Literature Report 4

Rhodium-Catalyzed Asymmetric Allylic Arylation of Racemic Halides with Arylboronic Acids

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Fletcher, S. P. *et al.*
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Introduction

1999	B.S., **Mount Allison University**
1999 – 2005	Ph.D., **University of Alberta** Advisor: Professor Clive D. L. J.
2005 – 2007	He joined the Feringa's group at the **University of Groningen**.
2007 – 2009	He joined the Clayden's group at the **University of Manchester**.
2009 – 2015	EPSRC Career Acceleration Fellow, **University of Oxford**
2015 –	Associate Professor and Official Fellow, **University of Oxford**

Research Interests:

Asymmetric Catalysis, Synthetic Engineering of Potential Energy Surfaces, Self-replicating Systems, Molecular Machines.

Introduction

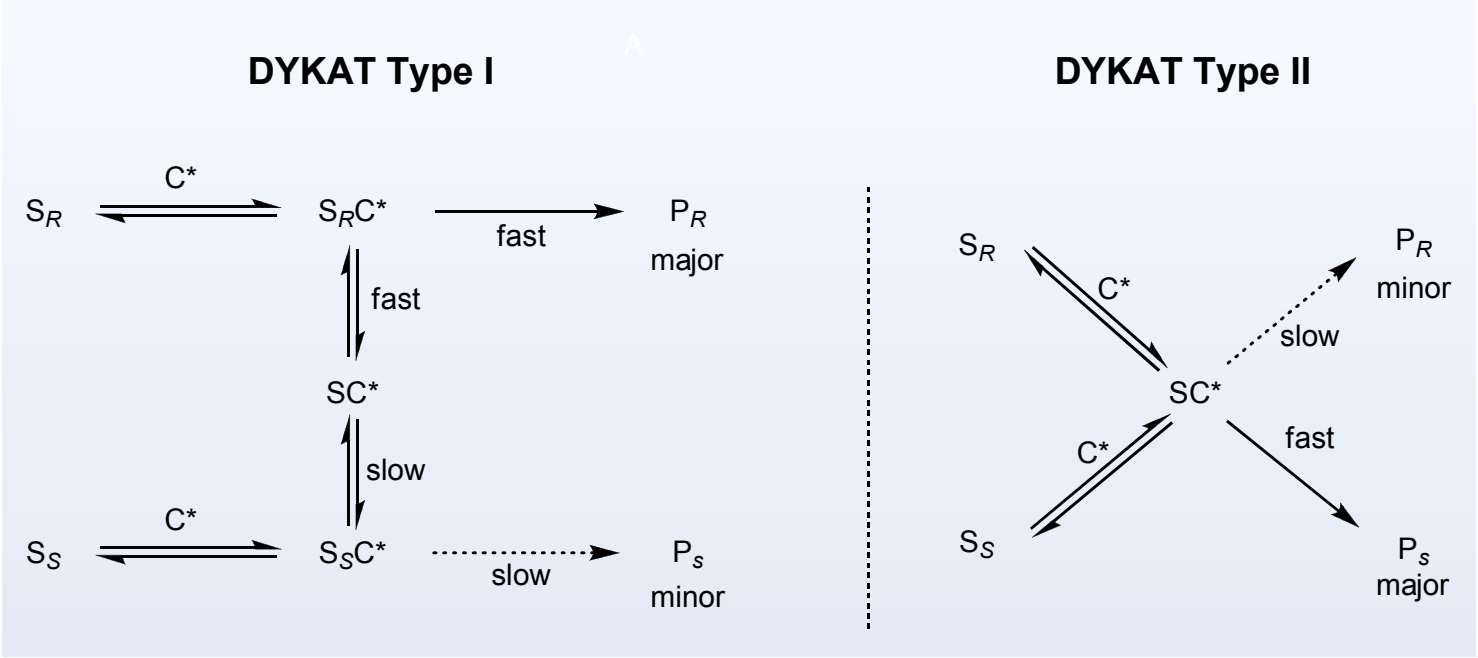
动态动力学不对称转化

动态动力学不对称转化（Dynamic Kinetic Asymmetric Transformation, DYKAT）：消旋的原料与手性催化剂作用，经过中间体的转化，利用不同异构体反应的速率差，将消旋体底物转化为单一对映体产物的过程。

- Metal Catalyzed DYKAT
- Organocatalytic DYKAT
- Enzyme Mediated DYKAT

Introduction

动态动力学不对称转化的主要类型



Introduction

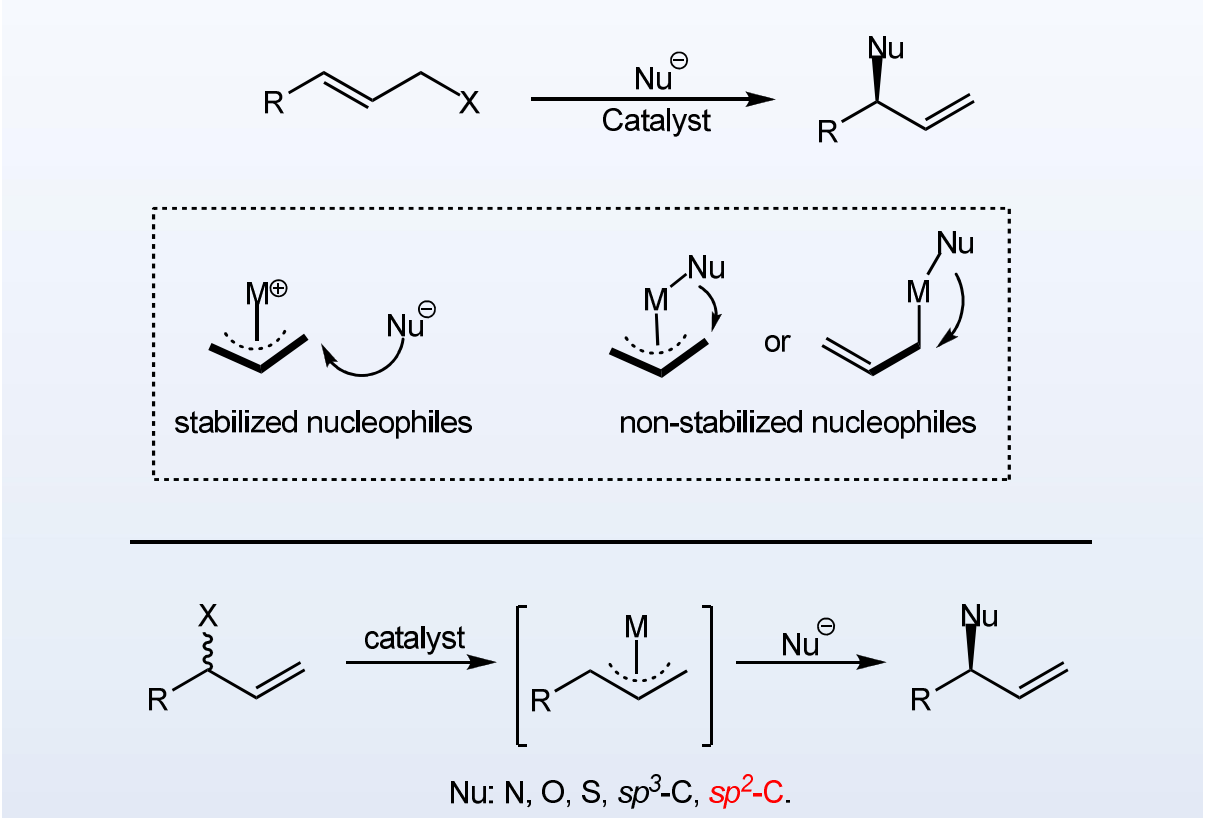
动态动力学不对称转化的优点

动态动力学不对称转化与其他的拆分手段相比，具有以下优点：

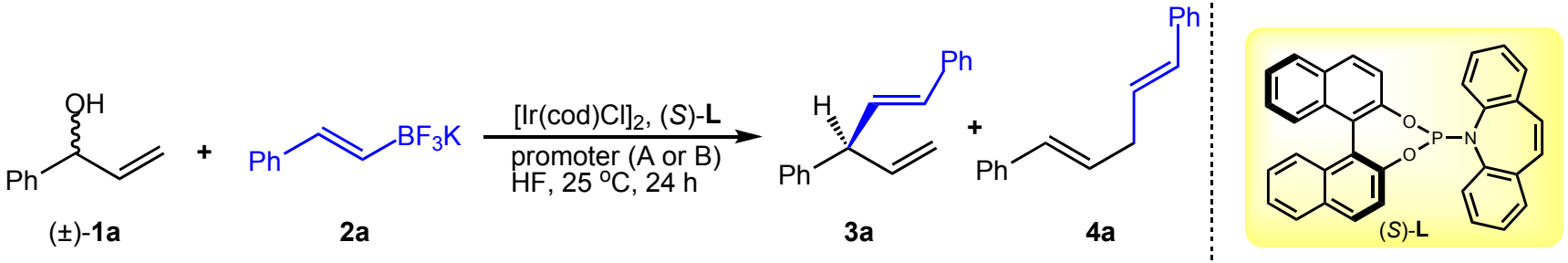
- 理论收率是100%，而不是50%
- 拆分的过程是一个转化，缩短了反应步骤
- 反应底物类型的多样化
- 兼容的催化体系广泛（金属催化，有机小分子催化和酶催化）

Introduction

Asymmetric allylic alkylation (AAA)



Optimization of Ir-Catalyzed Asymmetric Allylic Vinylation



entry	**2a** (equiv)	promoter (equiv)[a]	solvent	yield (%)[b]	**3a**:**4a**[c]	ee (%)[d]
1	1.0	A (0.5)	acetone	24	>50:1	99
2[e]	1.0	A (0.5)	acetone	40	>50:1	98
3	1.0	B (0.5)	acetone	53	>50:1	98
4	1.0	B (0.5)	MeCN	31	0.7:1	97
5	1.0	B (0.5)	DME	22	20:1	97
6	1.0	B (0.5)	$MeNO_2$	40	0.6:1	97
7	1.0	B (0.5)	dioxane	60	>50:1	98

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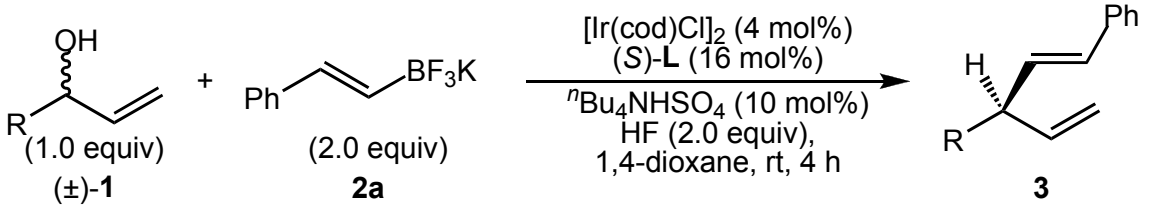
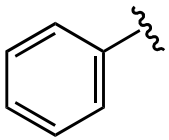
Optimization of Ir-Catalyzed Allylic Vinylation

8	1.0	B (0.1)	dioxane	57	>50:1	99
9[f]	2.0	B (0.1)	dioxane	75	>50:1	99
10[g]	2.0	B (0.1)	dioxane	89	>50:1	99

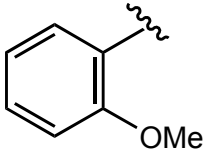
Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), $[Ir(cod)Cl]_2$ (2.0 mol%), [Ir]/(*S*)-**L** = 1:2, HF (50% aq. equimolar to **2a**), solvent (0.5 mL), 25 °C, 24 h. [a] A: di-*n*-butylphosphoric acid, B: $^{n}Bu_4NHSO_4$. [b] Determined by ^1H NMR integration relative to the internal standard. [c] Ratio of **3a** to **4a** determined by ^1H NMR integration. [d] Determined by SFC on a chiral stationary phase. [e] Tetra-*n*-butylammonium styryltrifluoroborate was used instead of **2a**. [f] 3.0 mol% $[Ir(cod)Cl]_2$ was used. [g] 4.0 mol% $[Ir(cod)Cl]_2$ was used.

Scope of the Asymmetric Allylic Vinylation

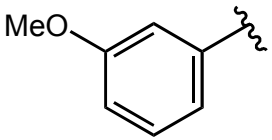




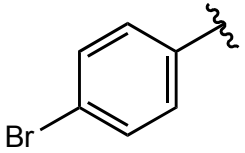
3a: 86% (>50:1)
>99% ee



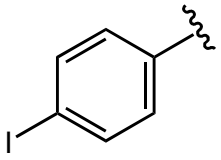
3b: 86% (31:1)
98% ee



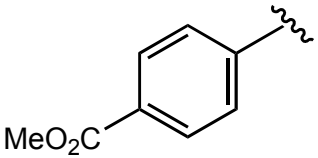
3c: 81% (>50:1)
>99% ee



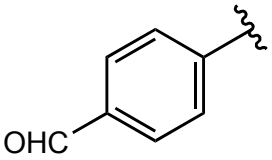
3d: 78% (>50:1)
98% ee



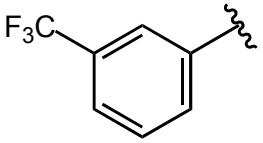
3e: 72% (>50:1)
99% ee



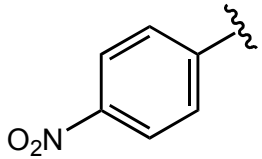
3f: 68% (31:1)
>99% ee



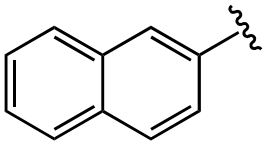
3g: 65% (>50:1)
99% ee



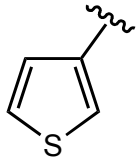
3h: 61% (>50:1)
>99% ee



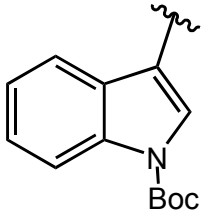
3i: 55% (>50:1)
>99% ee



3j: 90% (>50:1)
98% ee

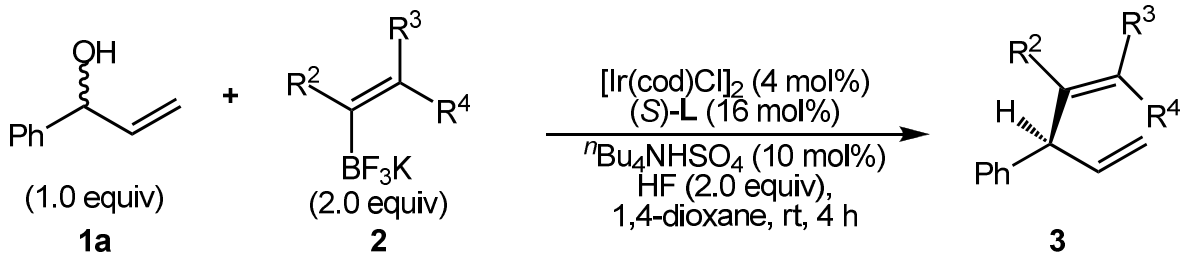


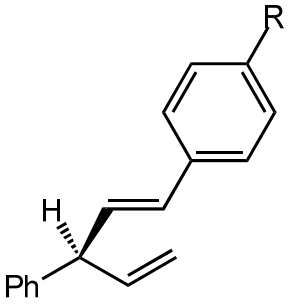
3k: 84% (>50:1)
97% ee



3l: 99% (3:1)
89% ee

Scope of the Asymmetric Allylic Vinylation

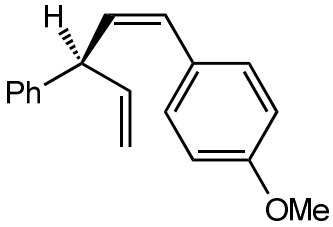




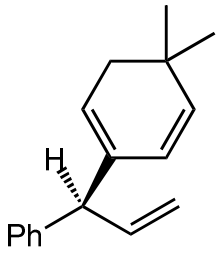
3a (R = H): 86% (>50:1)
>99% ee

3m (R = F): 76% (>50:1)
97% ee

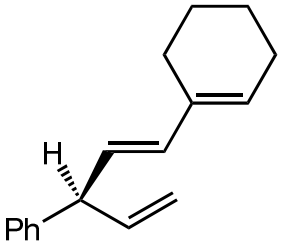
3n (R = MeO): 82% (>50:1)
95% ee



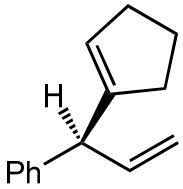
3o: 70% (>50:1)
>99% ee



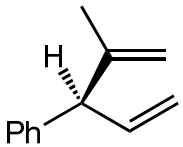
3p: 71% (>50:1)
97% ee



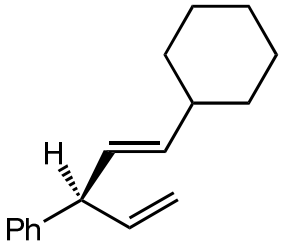
3q 65% (>50:1)
>99% ee



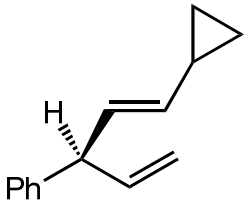
3r: 70% (3:1)
98% ee



3s: 63% (>50:1)
94% ee

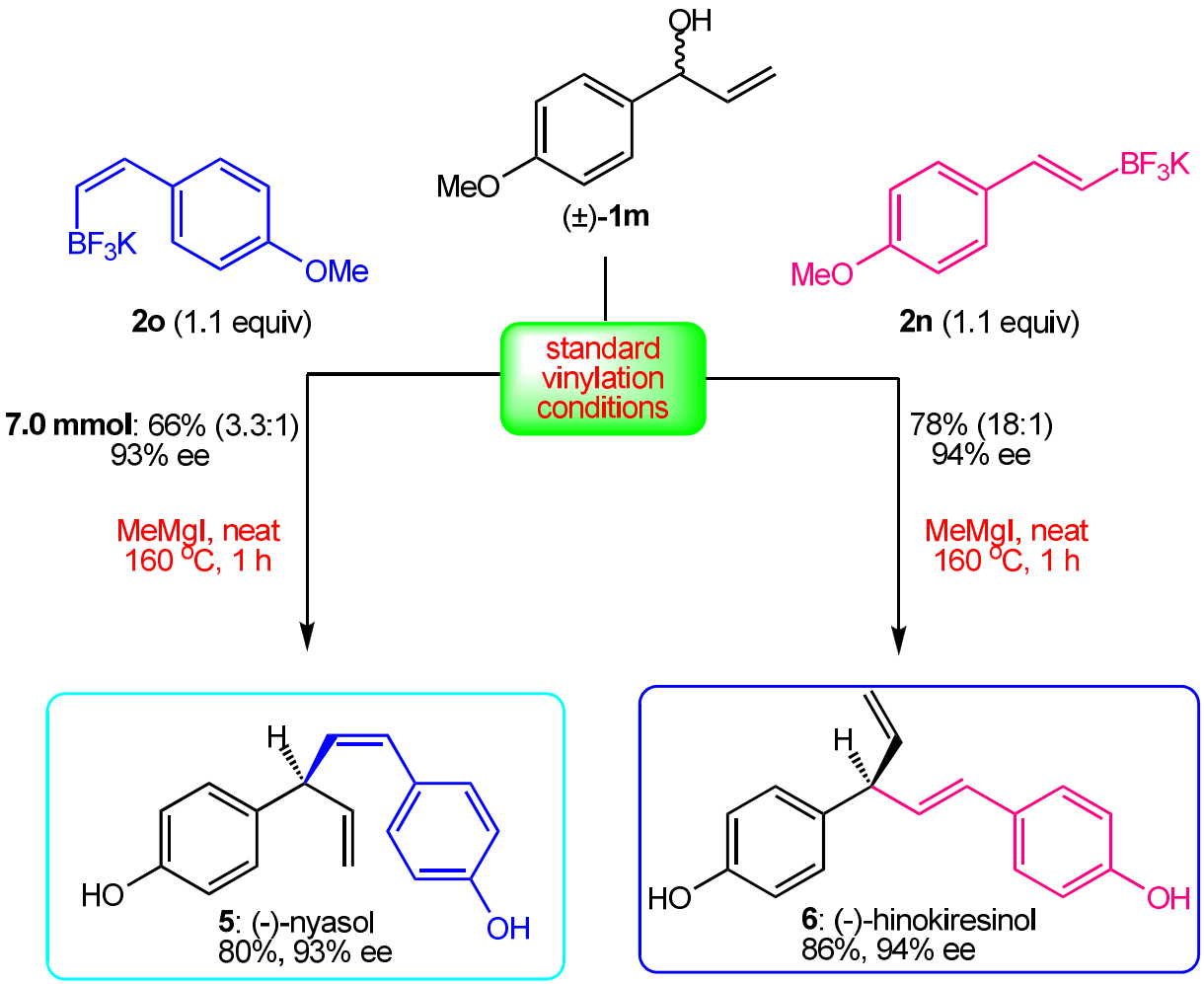


3t: 60% (>50:1)
>99% ee

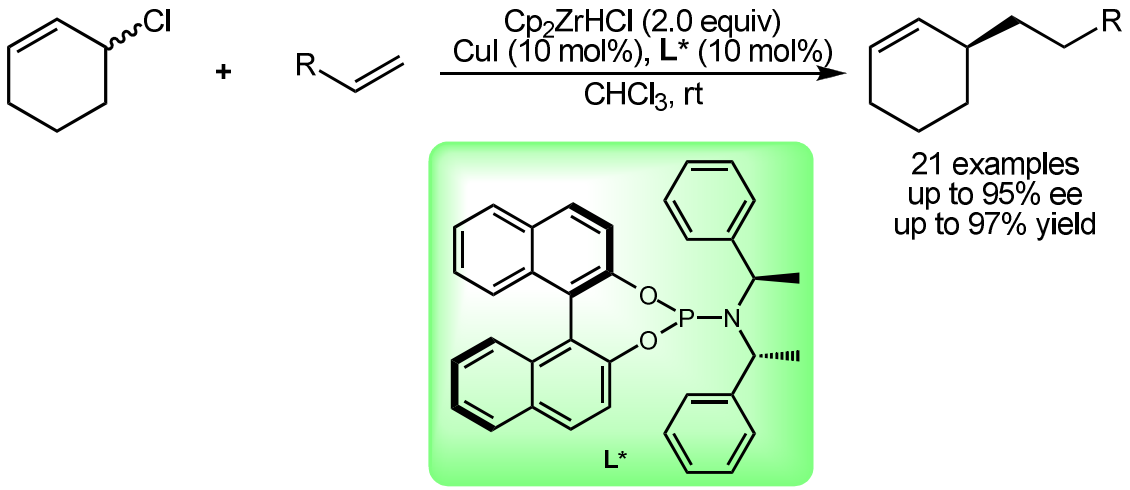


3u: 51% (>50:1)
99% ee

Synthesis of (−)-Nyasol and (−)-Hinokiresinol

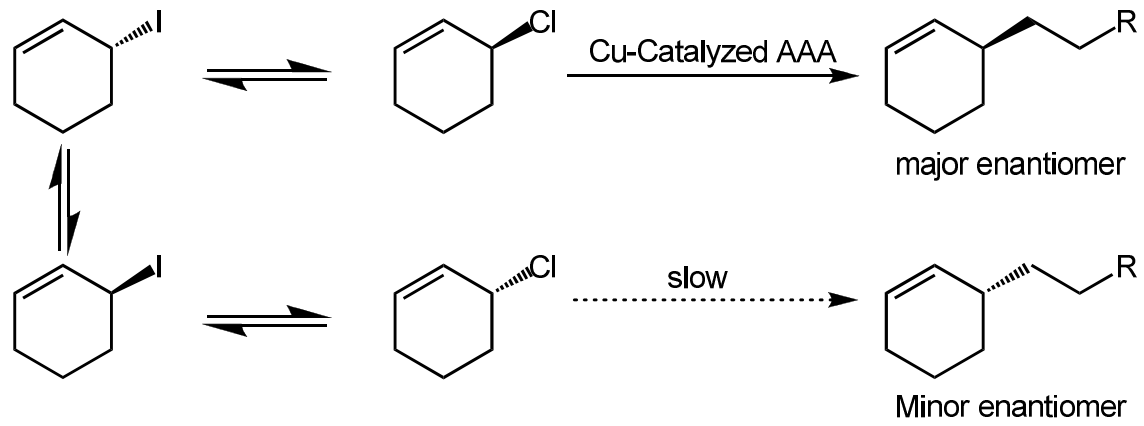


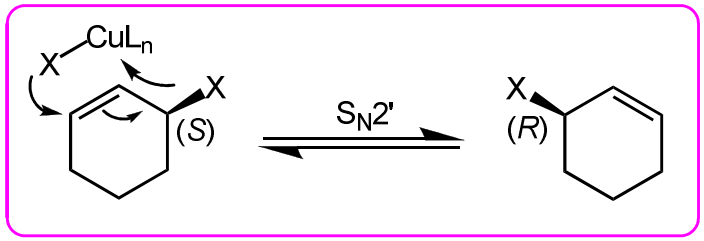
Cu-Catalysed Dynamic Kinetic Asymmetric Allylic Alkylation



Cu-Catalysed Dynamic Kinetic Asymmetric Allylic Alkylation

Proposed Mechanism





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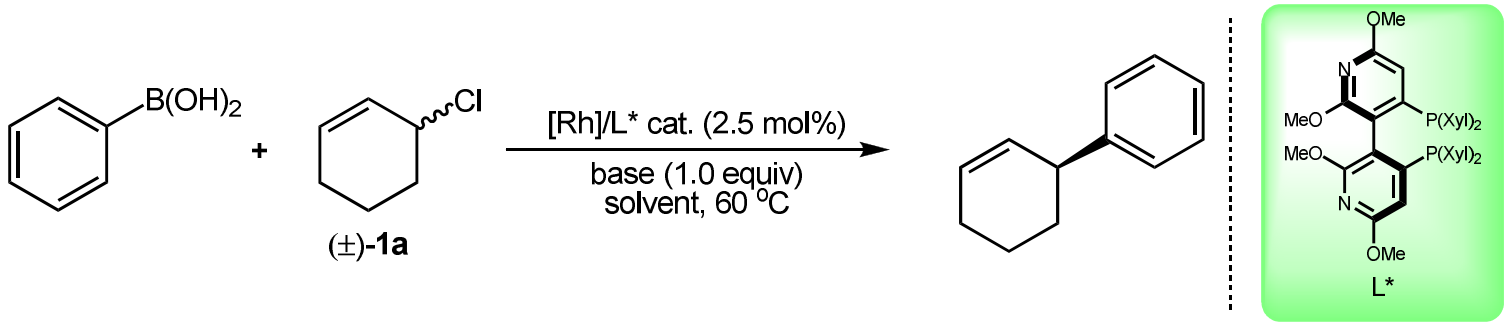
Rhodium-Catalysed Asymmetric Allylic Arylation



entry	catalyst	ligand	base	solvent	yield (%)[a]	ee (%)[b]
1[c]	$Rh(acac)(C_2H_4)_2$	(*S*)-BINAP	--	dioxane/H_2O	--	--
2	$Rh(acac)(C_2H_4)_2$	(*S*)-BINAP	Cs_2CO_3	THF	--	--
3	$[Rh(cod)(OH)]_2$	(*S*)-BINAP	Cs_2CO_3	THF	trace	ND
4	$[Rh(cod)(OH)]_2$	(*S*)-Xyl-P-Phos	Cs_2CO_3	THF	99	99

[a] Isolated yield; [b] Determined by HPLC; [c] 100 °C.

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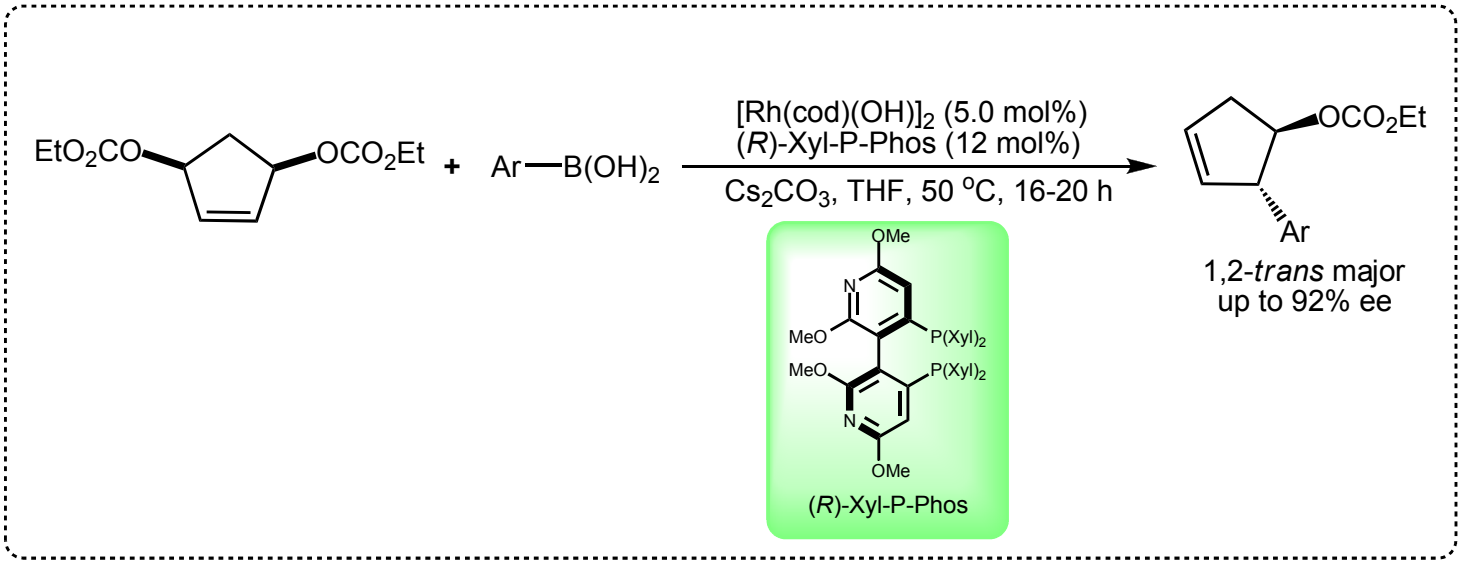
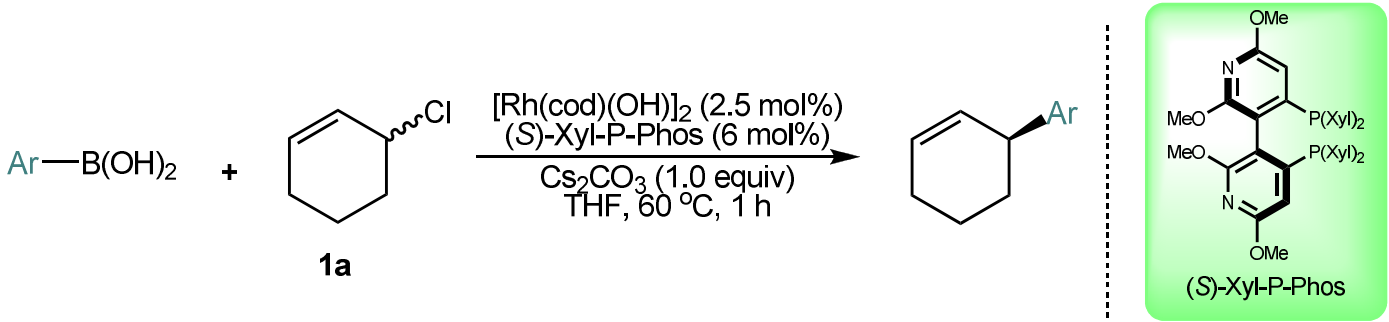
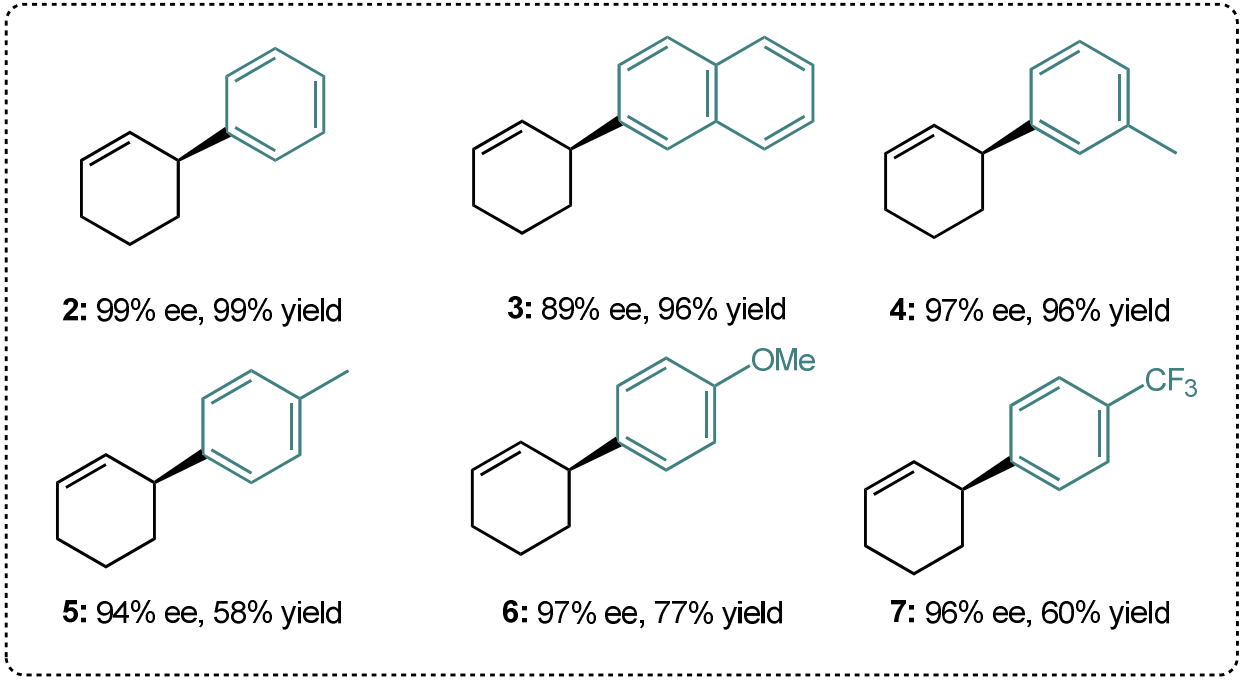
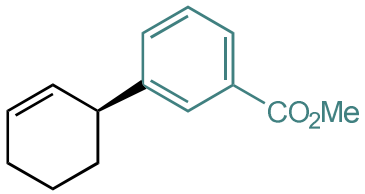

EtO2CO
OCO2Et
+
Ar—B(OH)2
[Rh(cod)(OH)]2 (5.0 mol%)
(R)-Xyl-P-Phos (12 mol%)
Cs2CO3, THF, 50 °C, 16-20 h
OMe
N
MeO
P(Xyl)2
MeO
P(Xyl)2
N
OMe
(R)-Xyl-P-Phos
OCO2Et
Ar
1,2-trans major
up to 92% ee

Substrate Scope

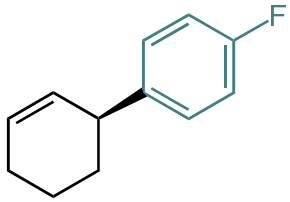




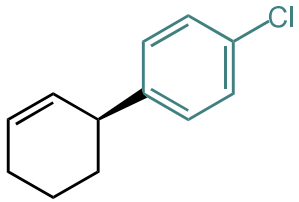
Substrate Scope



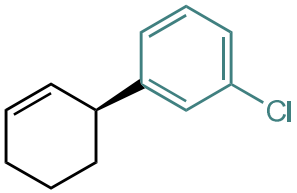
8: >99% ee, 86% yield



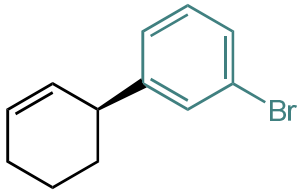
9: >99% ee, 54% yield



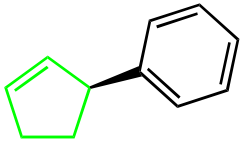
10: >99% ee, 81% yield



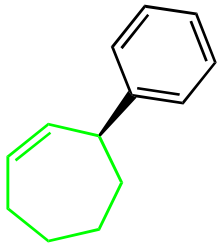
11: 99% ee, 70% yield



12: 96% ee, 56% yield

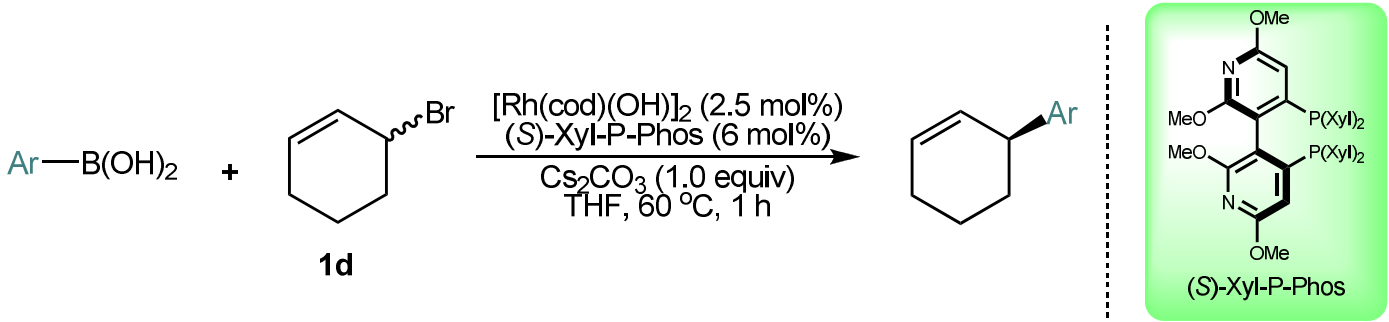


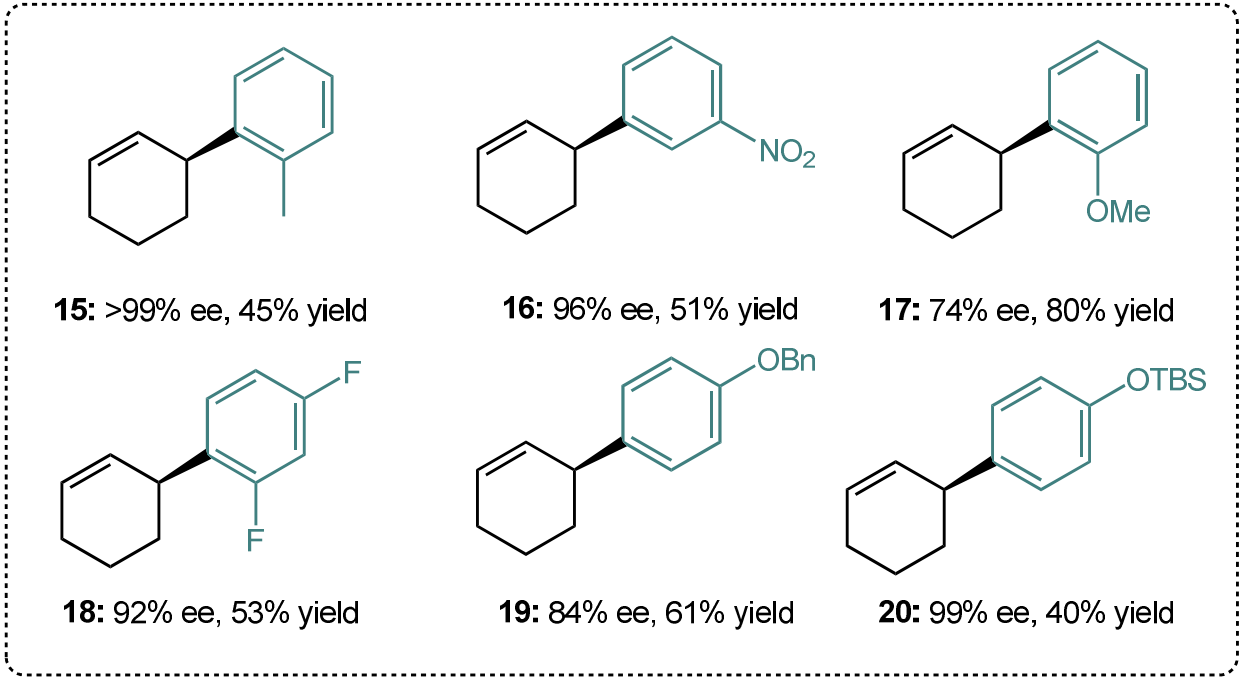
13: >99% ee, 67% yield



14: 97% ee, 62% yield

Substrate Scope





15: >99% ee, 45% yield

16: 96% ee, 51% yield

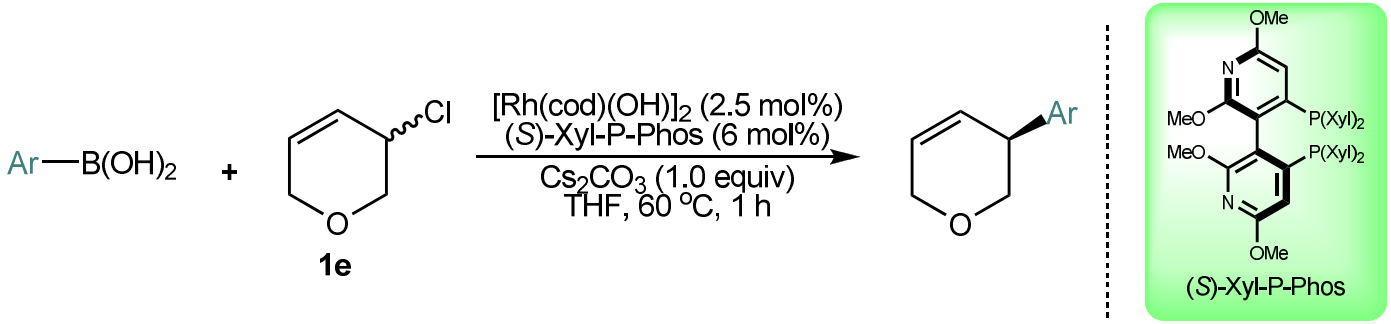
17: 74% ee, 80% yield

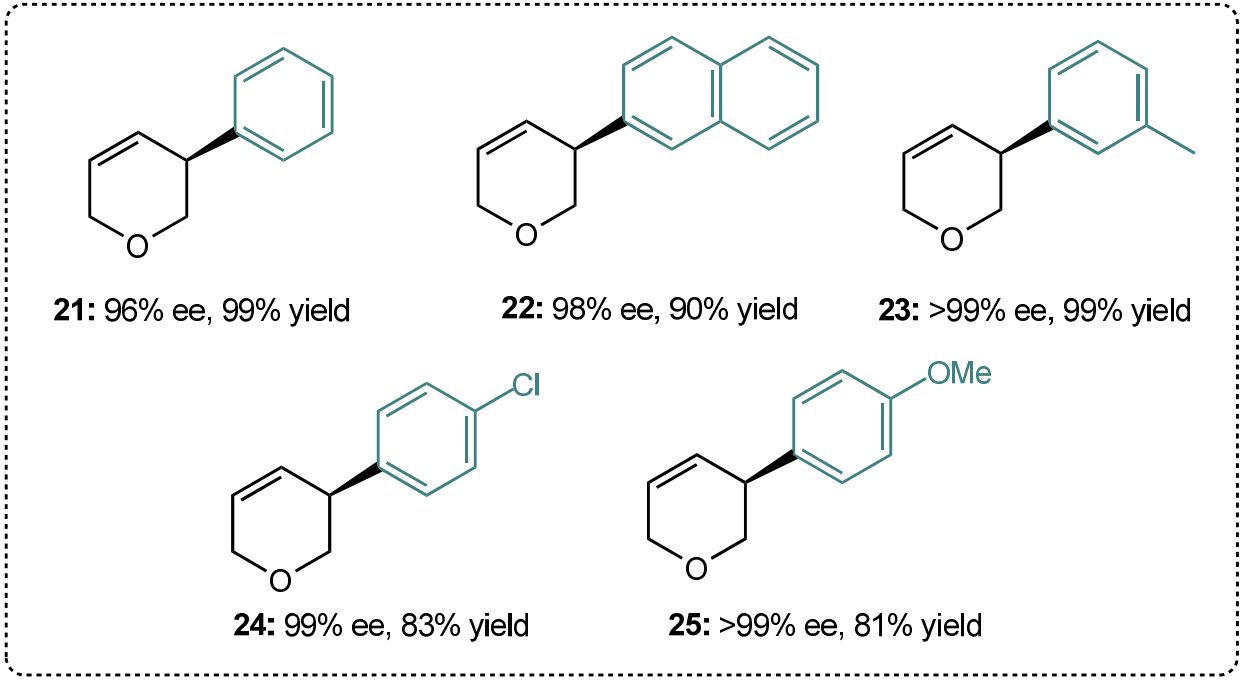
18: 92% ee, 53% yield

19: 84% ee, 61% yield

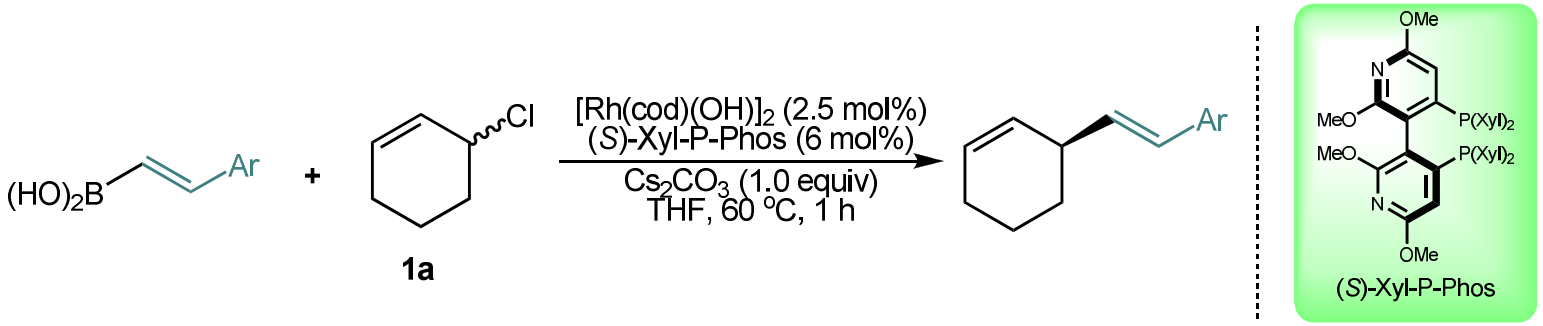
20: 99% ee, 40% yield

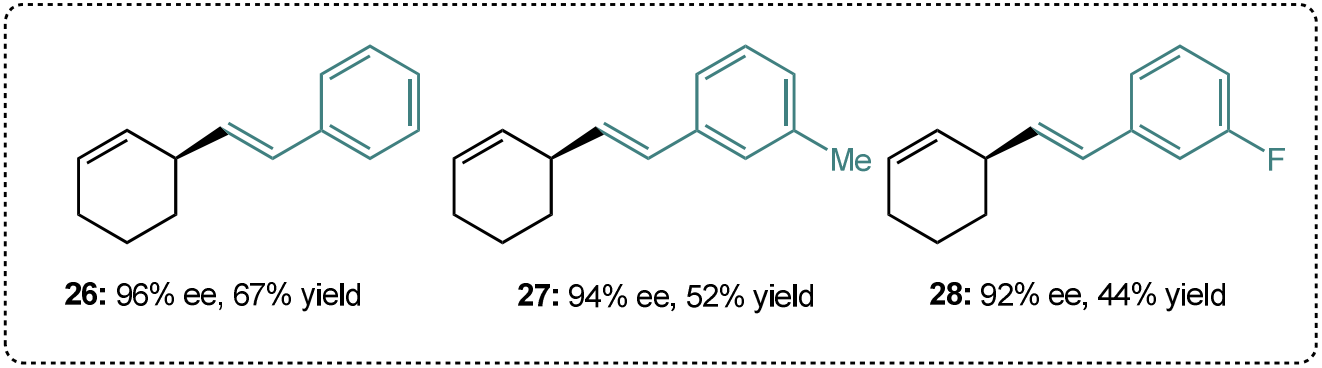
Substrate Scope



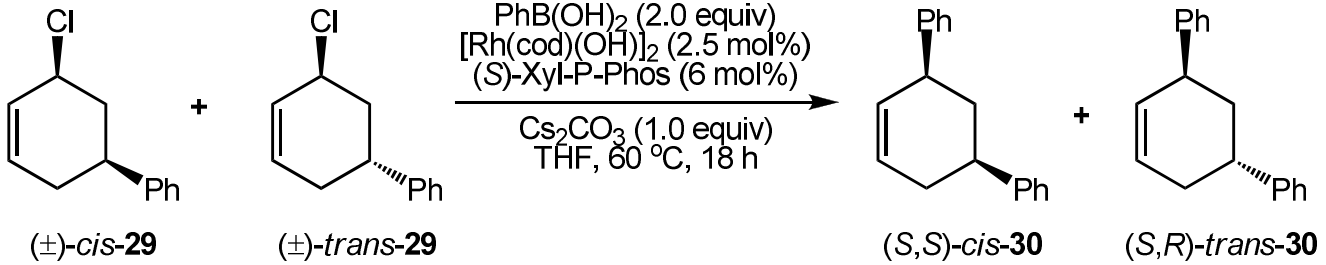


Substrate Scope





Stereoselectivity of Allylic Arylation

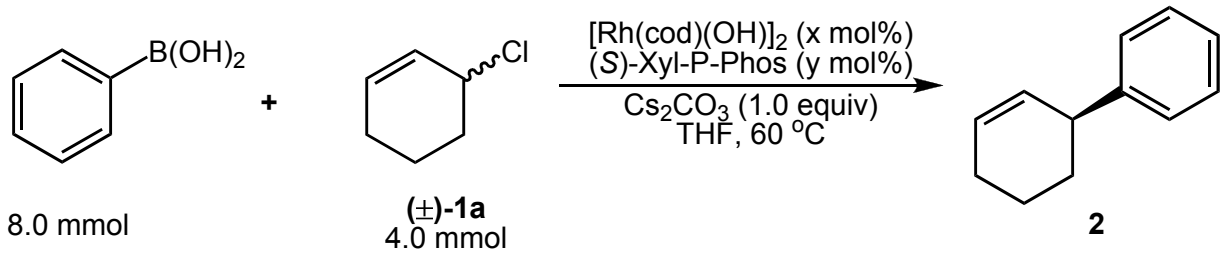


(±)-*cis*-**29** (±)-*trans*-**29** (*S*,*S*)-*cis*-**30** (*S*,*R*)-*trans*-**30**

entry	**29** *cis*:*trans*[a]	Conv. (%)	remaining **29** *cis*:*trans*[a]	**30** *cis*:*trans*[a]	*cis*-**30** ee (%)[b]	*trans*-**30** ee (%)[b]
1	1:25	100	–	25:1	>99	98
2	1:5.3	100	–	5.3:1	>99	>99
3	6.1:1	100	–	1:5.3	98	>99
4[c]	6.1:1	84	>50:1	1:4.5	97	>99

[a] Determined by ^{1}H NMR; [b] Determined by chiral HPLC; [c] Reaction stopped after three hours.

Scale-up Experiments



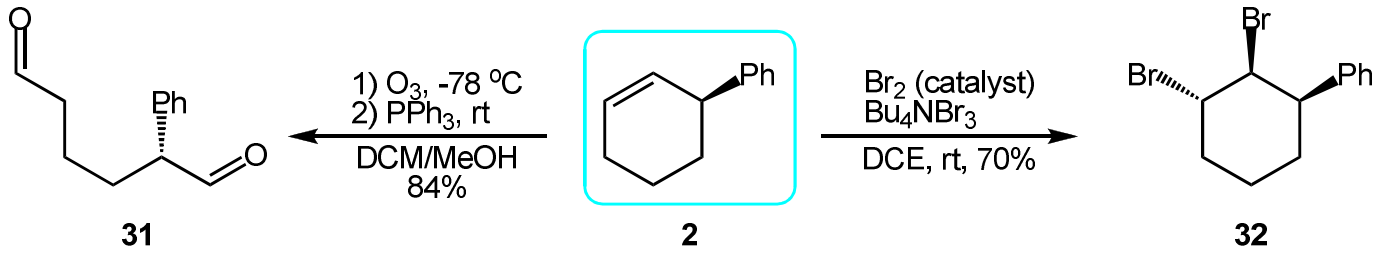
8.0 mmol

(±)-1a
4.0 mmol

2

Entry	x (mol%)	y (mol%)	Time (h)	yield (%)	ee (%)
1	1.25	3.0	1	96	>99
2	0.5	1.2	4	48	>99
3	0.25	0.6	18	–	–

Transformations of Alkene into Valuable Building Blocks

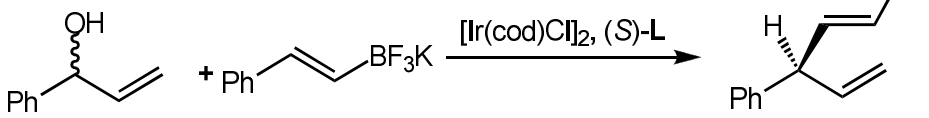


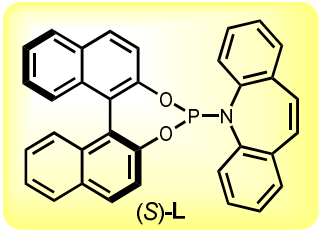
31 **2** **32**

25 **33**

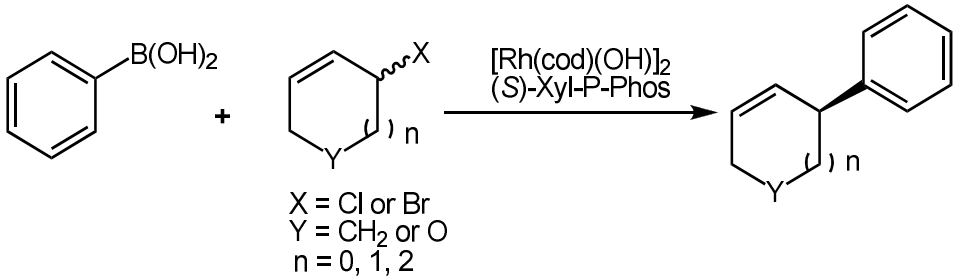
Summary

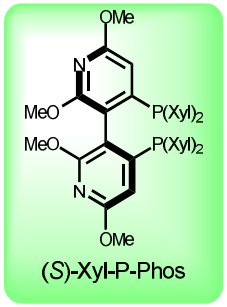
Carreira's work





Fletcher's work





One of the most widely used approaches to C-C bond formation in the fine-chemical, pharmaceutical and agrochemical industries, as well as in the synthesis of organic materials, is sp^2–sp^2 cross-coupling. In particular, the Suzuki–Miyaura reaction is robust, convenient and widely used in the synthesis of lead compounds for the development of new medicines, as it is well-suited to producing libraries of compounds. The Suzuki–Miyaura reaction uses aryl-boronic acid reagents, which are relatively stable in air and readily available. The generally favourable reactivity profile and high atom economy of boronic acids makes them highly desirable reaction partners in synthetic and medicinal chemistry, particularly when compared with alternative sp^2-hybridized organo-metallic reagents used in C–C bond-forming reactions.

To summarize, we have developed a novel dynamic kinetic asymmetric allylic arylation of racemic allylic halides using boronic acid nucleophiles and Rh catalysts. The mild and robust reaction conditions allow the use of a variety of different nucleophiles and electrophiles, and the reaction can be easily scaled up to 4.0 mmol with the catalyst loading decreasing to 1 mol% Rh. It is anticipated that this reaction will serve as the basis for the development of a broadly useful asymmetric variant of Suzuki–Miyaura coupling and that this approach will eventually allow the preparation of a wide variety of versatile building blocks for synthesis, medicinal and materials chemistry.