Literature Report IV

Rhodium-Catalyzed Asymmetric Cyclopropanation of Indoles with *N*-Triftosylhydrazones

Reporter: Yan-Xin Sun
Checker: Sheng-Mei Lu
Date: 2024-11-04

He, C.; Song, W.; Wei, D.; Zhao, W.; Yu, Q.; Bi, X. *et al. Angew. Chem. Int. Ed.* **2024**, e202408220

CV of Prof. Xihe Bi

Background:

- **1996-2000** B.S., Northeast Normal University
- **2000-2006** Ph.D., Northeast Normal University
- **2006-2008** Postdoc., Universität Bonn
- **2005-2008** Assistant Professor, Northeast Normal University
- **2009-now** Associate Professor, Professor, Northeast Normal University

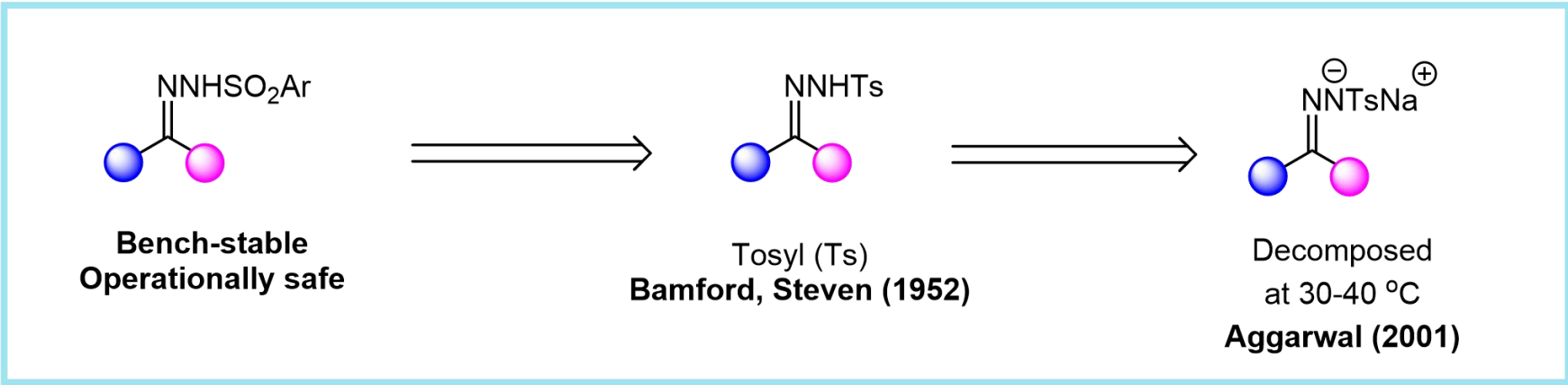
Research:

- **Carbene Chemistry**
- **Silver Catalyzed Organic Synthesis and Theoretical Research**

Contents

Introduction

Widely Utilized *N*-Sulfonylhydrazones as Diazo Precursors



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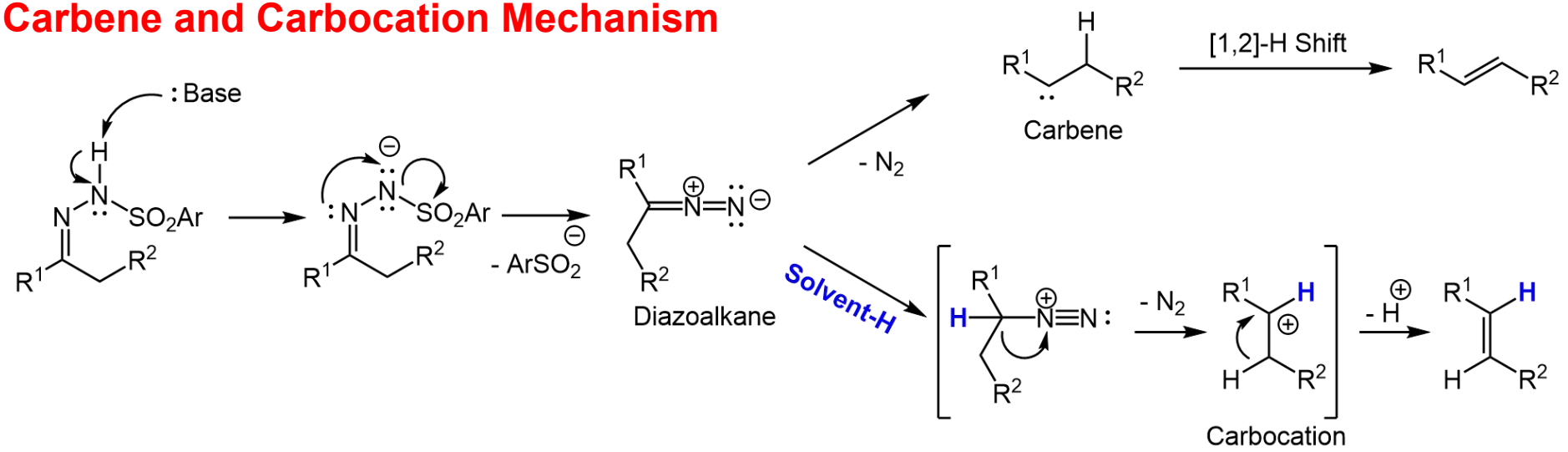
Introduction - Bamford-Stevens Reaction

Bamford-Stevens Reaction

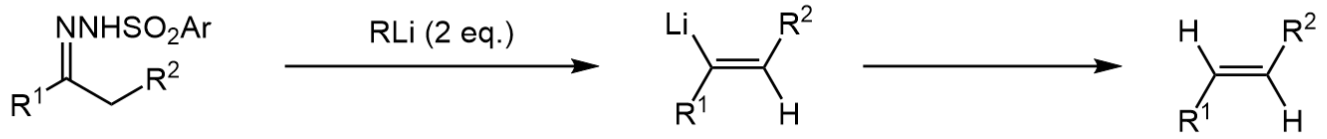
Carbene and Carbocation Mechanism



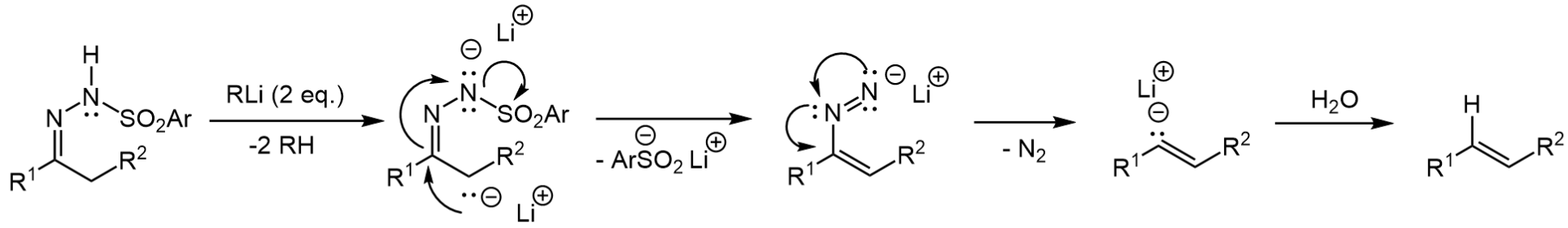
Bamford, W. R.; Stevens, T. S. M. *J. Chem. Soc.* **1952**, 4735

Introduction - Shapiro Reaction

Shapiro Reaction



Carbanion Mechanism



Shapiro, R. H. *Org. React*. **1976**, *23*, 405

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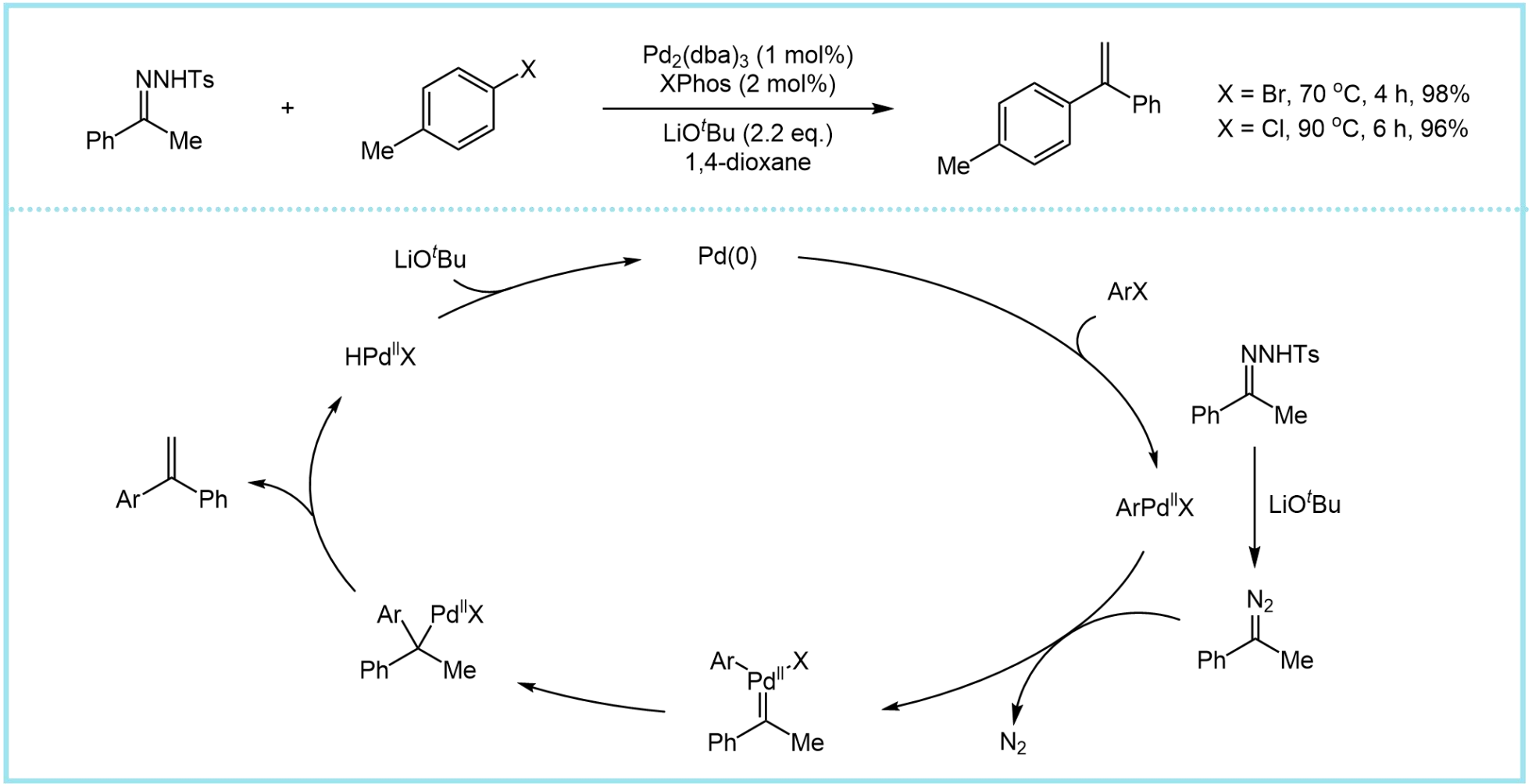

Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed*. **2007**, *46*, 5587

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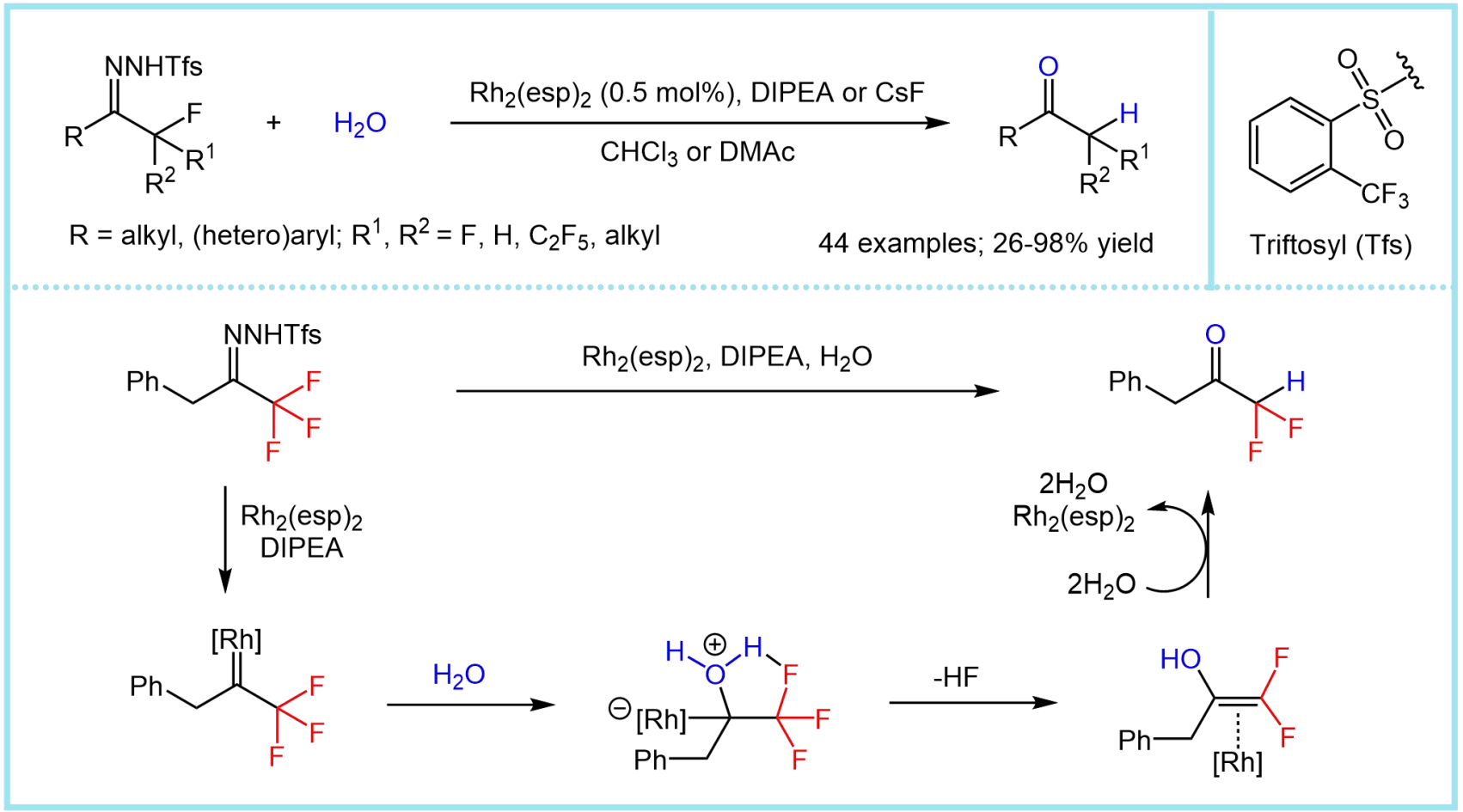

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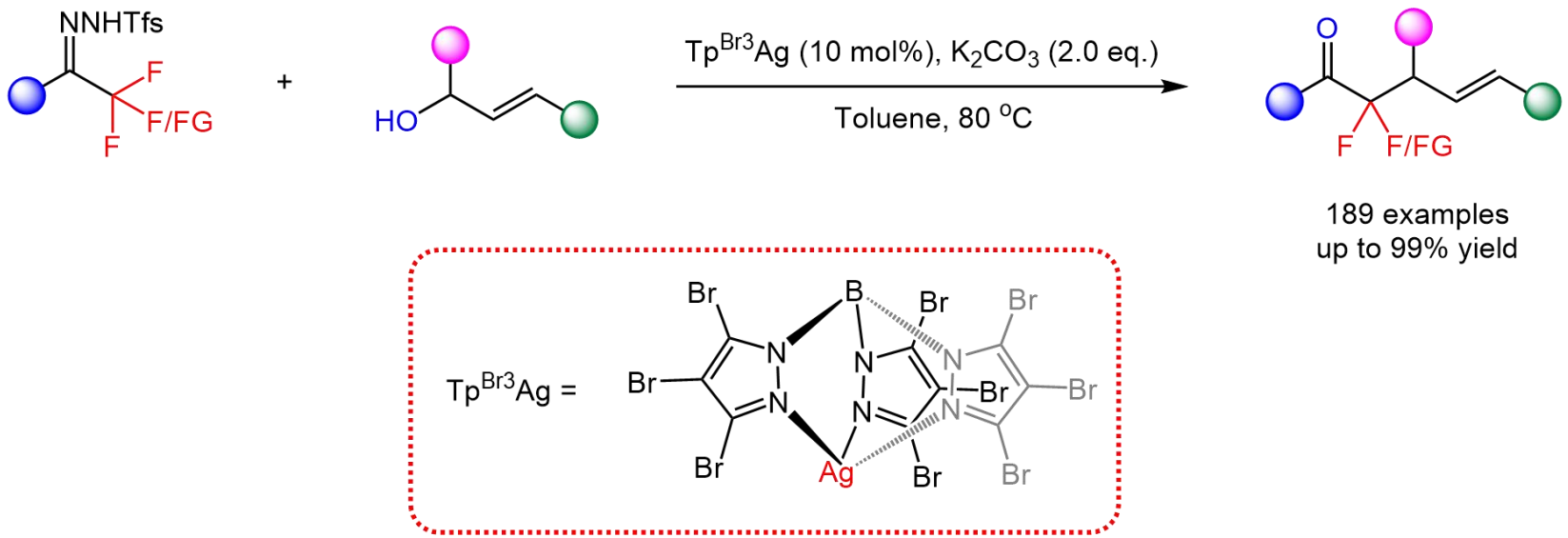
Introduction



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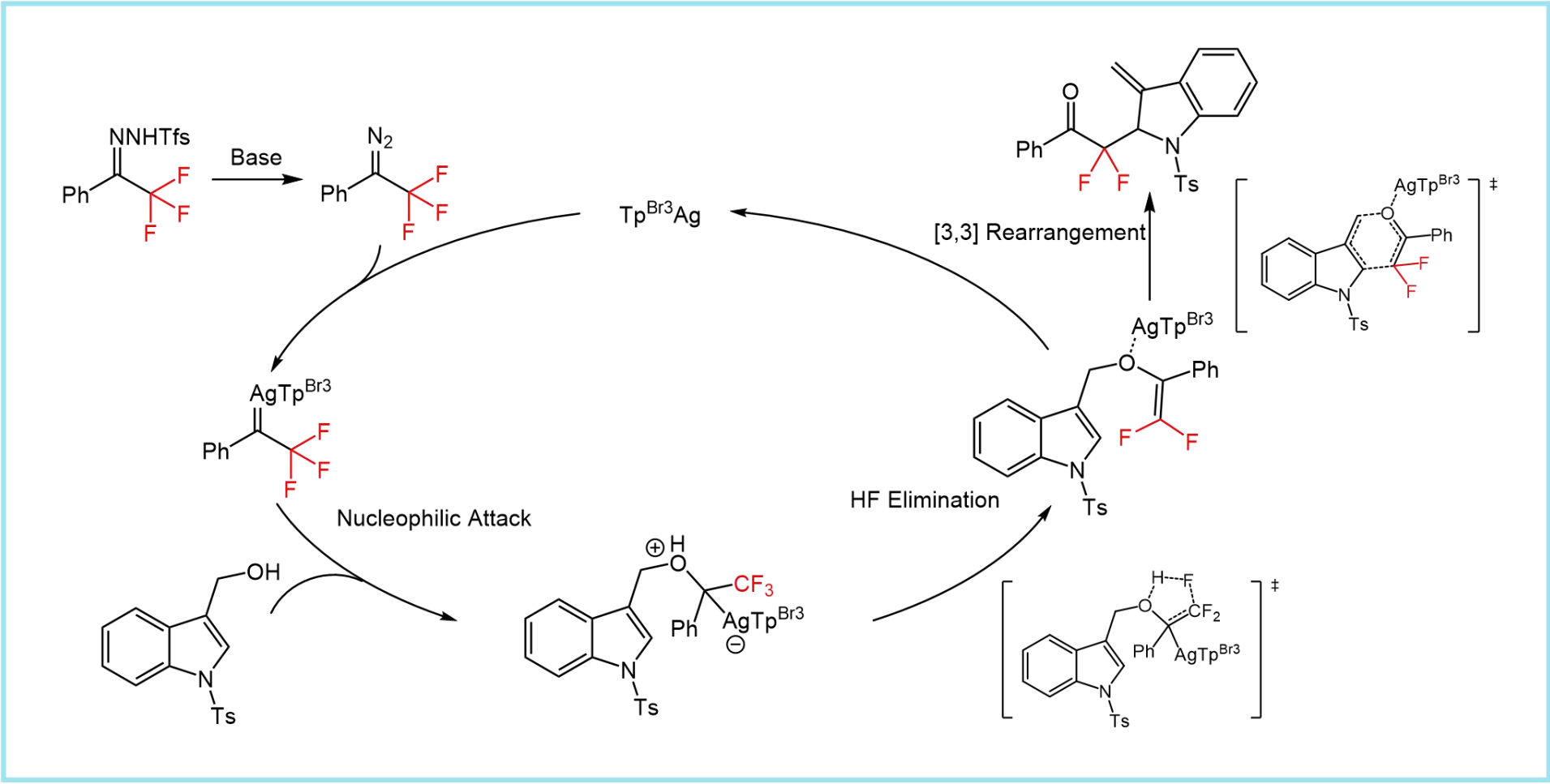
Introduction



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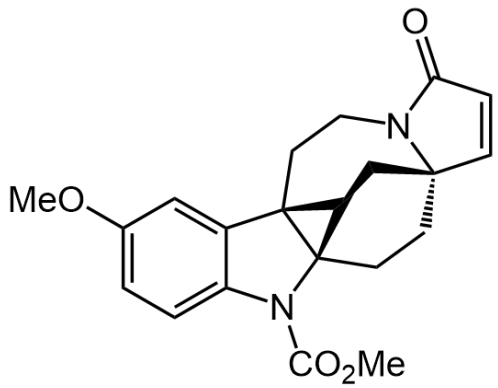
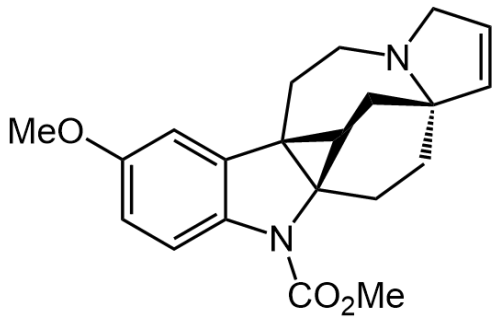
Introduction

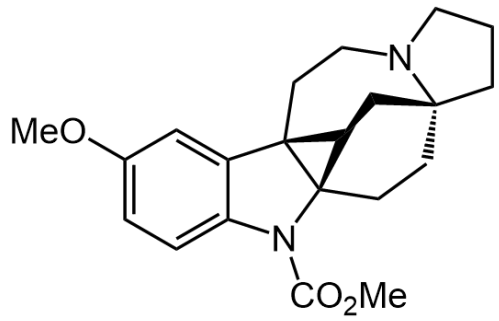
Relevant Natural Products



(-)-Lundurine A



(-)-Lundurine B



(-)-Lundurine C

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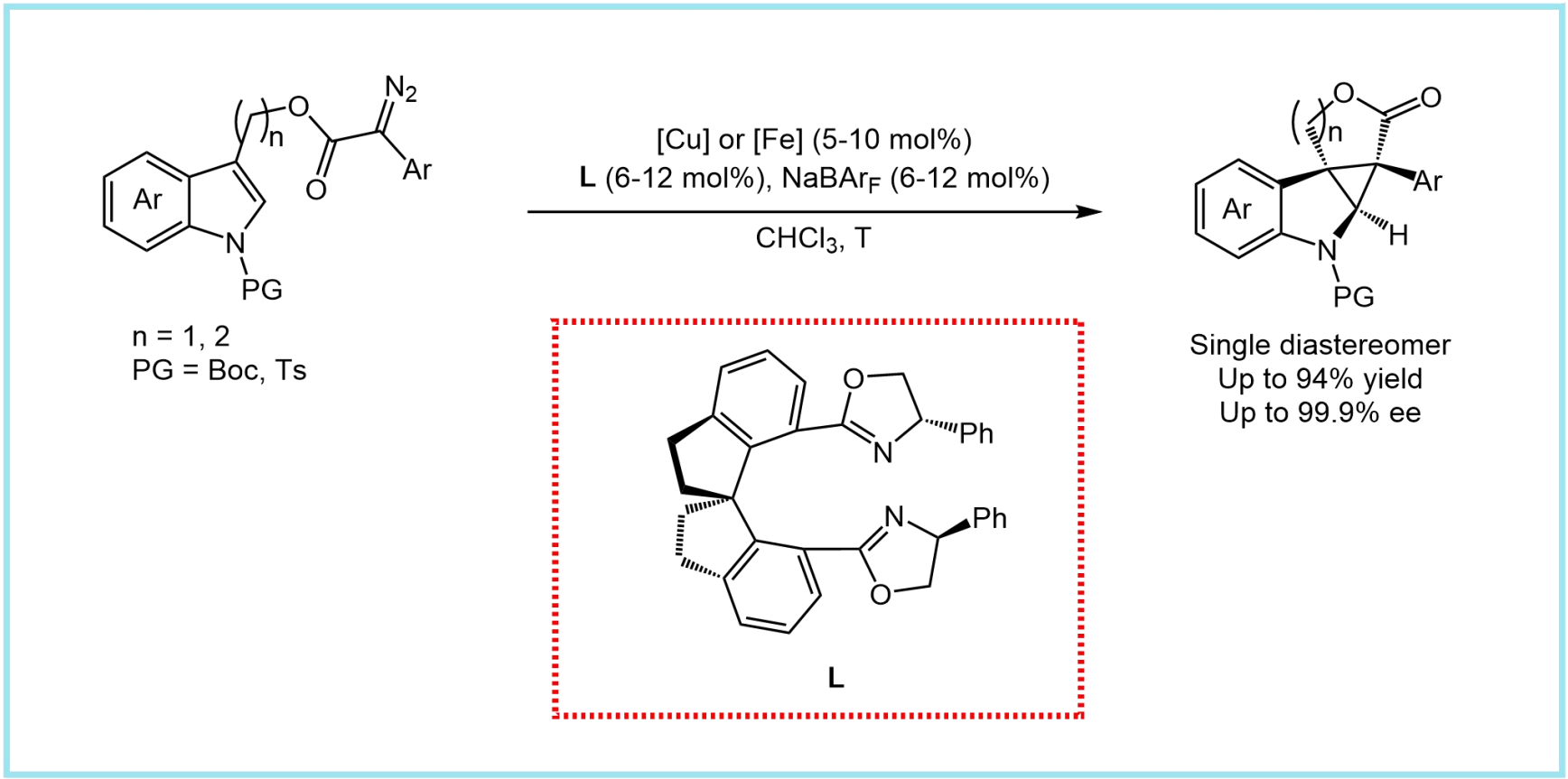
Introduction



Xu, H.; Li, Y.; Cai, Y.; Wang, G.-P.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 7697

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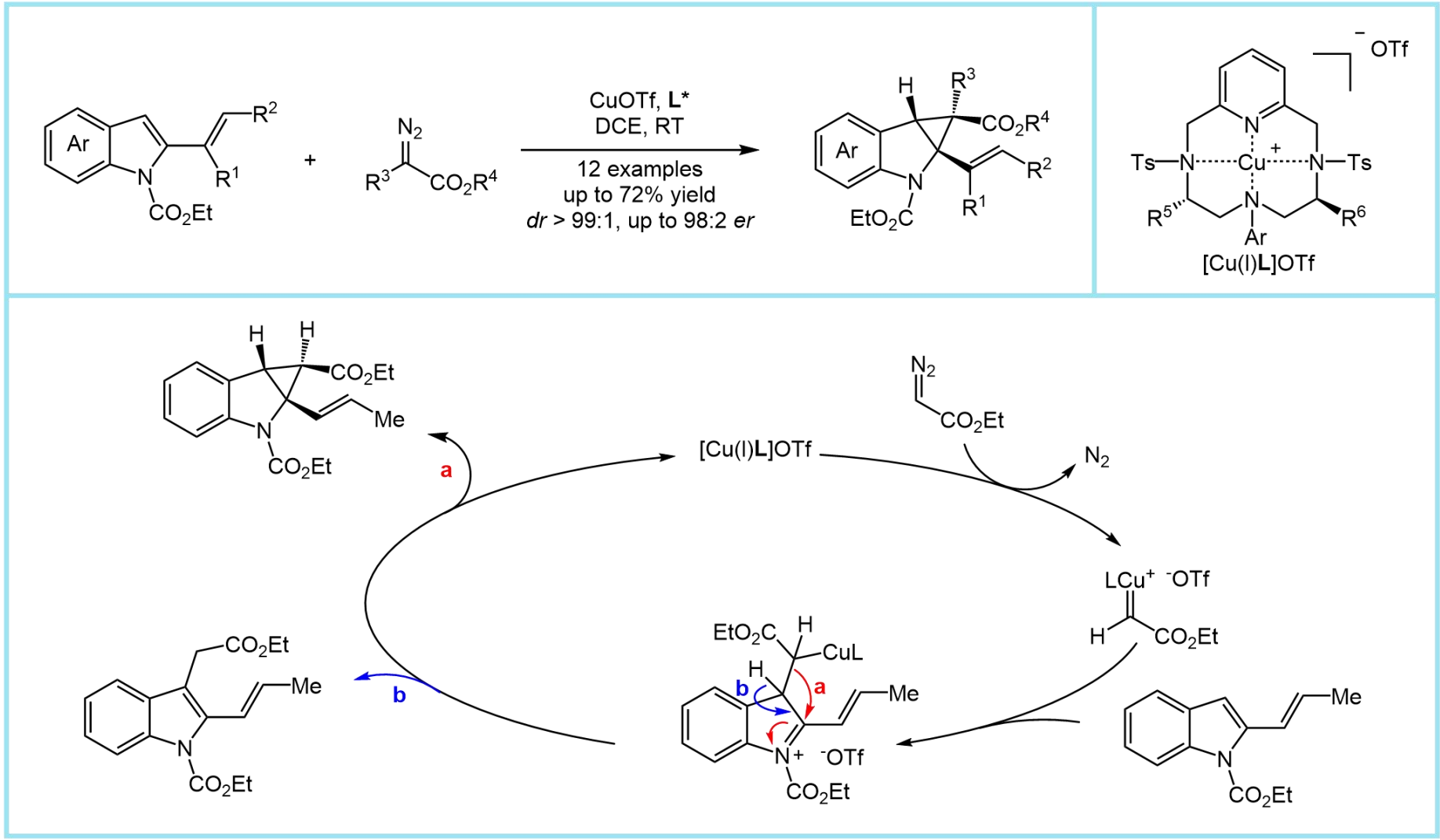
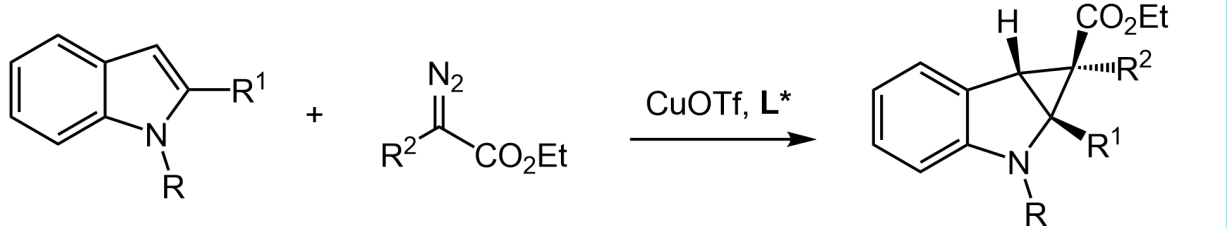


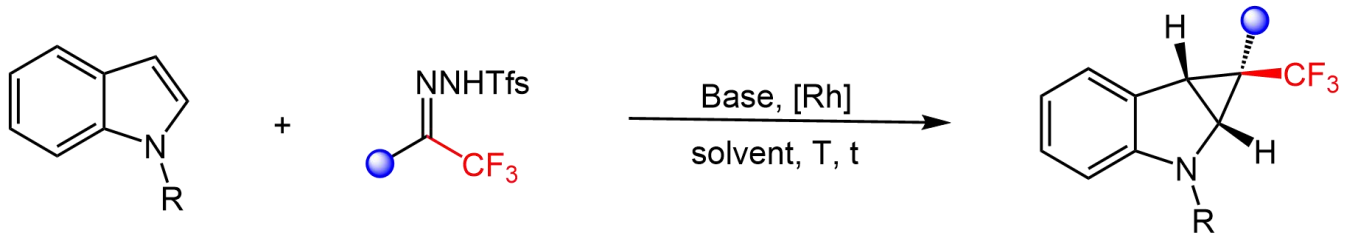
Pirovano, V.; Brambilla, E.; Tseberlidis, G. *Org. Lett.* **2018**, *20*, 405

Project Synopsis



- **Uses Energetic Diazoesters**
- **Limited to Indole-*N*-carboxylates**
- **Poor FG Tolerance**
- **Moderate Enantioselectivities**

This Work:



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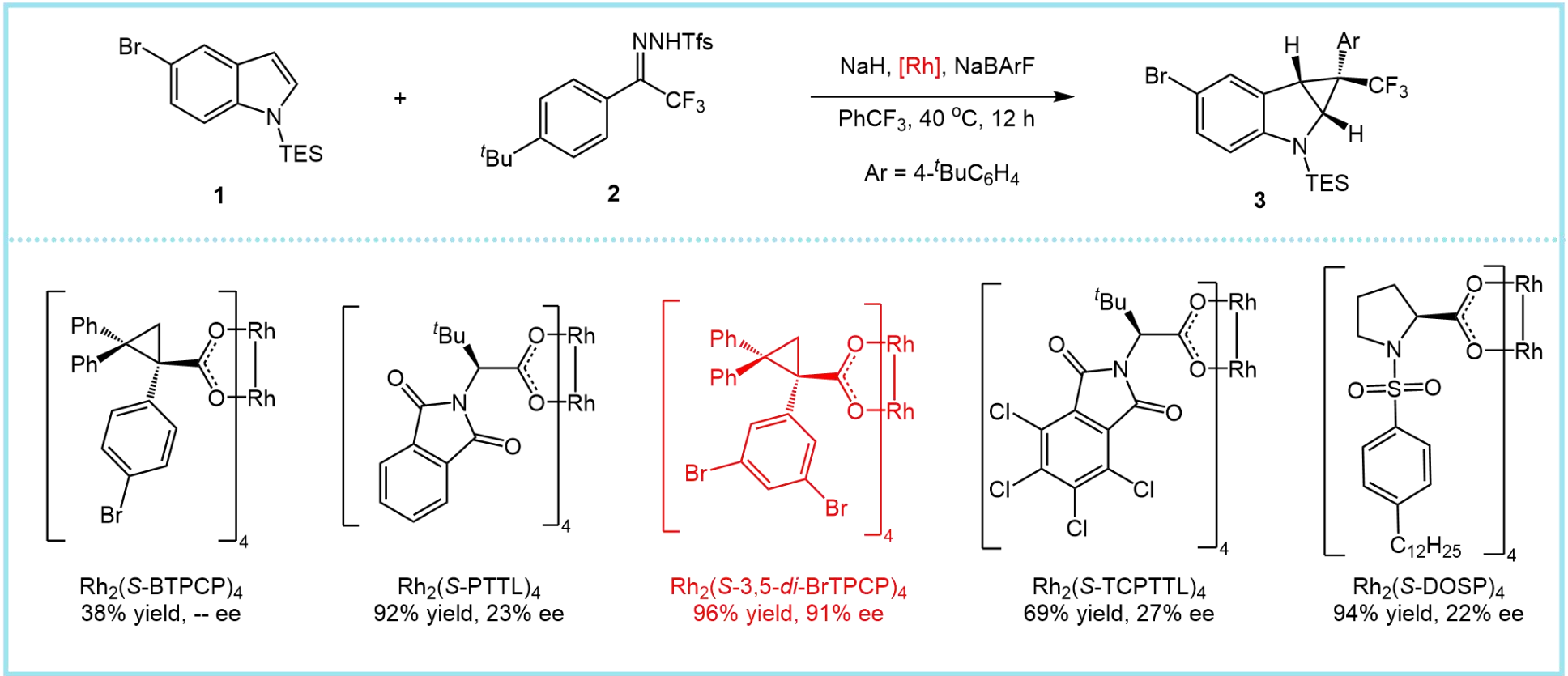
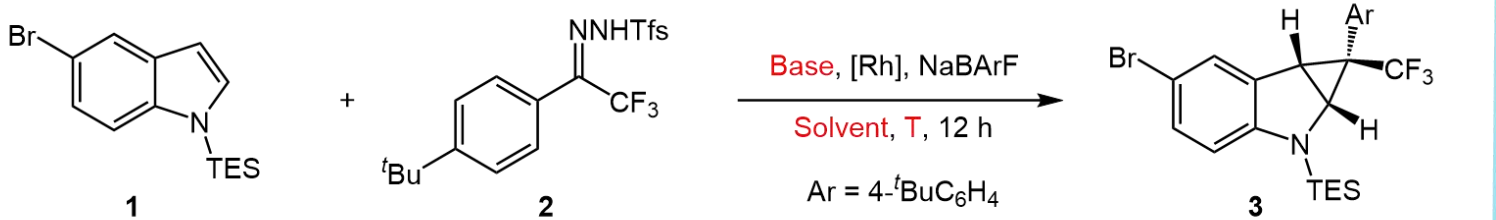
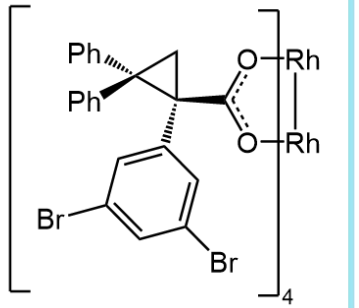
Optimization of the Reaction Conditions



Optimization of the Reaction Conditions





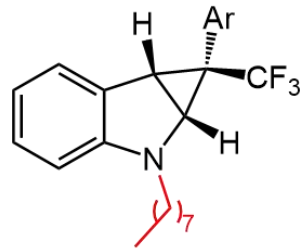
Rh_2(*S*-3,5-*di*-BrTPCP)$_4$

Entry	T (°C)	Base (4 eq.)	Solvent (5 mL)	Yield (%)	Ee (%)
1	40	NaH	$PhCF_3$	96	91
2[a]	40	NaH	$PhCF_3$	51	--
3	30	NaH	$PhCF_3$	95	93
4	30	K_2CO_3	$PhCF_3$	n.d.	--
5	30	DIPEA	$PhCF_3$	11	--
6	30	NaH	DCM	47	--
7	30	NaH	DCE	80	88
8	30	NaH	THF	21	--
9	30	NaH	CH_3CN	0	--

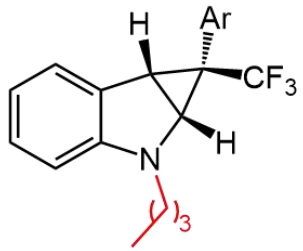
[a] without NaBArF

Substrate Scope

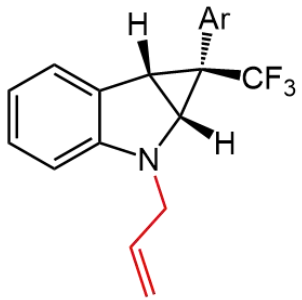
Ar = 4-^{t}BuC$_6$H$_4$



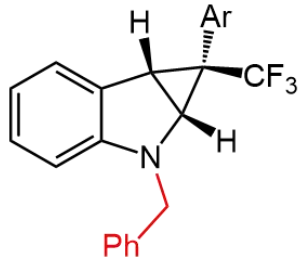
4, 94%, >20:1 dr, 90% ee



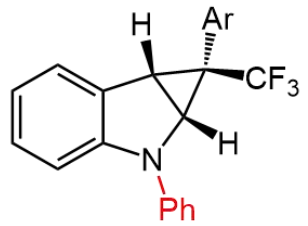
5, 97%, >20:1 dr, 87% ee



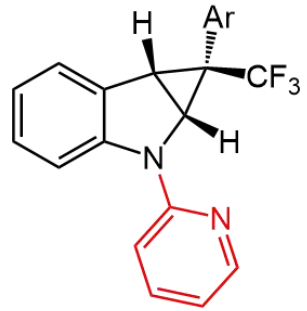
6, 74%, >20:1 dr, 95% ee



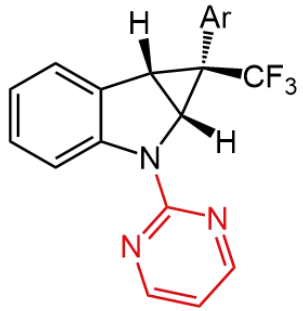
7, 88%, >20:1 dr, 93% ee



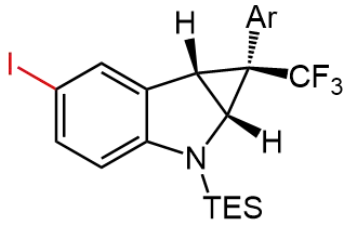
8, 97%, >20:1 dr, 94% ee



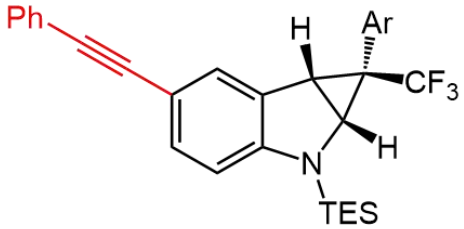
9, 91%, >20:1 dr, 99% ee



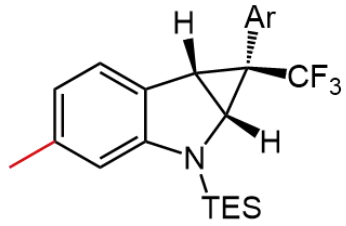
10, 28%, >20:1 dr, 98% ee



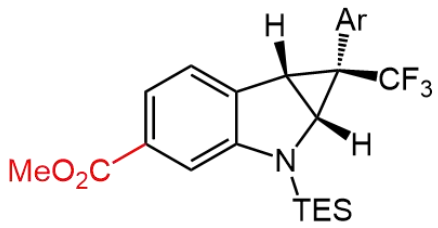
11, 76%, >20:1 dr, 94% ee



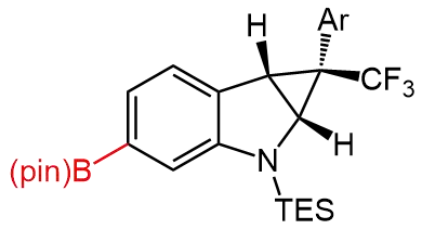
12, 96%, >20:1 dr, 98% ee



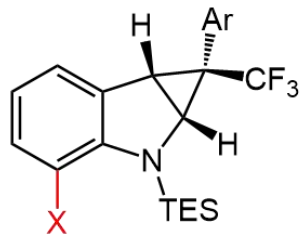
13, 95%, 2:1 dr, 94% ee



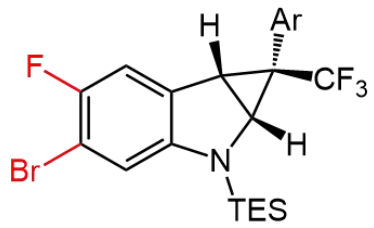
14, 97%, >20:1 dr, 93% ee



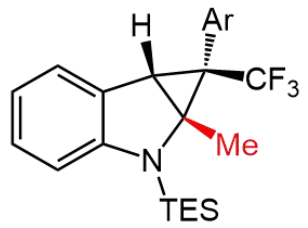
15, 95%, >20:1 dr, 93% ee



16, X = F, 97%, >20:1 dr, 96% ee
17, X = Cl, 98%, >20:1 dr, 99% ee

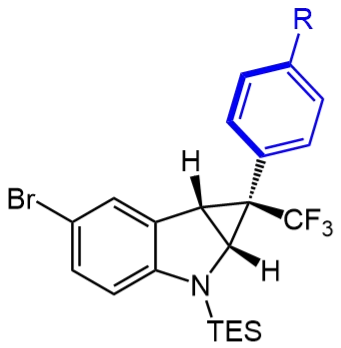


18, 98%, >20:1 dr, 96% ee

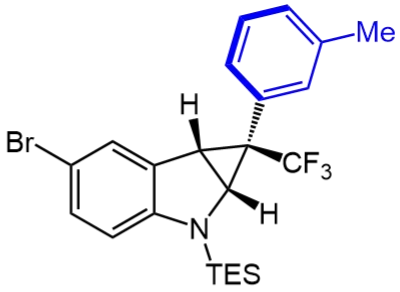


19, 55%, >20:1 dr, 93% ee

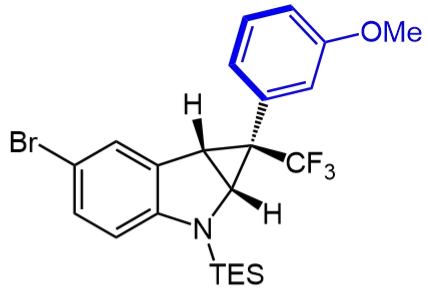
Substrate Scope



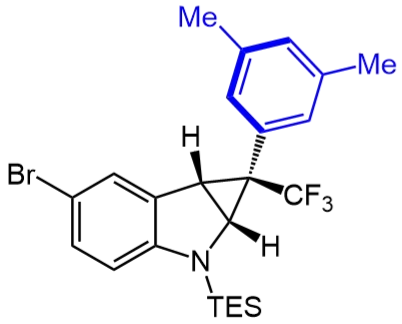
20, R = 4-OMe, 96%, >20:1 dr, 90% ee
21, R = 4-^{i}Pr, 97%, >20:1 dr, 93% ee
22, R = 4-Me, 98%, >20:1 dr, 99% ee
23, R = 4-Ph, 70%, >20:1 dr, 90% ee
24, R = 4-Cl, 95%, >20:1 dr, 96% ee
25, R = 4-Br, 98%, >20:1 dr, 98% ee
26, R = 4-CF_3, 96%, >20:1 dr, 96% ee
27, R = 4-OCF_3, 97%, >20:1 dr, 90% ee



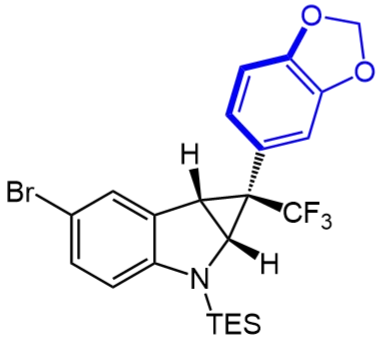
28, 60%, >20:1 dr, 99% ee



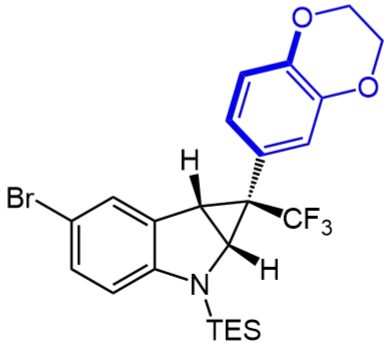
29, 96%, >20:1 dr, 90% ee



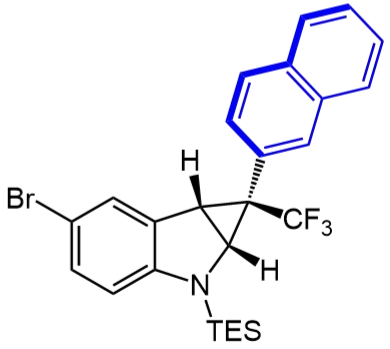
30, 96%, >20:1 dr, 93% ee



31, 96%, >20:1 dr, 97% ee

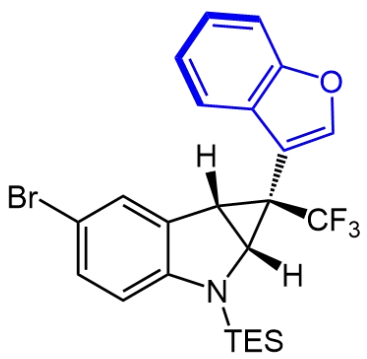


32, 97%, >20:1 dr, 90% ee

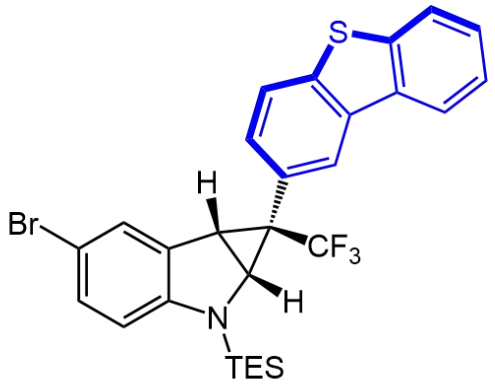


33, 97%, >20:1 dr, 92% ee

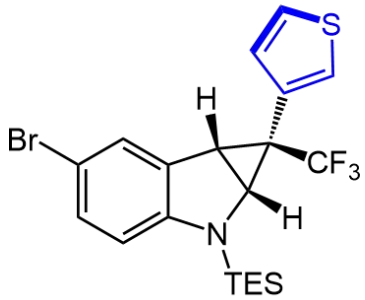
Substrate Scope



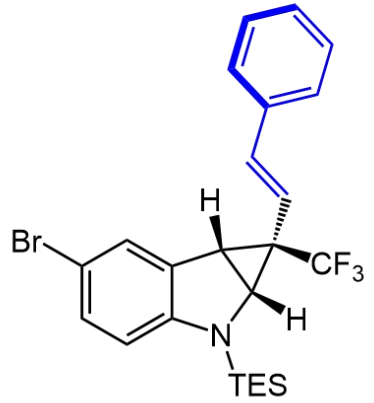
34, 96%, >20:1 dr, 99% ee



35, 97%, >20:1 dr, 89% ee



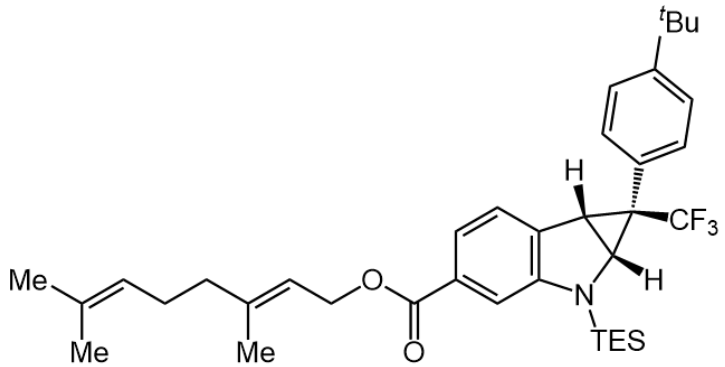
36, 84%, >20:1 dr, 99% ee



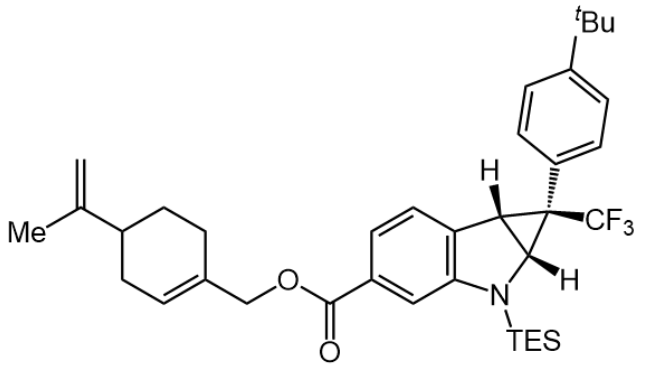
37, 82%, >20:1 dr, 90% ee

Synthetic Applications

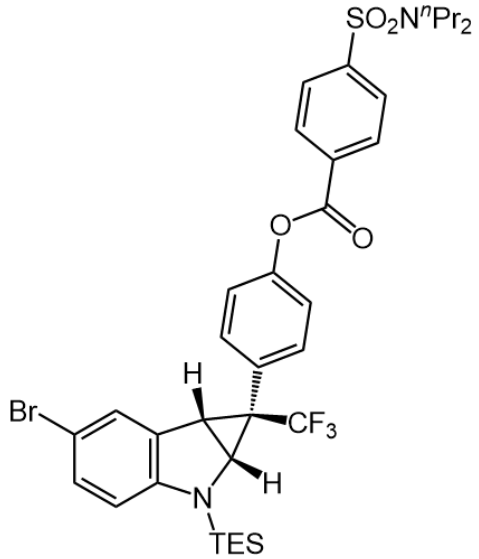
Cyclopropanation Involving Drug Molecules



38, 80%, >20:1 dr, 92% ee
(From Geraniol)



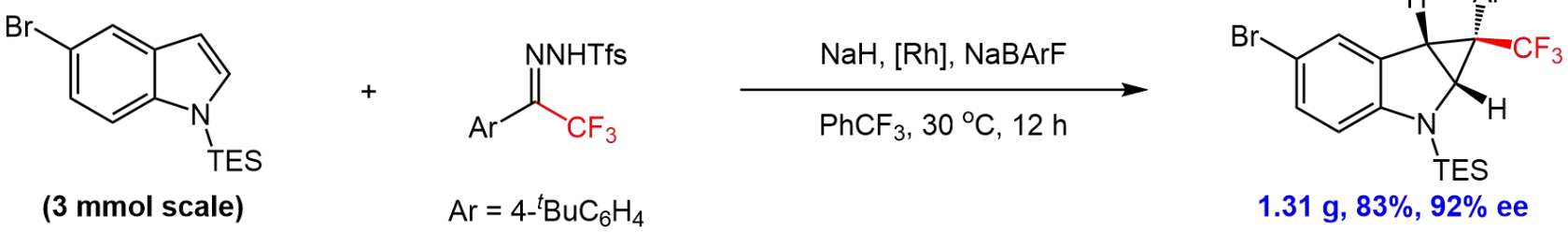
39, 62%, >20:1 dr, 95% ee
(From Dihydrocuminyl Alcohol)



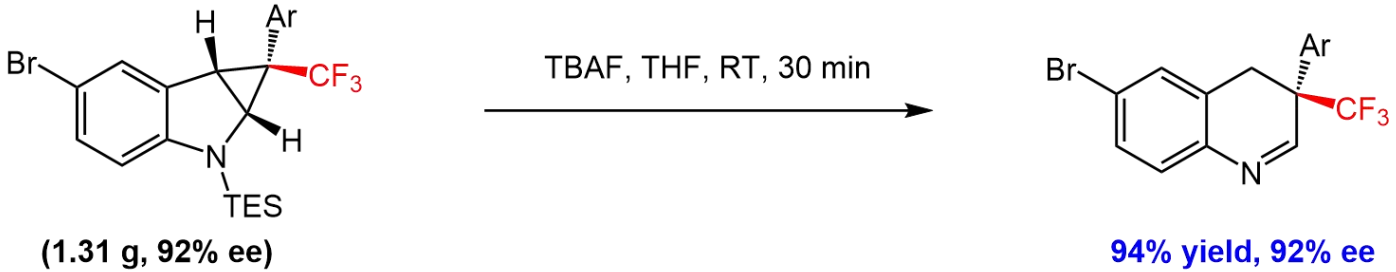
40, 85%, >20:1 dr, 95% ee
(From Probenecid Acid)

Synthetic Applications

Gram Scale Synthesis

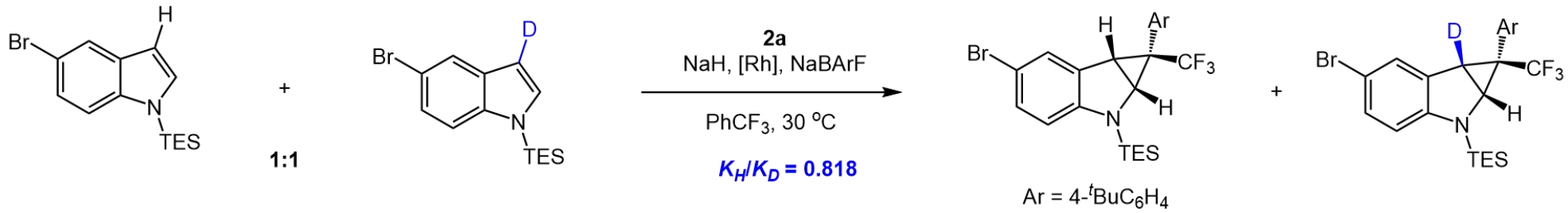


Further Transformation

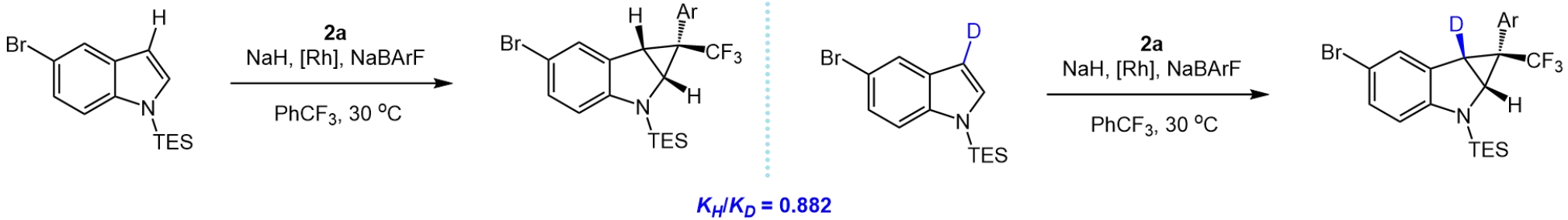


Mechanism Studies

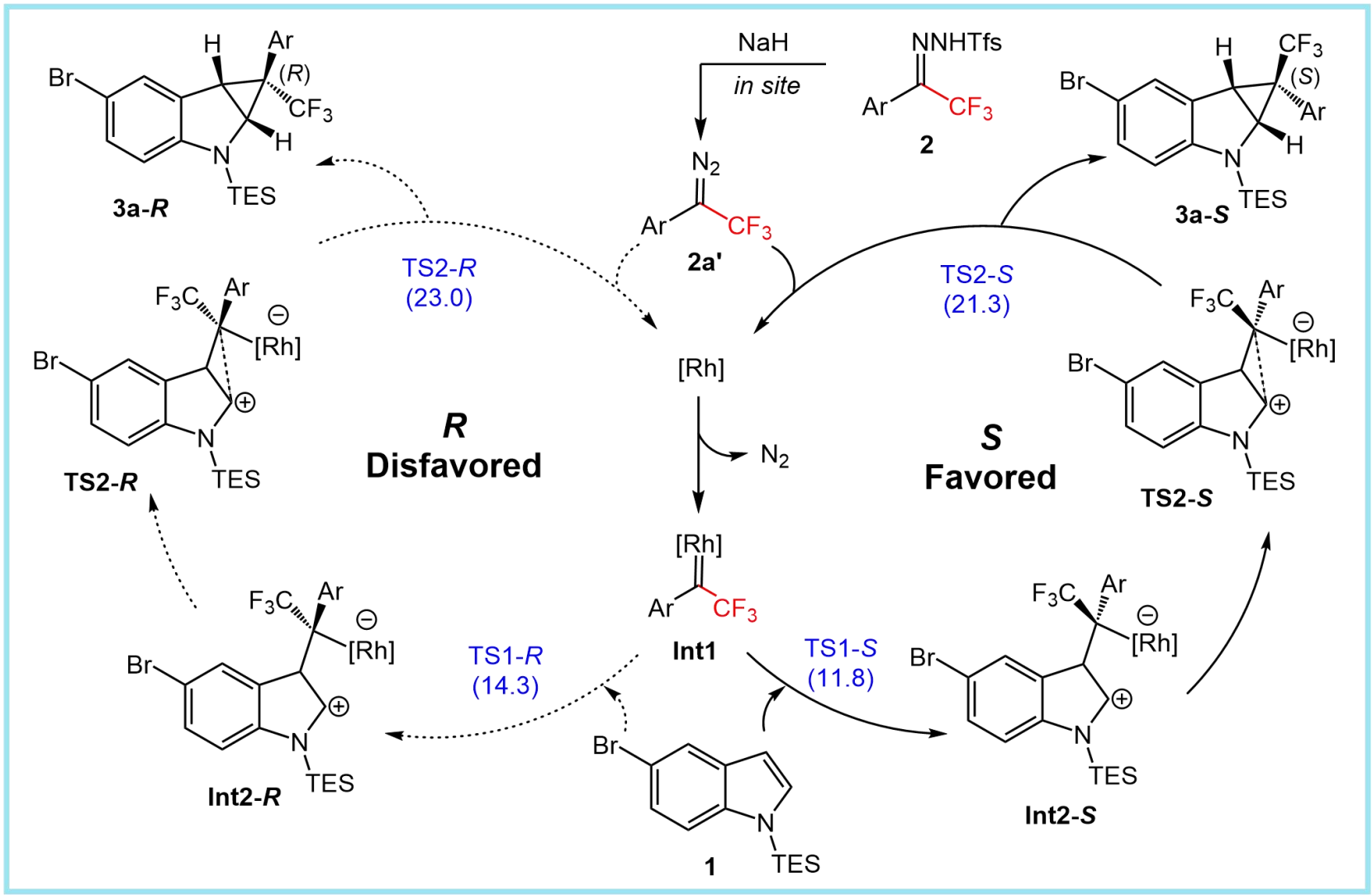
One-pot Competition KIE Experiment



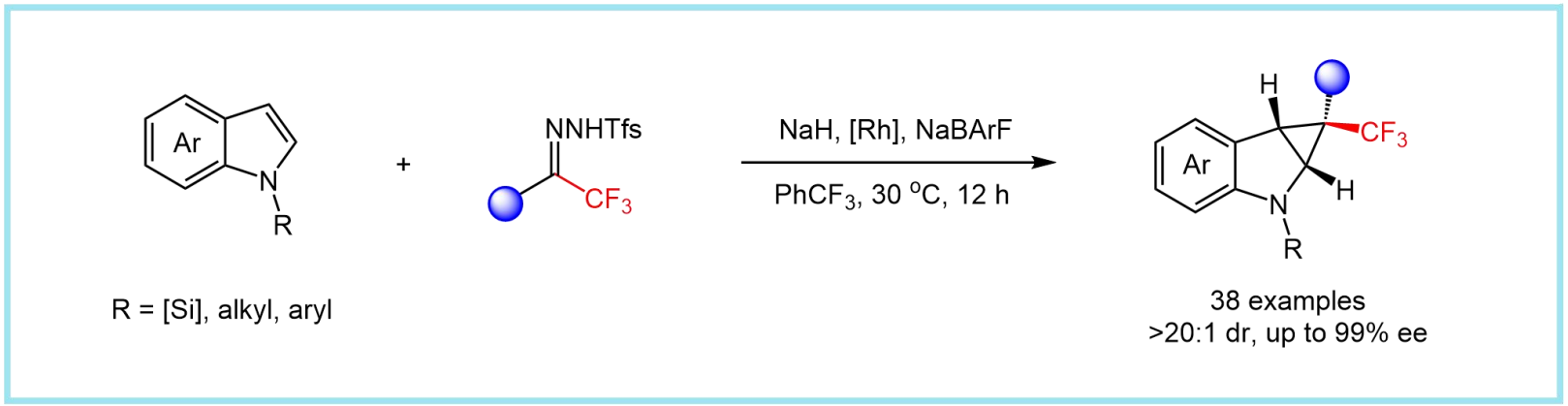
KIE for Two Parallel Reactions



Proposed Mechanism



Summary



- **Uses Fluoroalkyl *N*-Triformylhydrazone**
- **Excellent Enantio- and Diastereoselectivities**
- **Good FG Tolerance**
- **Late-stage Diversifications**

Strategy for Writing The First Paragraph

含环丙烷结构的吲哚类化合物
应用前景广泛

合成该类化合物所面临的挑战

引出本文工作

- ✓ Indole-containing polycyclic scaffolds are one of the most commonly encountered structural motifs in the scaffold of diverse biologically active species...
- ✓ Accessing these cyclopropane fused indolines is not trivial...These protocols, however, generally exhibit only moderate enantioselectivity and are limited to using highly energetic diazo carbonyl compounds as carbene precursors, and thus the methodology is unsuitable for late-stage modifications...
- ✓ It is advantageous to develop new methodologies that use operationally safe carbene precursors capable of delivering cyclopropane fused indolines and with high enantioselectivities.

Strategy for Writing The Last Paragraph

总结工作

强调亮点

提出展望

✓ In conclusion, we have developed a chiral dirhodium-catalyzed asymmetric dearomative cyclopropanation of *N*-protected indoles using trifluoromethyl *N*-triftosylhydrazones as trifluoromethyl carbene precursors.

✓ This method allows for the practical synthesis of a diverse set of cyclopropane fused indolines bearing a chiral quaternary carbon stereocenter with high yields and good enantio- and diastereo-selectivities...

✓ Given the overall mildness and general applicability of the here-in-developed protocol, we anticipate this enantioselective dearo-mative cyclopropanation process will find diverse applications in synthetic and pharmaceutical sciences.

Representative Examples

- Indole-containing polycyclic scaffolds are one of the most commonly encountered structural motifs in the scaffold of diverse biologically active species. (encounter, v. 遇到，遭遇，邂逅；n. 突然遇到)
- Accessing these cyclopropane fused indolines is not trivial. (trivial, adj. 琐碎的，不重要的)
- At the outset of our investigation, we chose *N*-triethylsilyl protected 5-bromoindole and *N*-triftosylhydrazone as the model substrates for optimizing the reaction conditions. (At the outset of... 在一开始...)

Acknowledgement

Thanks for Your Attention!