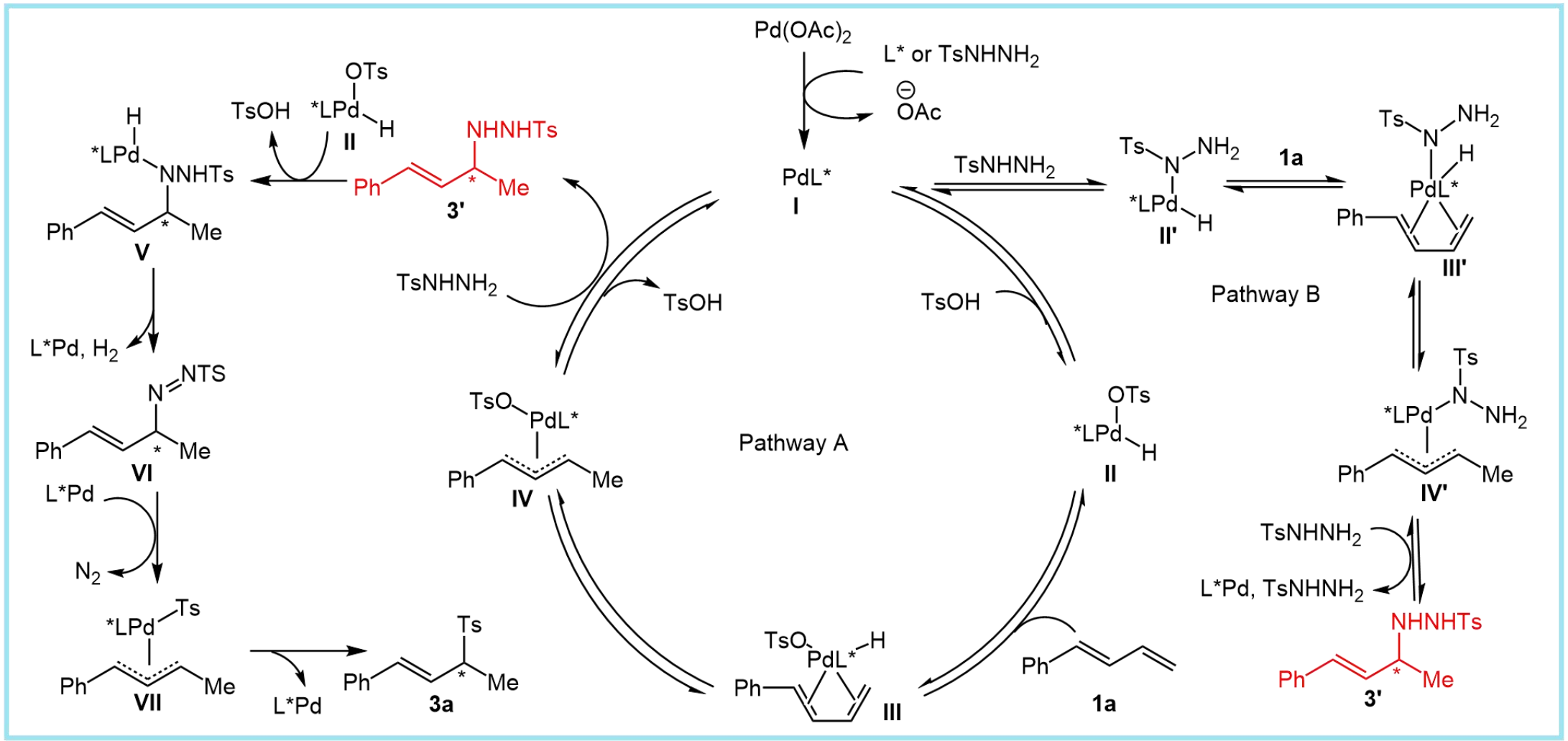
Introduction

Asymmetric Hydrosulfonylation of 1,3-Dienes with Sulfonyl Hydrazides



Li, M.-M.; Cheng, L.; Xiao, L.-J.; Xie, J.-H.; Zhou, Q.-L.* *Angew. Chem. Int. Ed.* **2021**, *60,* 2948

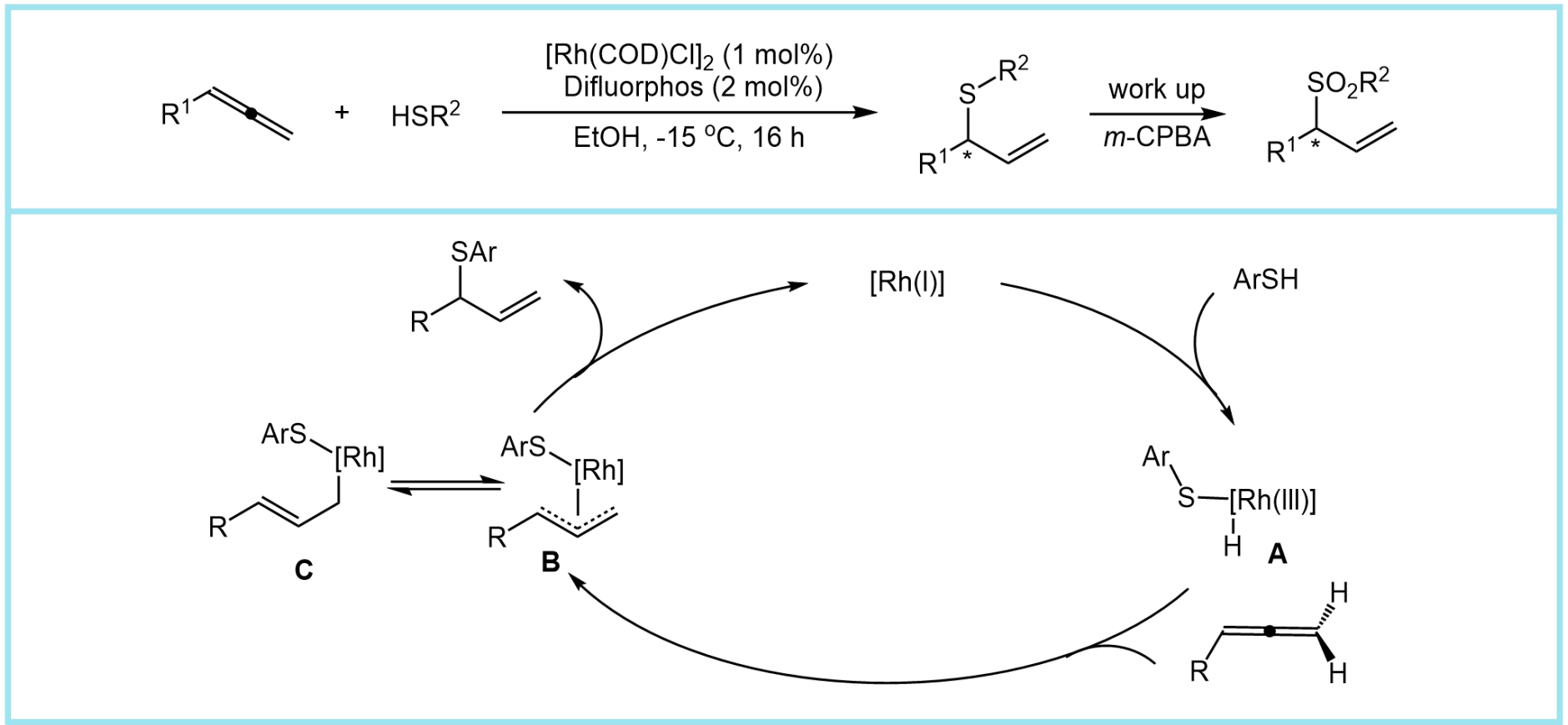
Introduction



Li, M.-M.; Cheng, L.; Xiao, L.-J.; Xie, J.-H.; Zhou, Q.-L.* *Angew. Chem. Int. Ed.* **2021**, *60,* 2948

Introduction

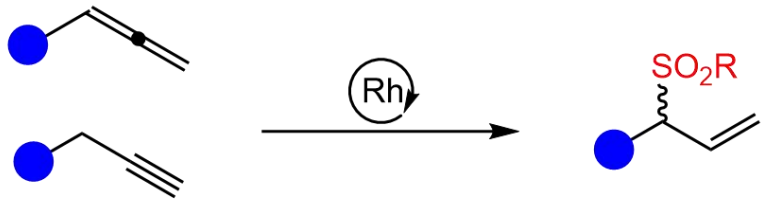
Indirect Enantioselective Hydrosulfonylation



Pritzius, A. B.; Breit, B.* *Angew. Chem. Int. Ed.* **2015**, *54,* 3121

Project Synopsis

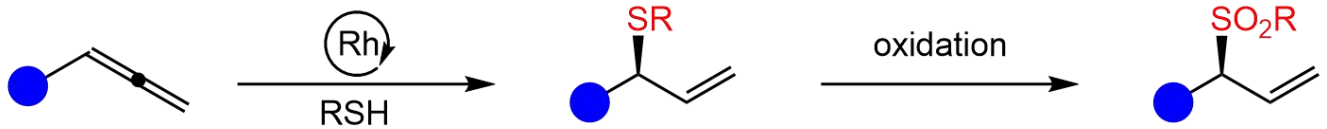
A: Direct Hydrosulfonylation, Racemic



Breit (2014, 2017): racemic

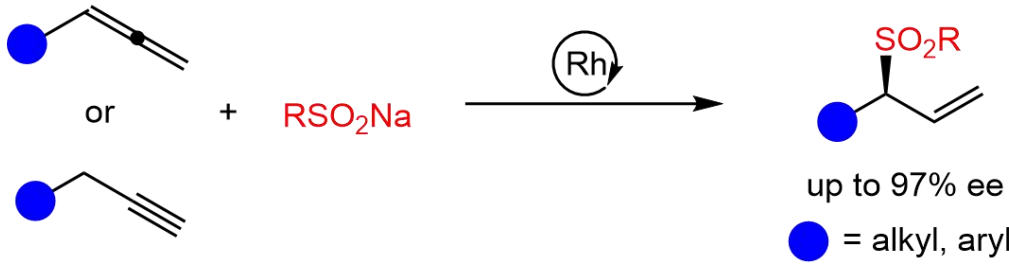
● = alkyl

B: Indirect Enantioselective Hydrosulfonylation



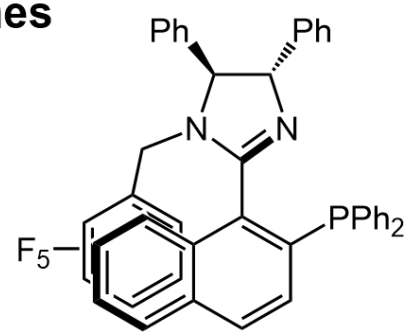
Breit (2015)
high yield, high ee

Direct Enantioselective Hydrosulfonylation of Allenes and Alkynes



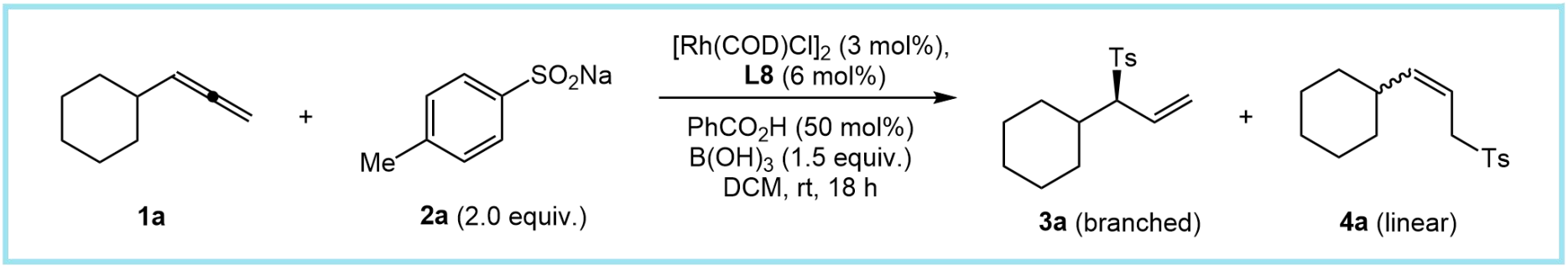
up to 97% ee

● = alkyl, aryl

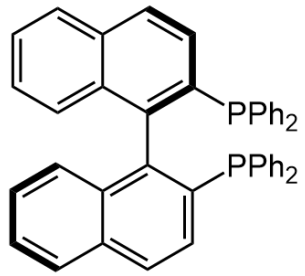


(*Rax,S,S*)-StackPhim

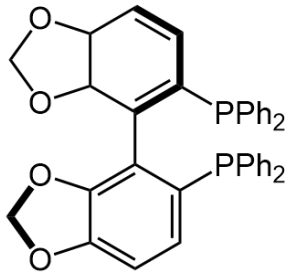
Optimization of the Reaction Conditions: Ligand



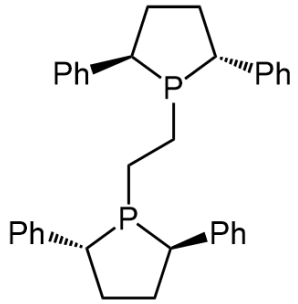
1a + **2a** (2.0 equiv.) → **3a** (branched) + **4a** (linear)



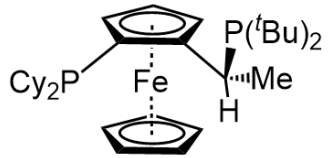
L1
79%, b/l = 1:1.7, 50% ee



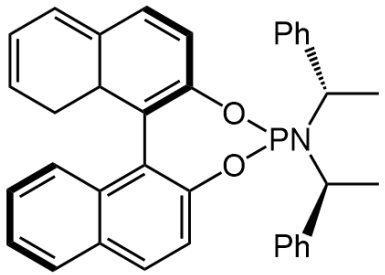
L2
75%, b/l = 1.4:1, 86% ee



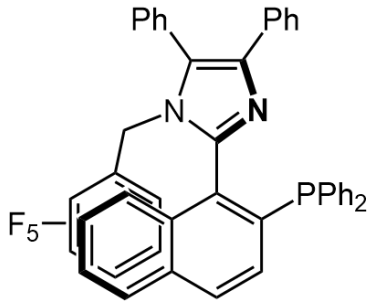
L3
61%, b/l > 20:1, 45% ee



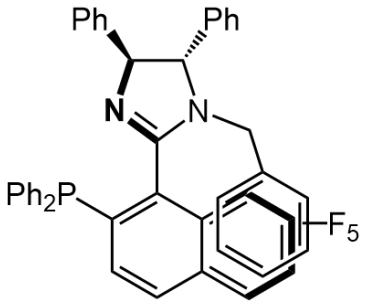
L4
32%, b/l > 20:1, -43% ee



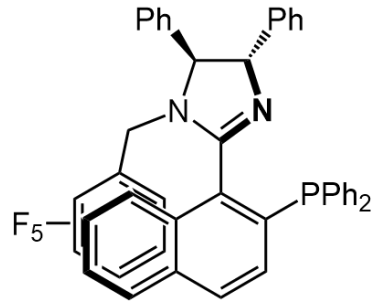
L5
trace



L6 (R_{ax})-StackPhos
6%, b/l > 20:1, 13% ee

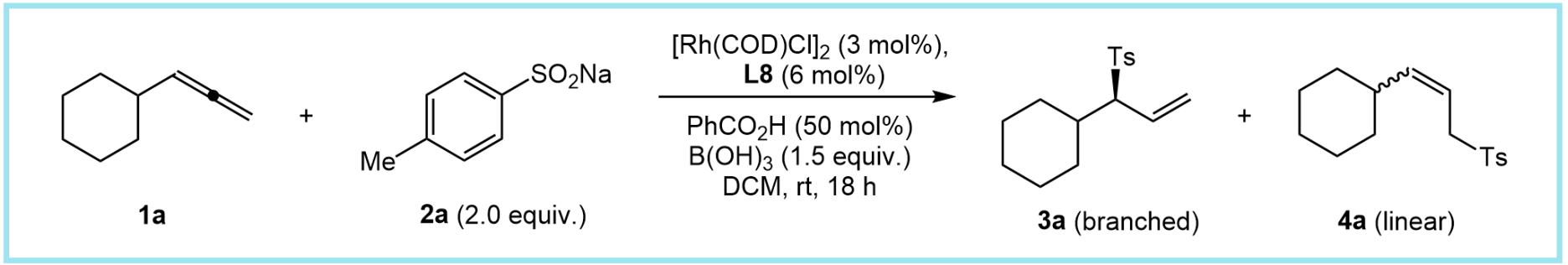


L7 (S_{ax},S,S)-StackPhim
trace



L8 (R_{ax},S,S)-StackPhim
75%, b/l > 20:1, 92% ee

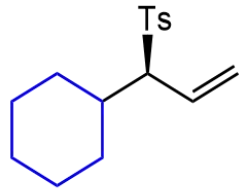
Optimization of the Reaction Conditions



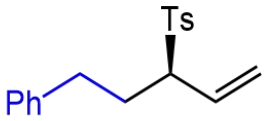
1a + **2a** (2.0 equiv.) → **3a** (branched) + **4a** (linear)

Entry	Variation from standard condition	Yield (%) of **3a+4a**	**3a:4a**	ee of **3a** (%)
1	no $B(OH)_3$	43	>20:1	91
2	no $PhCO_2H$	29	>20:1	95
3	$PhCO_2H$ (100 mol%)	40	>20:1	86
4	$B(OH)_3$ (2 equiv.)	64	>20:1	89
5	$PhCO_2H$ (100 mol%), no $B(OH)_3$	36	>20:1	91
6	$PhCO_2H$ (200 mol%), no $B(OH)_3$	68	>20:1	95
7	toluene as solvent	50	>20:1	97
8	DCM/EtOH (1:1) as solvent	47	>20:1	96
9	$TolSO_2NHNH_2$ instead of **2a**	7	1:1.2	86
10	no ligand	--	--	--

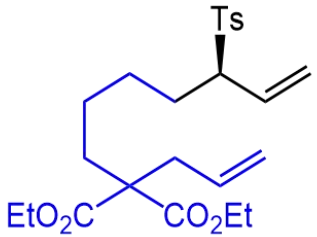
Substrate Scope: Allene



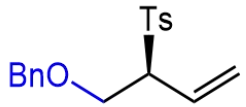
3a, 75%, 92% ee



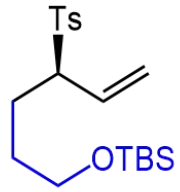
3b, 86%, 88% ee



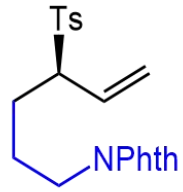
3c, 84%, 93% ee



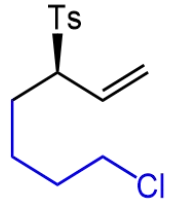
3d, 54%, 93% ee



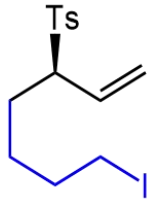
3e, 82%, 93% ee



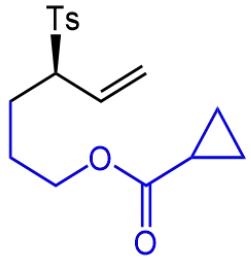
3f, 89%, 94% ee



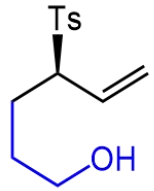
3g, 70%, 92% ee



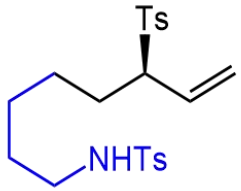
3h, 90%, 92% ee



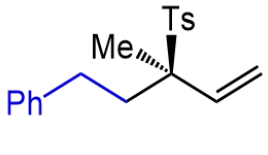
3i, 81%, 92% ee



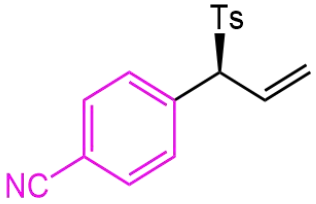
3j, 90%, 96% ee



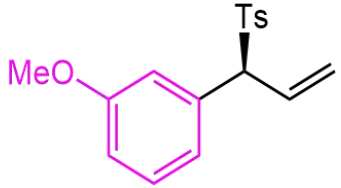
3k, 88%, 96% ee



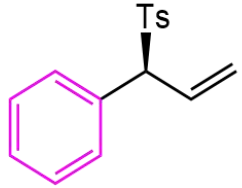
3l, 22%, 31% ee



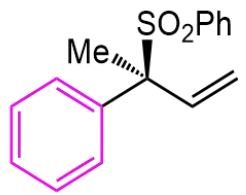
3m, 80%, 96% ee



3n, 83%, 87% ee

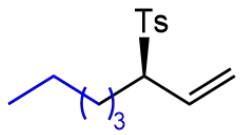


3o, 48%, 85% ee

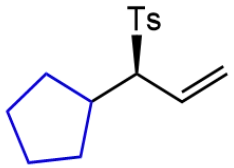


3p, 82%, 77% ee

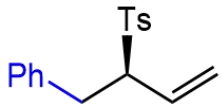
Substrate Scope: Alkyne



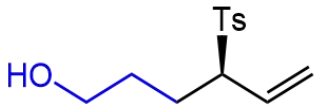
3q, 68%, 94% ee



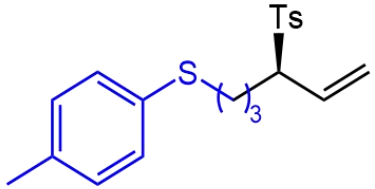
3r, 53%, 97% ee



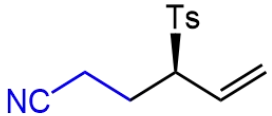
3s, 59%, 88% ee



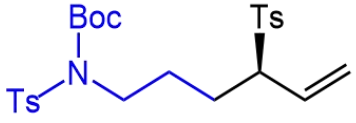
3j, 90%, 97% ee



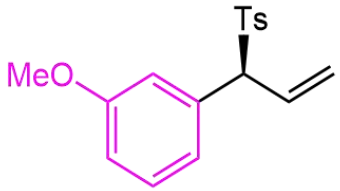
3t, 89%, 92% ee



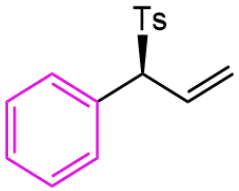
3u, 60%, 91% ee



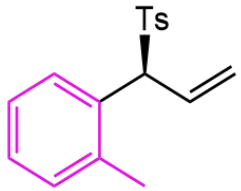
3v, 51%, 94% ee



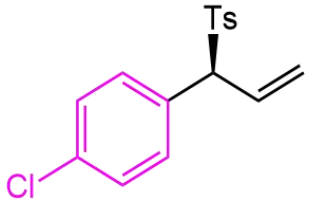
3n, 43%, 91% ee



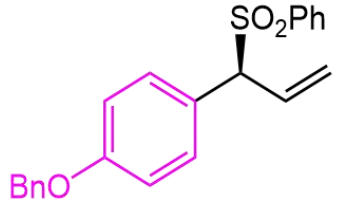
3o, 77%, 91% ee



3w, 60%, 92% ee

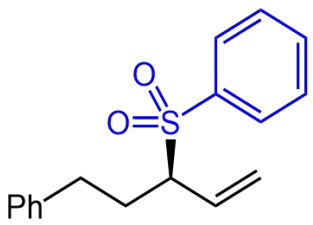


3x, 65%, 92% ee

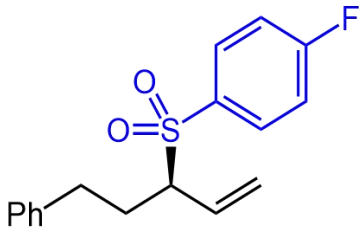


3y, 77%, 95% ee

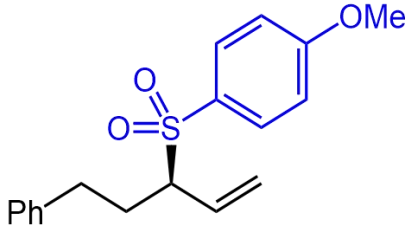
Substrate Scope: RSO_2Na



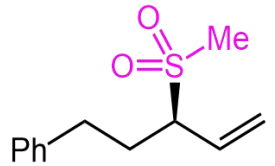
3z, 87%, 93% ee



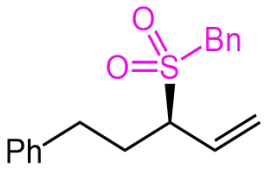
3aa, 79%, 91% ee



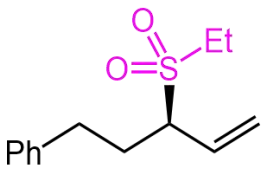
3ab, 79%, 91% ee



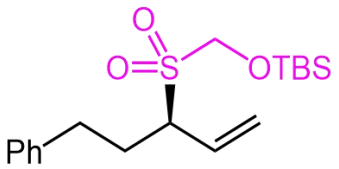
3ac, 85%, 81% ee



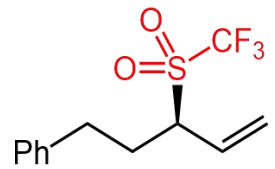
3ad, 73%, 82% ee



3ae, 76%, 84% ee



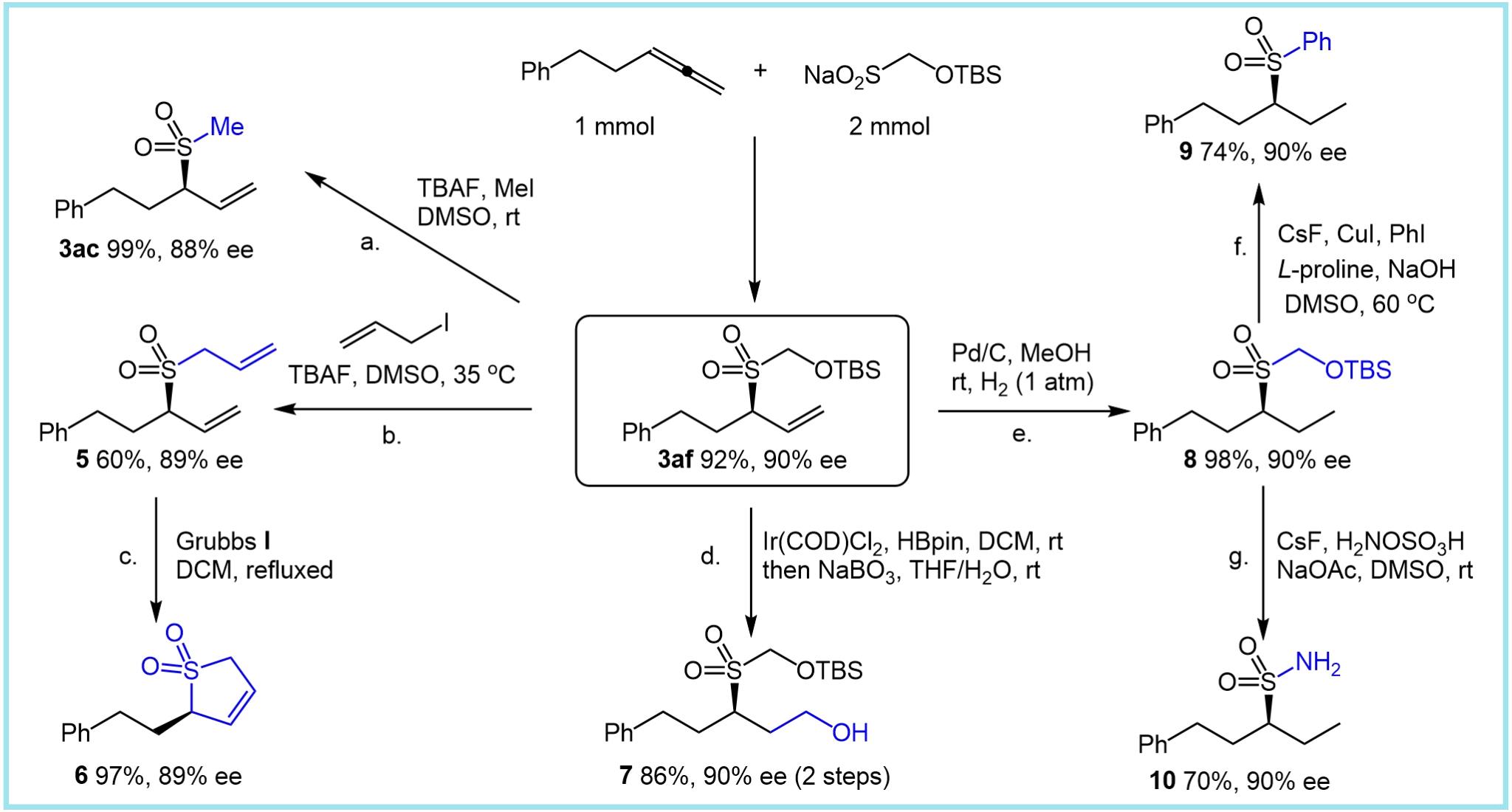
3af, 90%, 90% ee[a]



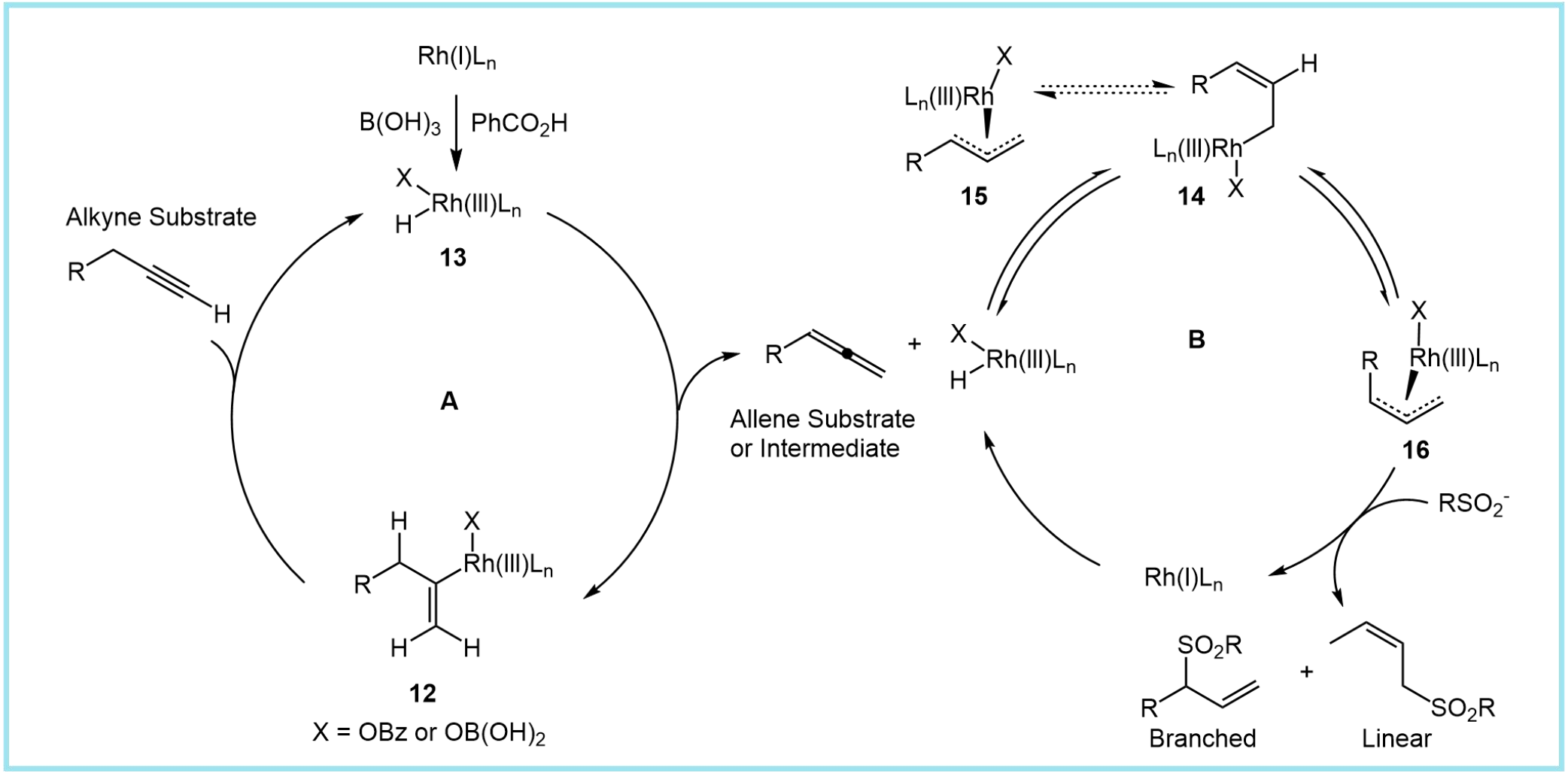
3ag, no observed

[a]The reaction was carried out at 0.2 mmol scale.

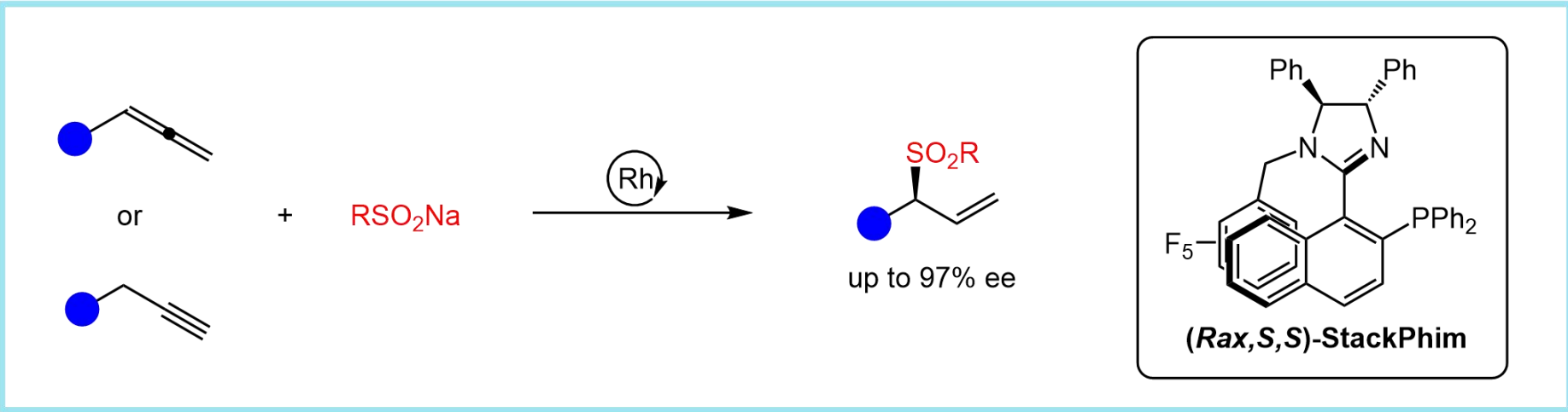
Synthetic Applications



Proposed Mechanism



Summary



- Direct C-S Bond Formation
- Commercially Available Sulfone Source
- High Regioselectivity & Enantioselectivity
- High Functional Group Tolerance

Strategy for Writing The First Paragraph

砜的应用前景广泛

引出本文工作

- ✓ Sulfones are privileged motifs in pharmaceuticals and bioactive molecules, versatile intermediates in organic synthesis, and also bioisosteres to carbonyl groups that often provide stronger hydrogen bonding between the bioactive compound and its molecular target. For these reasons, the development of the efficient methods for the preparation of sulfone-containing compounds continues to be an active research area of great interest, especially α-chiral sulfones.

- ✓ Although methods for the preparation of α-chiral sulfones have increasingly gained attention, methods to prepare these important moieties with high enantiocontrol remain a formidable challenge, and the current methodologies are not without their drawbacks.

Strategy for Writing The Last Paragraph

总结工作

强调亮点

✓ In conclusion, we have developed the first direct rhodium-catalyzed enantioselective hydrosulfonylation of allenes and alkynes.

✓ The current protocol is atom-economical and operationally simple, and the reaction is high-yielding and highly regio- and enantioselective over a broad scope of substrates to provide the products in a single step..... It is also noteworthy that the reaction is enabled by the C1-symmetric, axially chiral P,N-ligand (*Rax*,*S*,*S*)-StackPhim, when more common ligands failed to produce satisfactory results. This is the first application of a Stack ligand in an enantioselective Rh-catalyzed reaction, and further studies are underway in our laboratory to expand the use of this ligand to other Rh-catalyzed processes.

Representative Examples

- Ligand screening studies demonstrated the indispensable role of the (*Rax,S,S*)-StackPhim for achieving both high regioselecitivity and enantioselectivity.(indispensable, adj. 不可缺少的；绝对必要的；责无旁贷的；不可避开的)
- .....which could potentially change the intrinsic reactivity of the ligands, impacting the reaction profile. (intrinsic, adj. 内在的，固有的)
- And further studies are underway in our laboratory to expand the use of this ligand to other Rh-catalyzed processes..(underway, adj. 进行中的；起步的；航行中的)

Acknowledgement

Thanks for Your Attention!