Literature Report IV

Palladium-Catalyzed Decarboxylative Allylic Alkylation of Acyclic Fully Substituted Enolates

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Checker：Han Wang

Date：2018-11-5

Marek, I. *et al. J. Am. Chem. Soc.* **2017**, *139*, 9615
Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 10109

Contents

CV of Brian M. Stoltz

Brian M. Stoltz

Education:

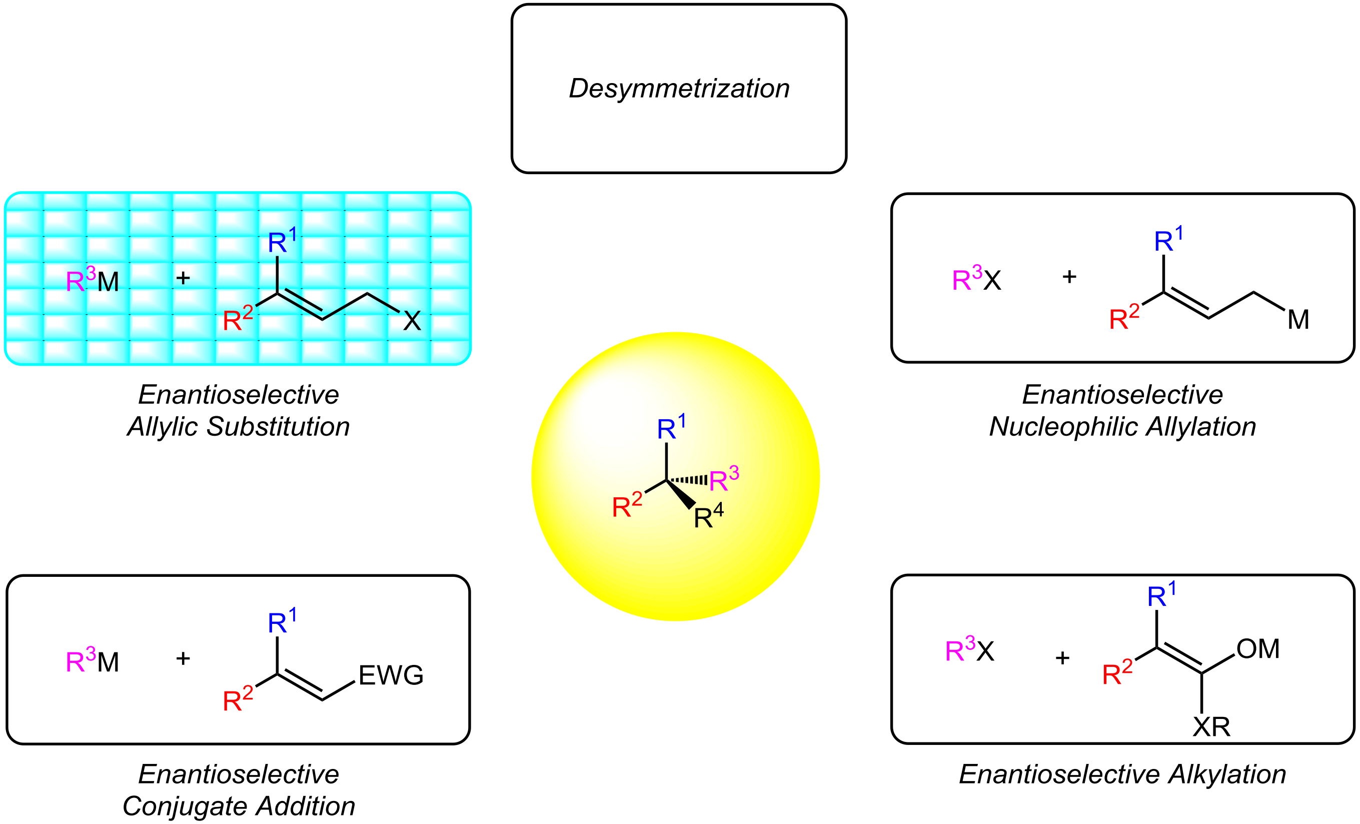
- **1989–1993** B.S., Indiana University of Pennsylvania
- **1993–1996** M.S., Yale University (John L. Wood)
- **1996–1997** Ph.D., Yale University (John L. Wood)
- **1998–2000** NIH Postdoctoral Fellow, Harvard University (Elias J. Corey)
- **2000–2006** Assistant professor, California Institute of Technology
- **2006–now** Professor, California Institute of Technology

Research:

- Developing new methodology for synthetic chemistry, such as oxidative kinetic resolution, enantioselective allylic alkylation and aerobic oxidative annulation etc;
- Designing new strategies for the preparation of complex molecules, such as Cyanthiwigin F and Aspewentins A, B, C etc.

Introduction

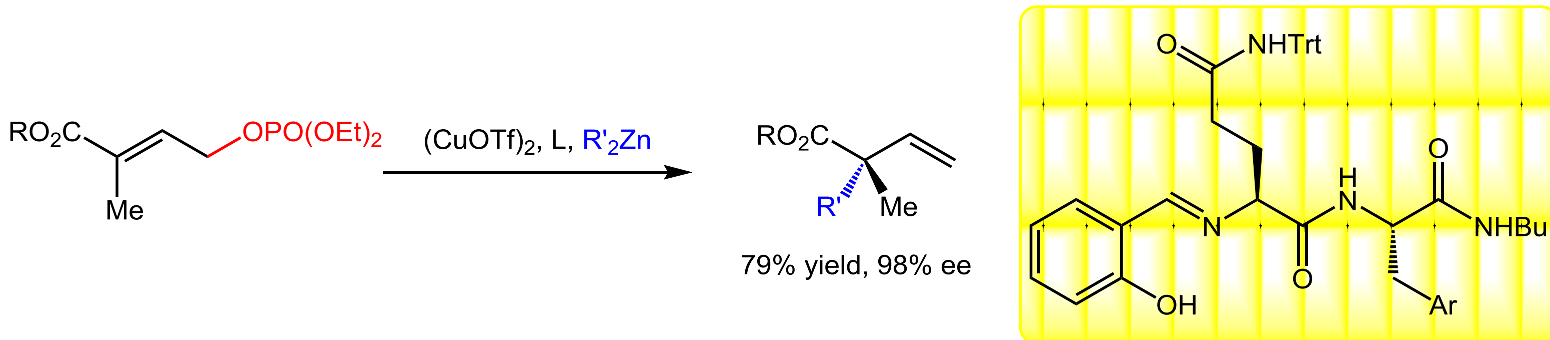
Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems



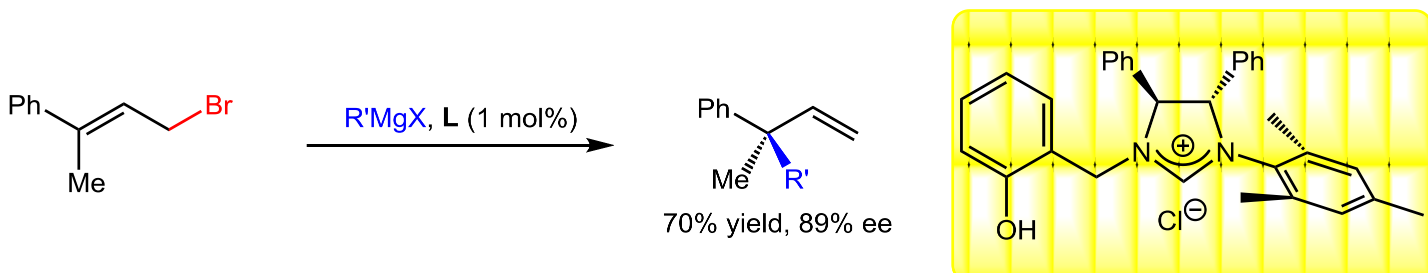
Marek, I. *et al. Chem. Commun.* **2011**, *47*, 4593

Introduction

Enantioselective allylic substitution



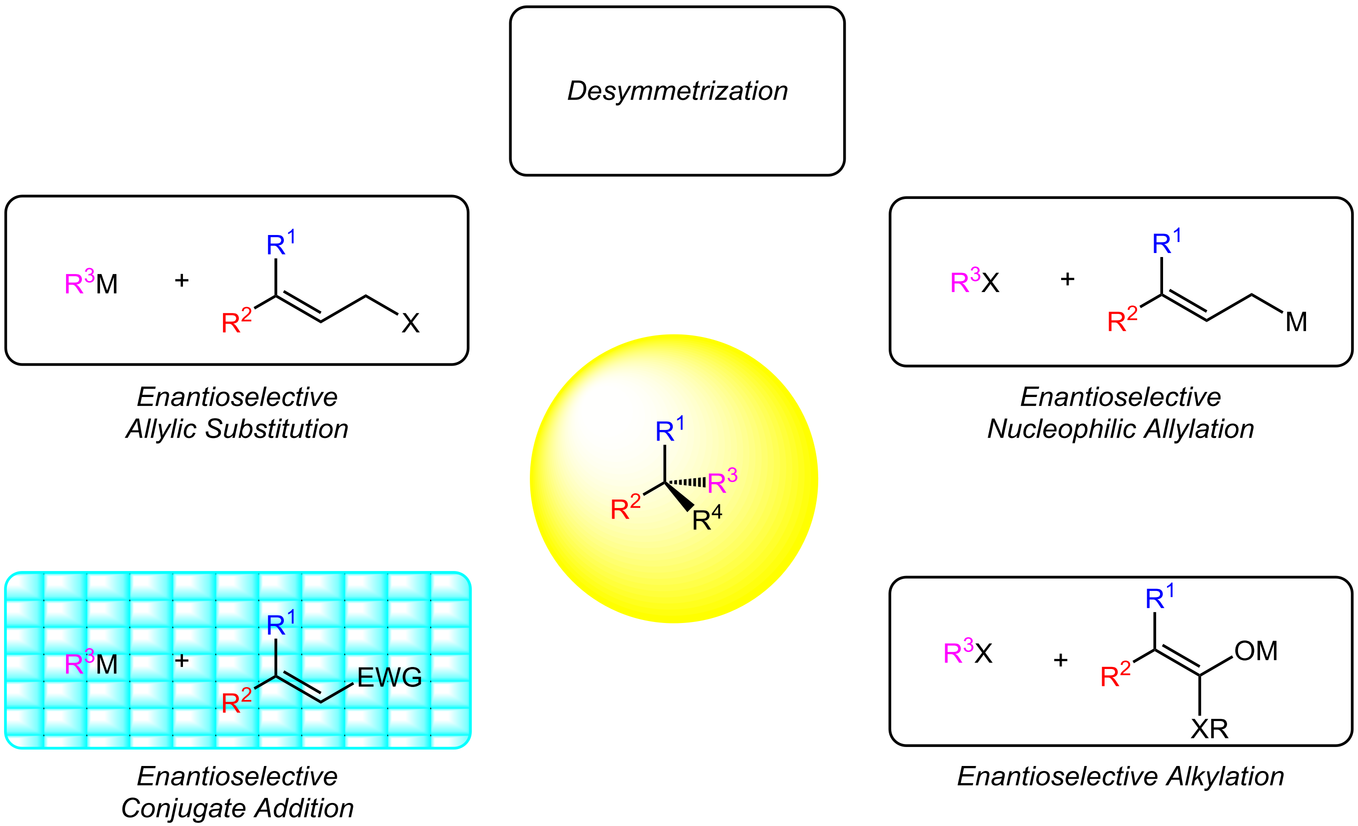
Hoveyda, A. H. *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 1456



Alexakis, A. *et al. Angew. Chem., Int. Ed.* **2010**, *49*, 3346

Introduction

Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems



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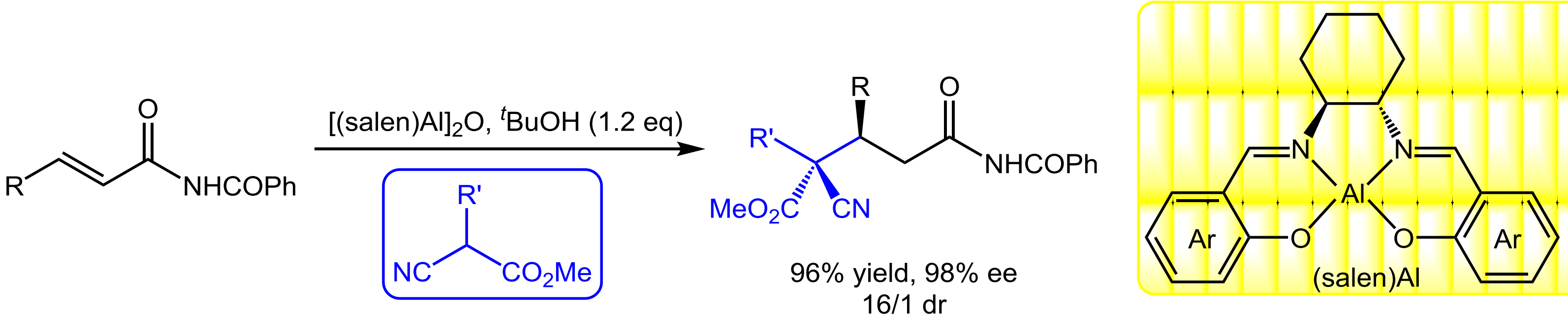
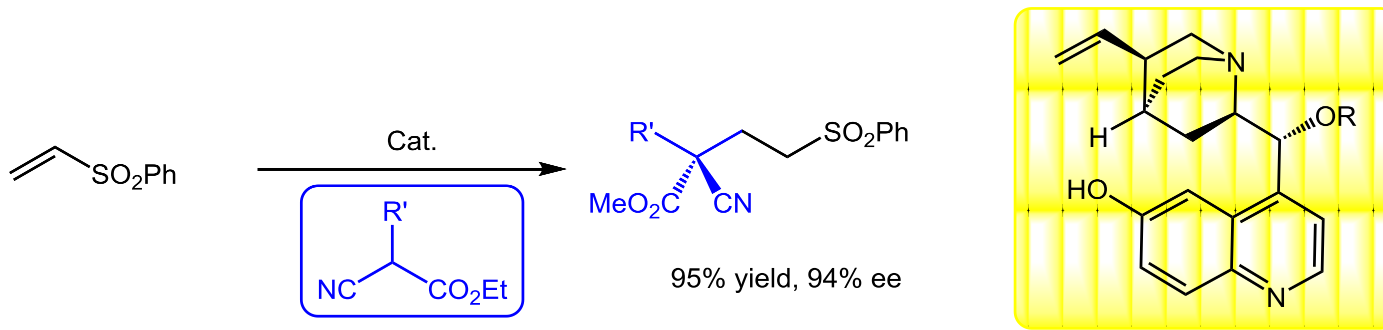
Introduction

Enantioselective conjugate addition



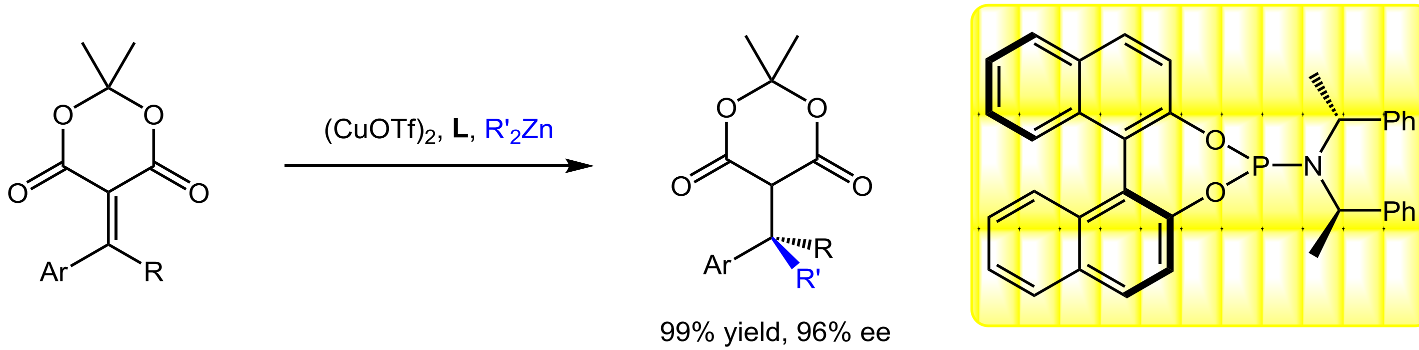
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2003**, *125*, 11204



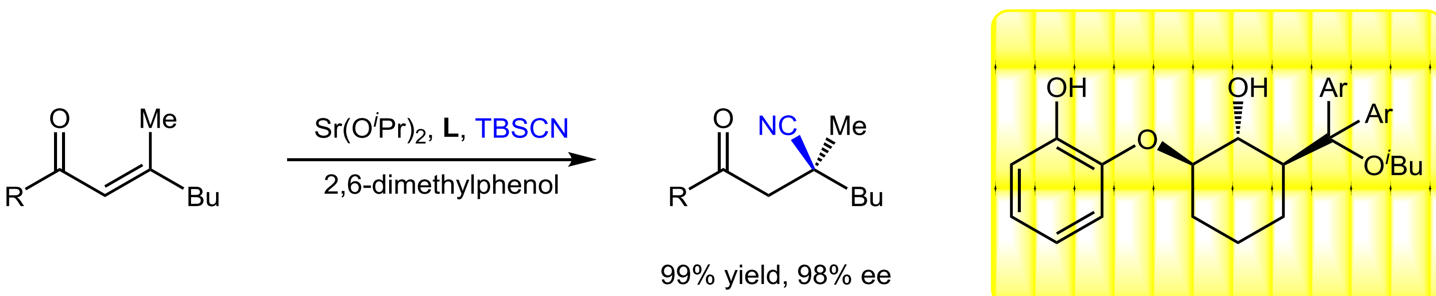
Deng, L. *et al. J. Am. Chem. Soc.* **2005**, *127*, 8949

Introduction

Enantioselective conjugate addition



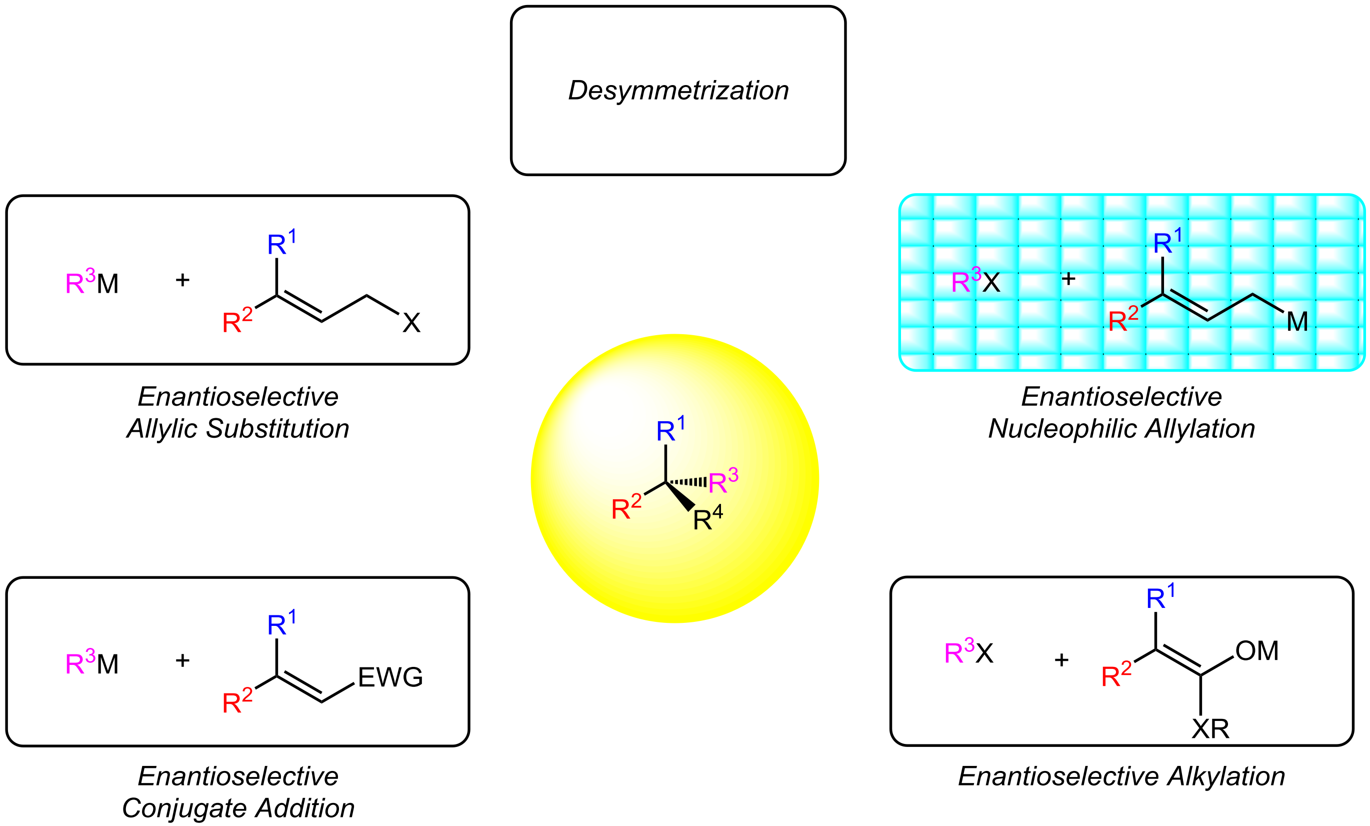
Fillion, E. *et al. Org. Lett.* **2008**, *10*, 2801



Shibasaki, M. *et al. J. Am. Chem. Soc.* **2010**, *132*, 8862

Introduction

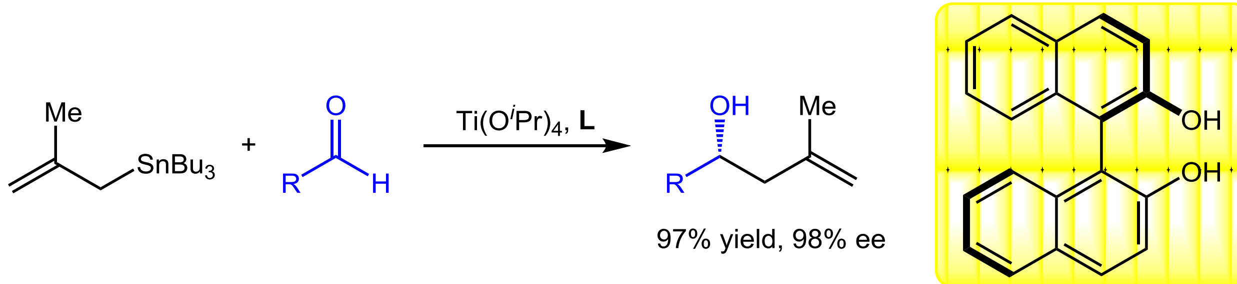
Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems



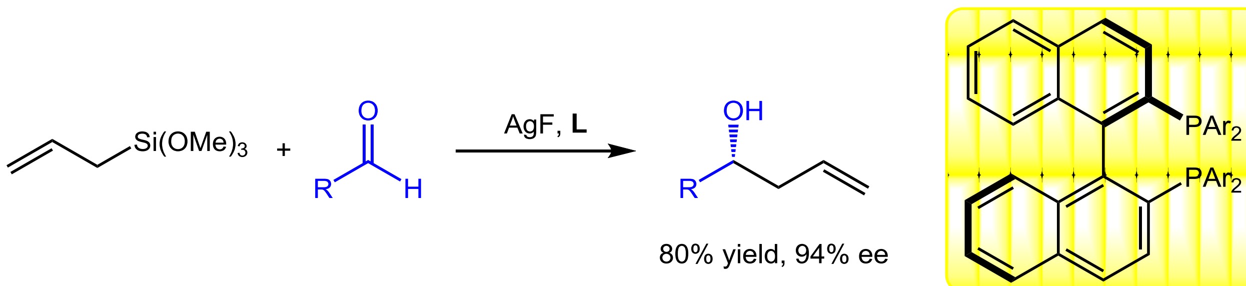
Marek, I. *et al. Chem. Commun.* **2011**, *47*, 4593

Introduction

Enantioselective nucleophilic allylation



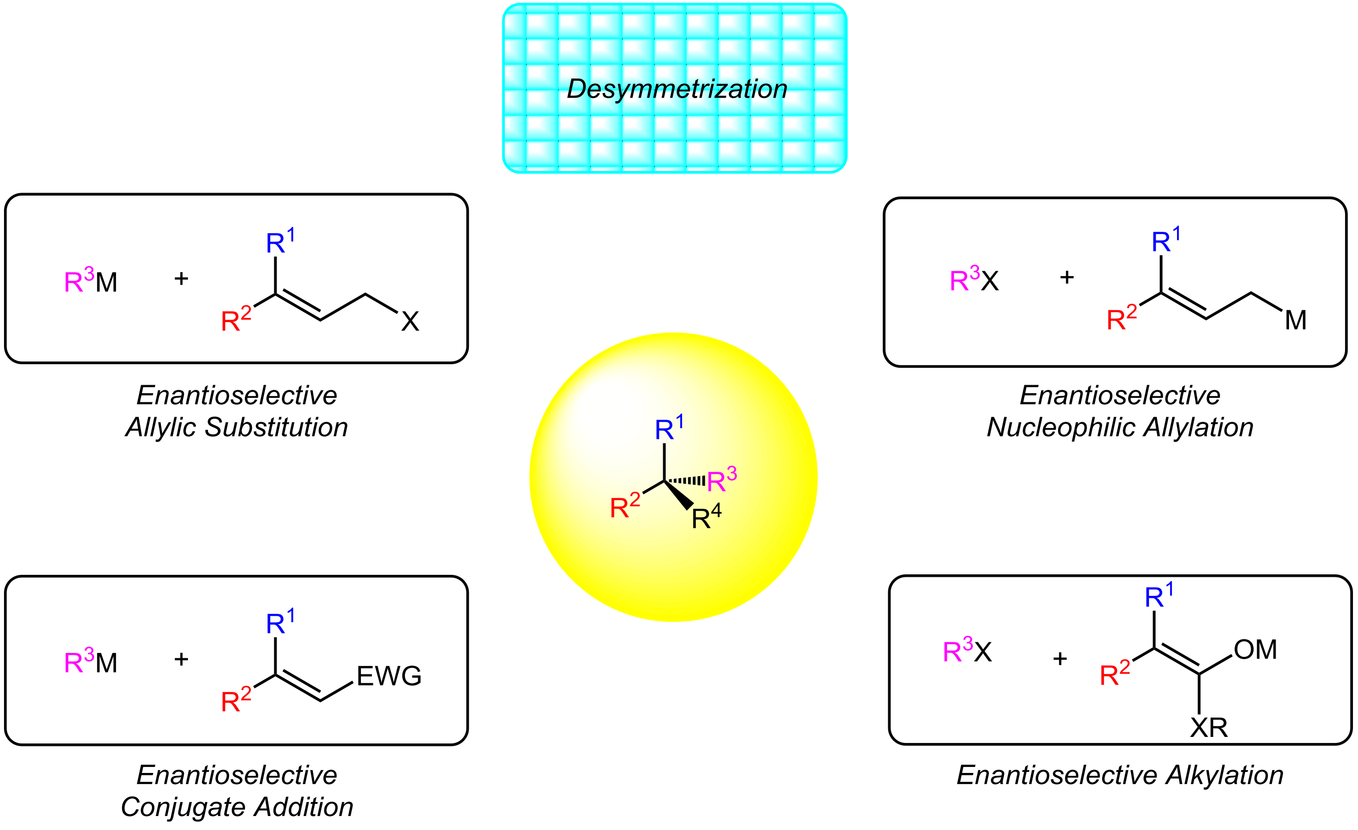
Grier, M. C. *et al. J. Org. Chem.* **1993**, *58*, 6543



Yamamoto, H. *et al. Angew. Chem., Int. Ed.* **1999**, *38*, 3701

Introduction

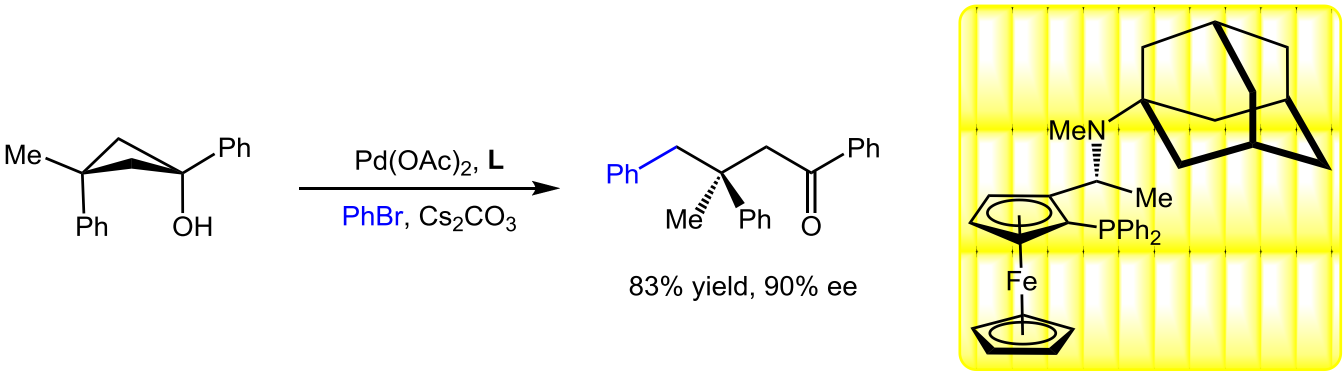
Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems



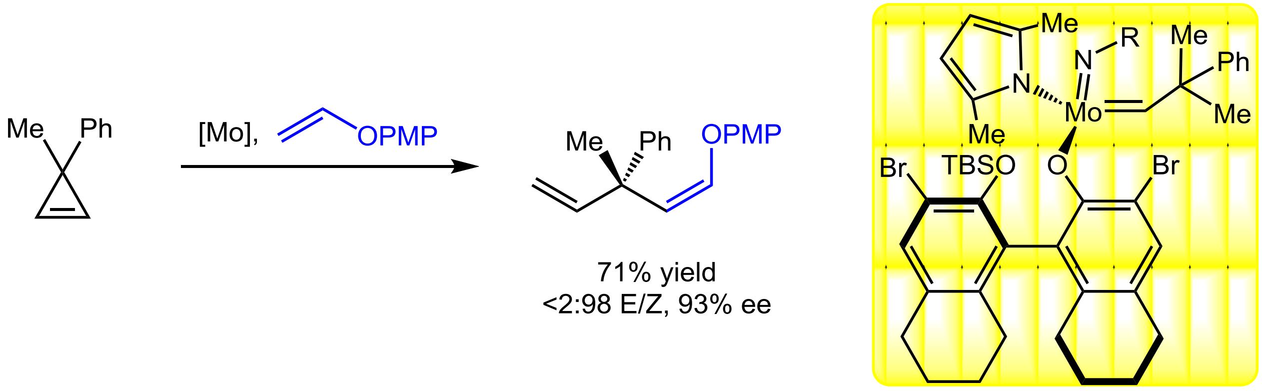
Marek, I. *et al. Chem. Commun.* **2011**, *47*, 4593

Introduction

Desymmetrization



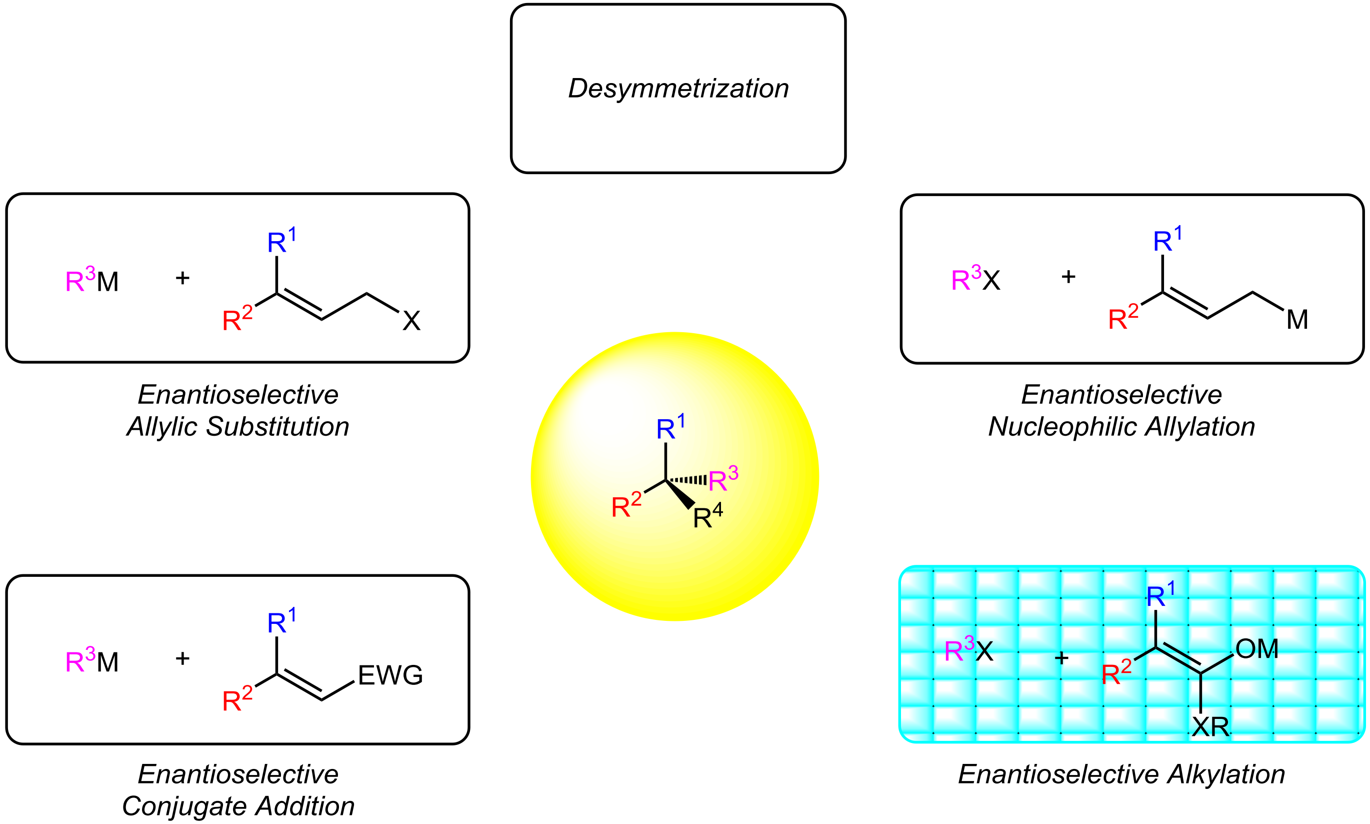
Uemura, S. *et al. J. Am. Chem. Soc.* **2003**, *125*, 8862



Hoveyda, A. H. *et al. J. Am. Chem. Soc.* **2012**, *134*, 2788

Introduction

Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems



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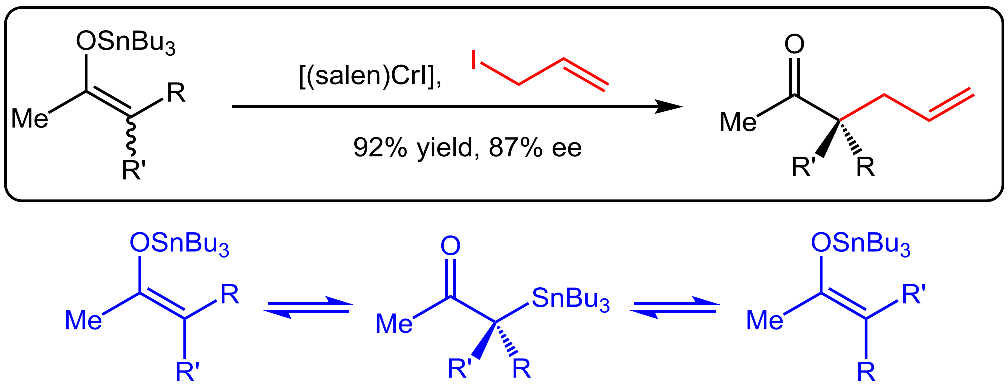
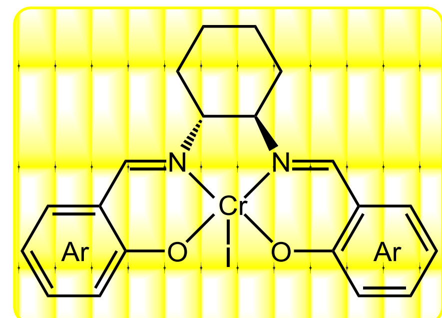
Introduction

Enantioselective alkylation

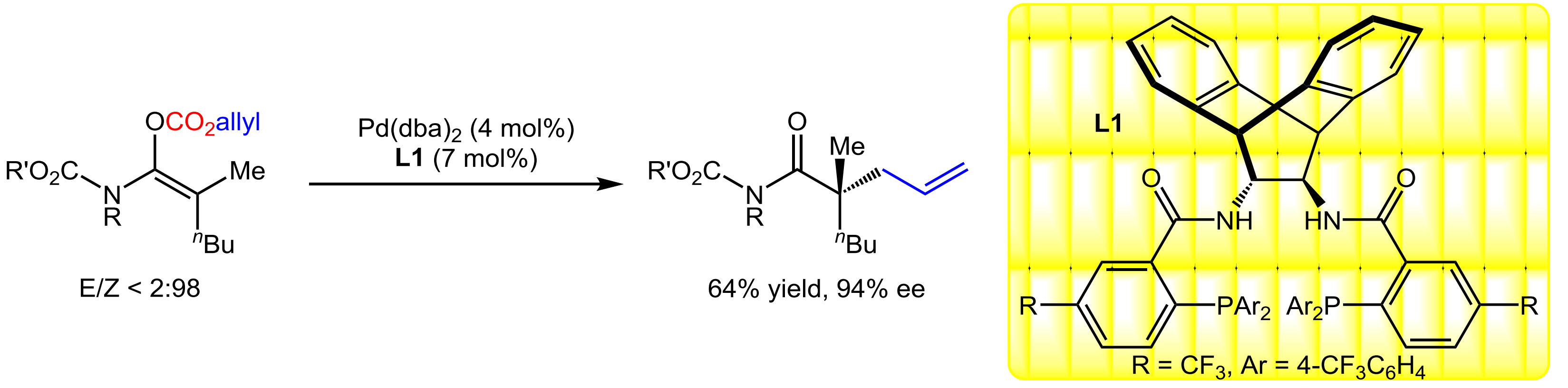




Jacobsen, E. N. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 3701

Introduction

Enantioselective alkylation



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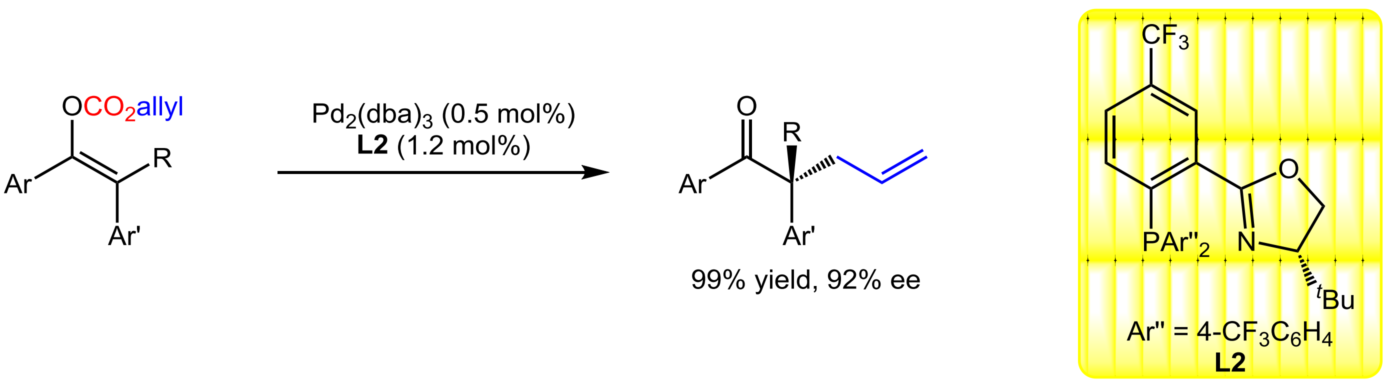
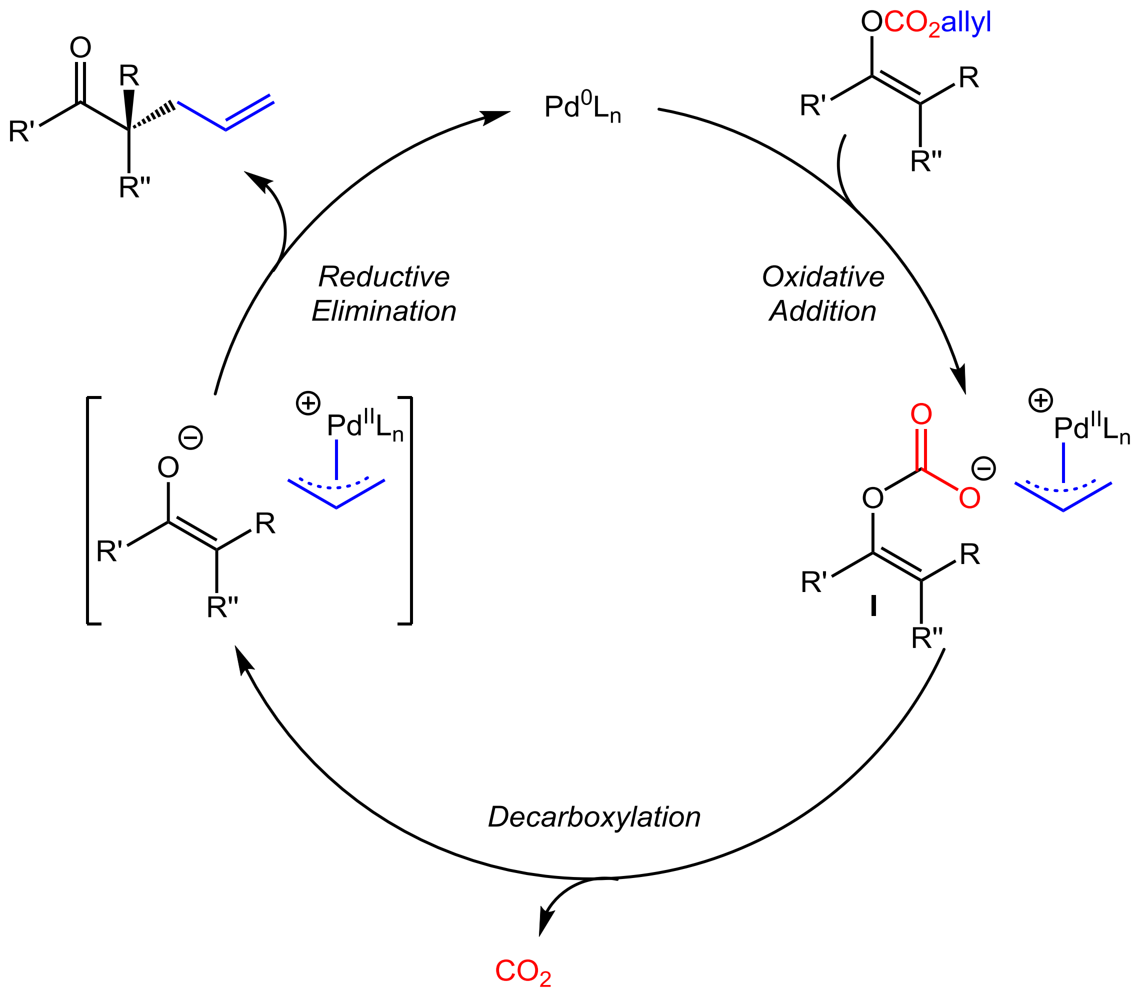


Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 10109

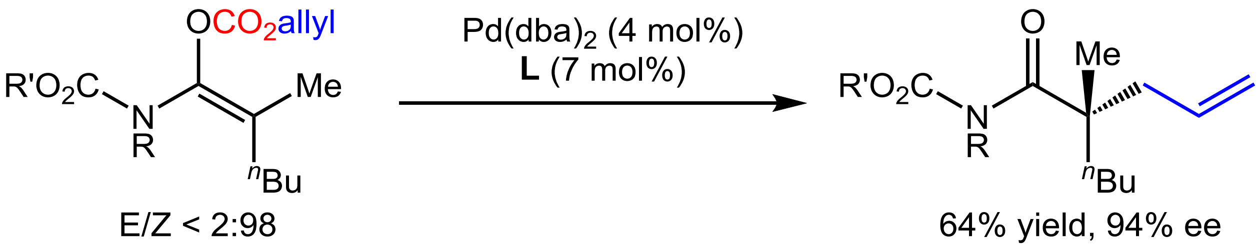
Mechanism

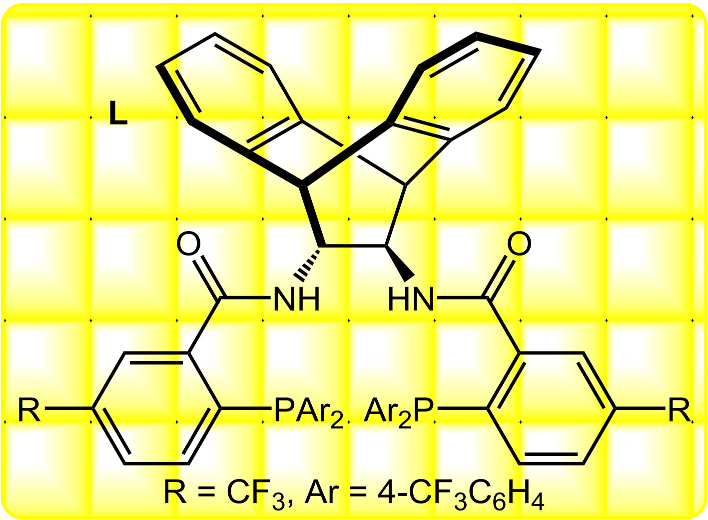


Trost, B. M. *et al. J. Am. Chem. Soc.* **2009**, *131*, 18343

DAA of Amide Enolates

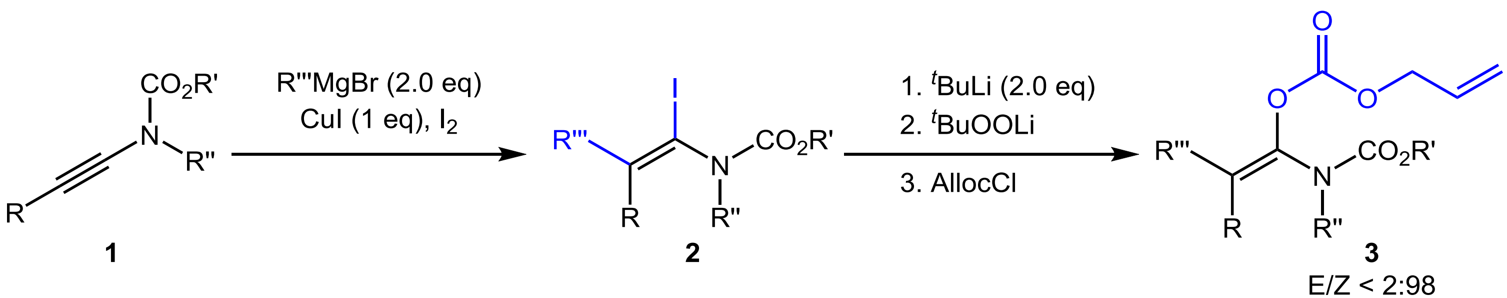
Pd-catalyzed allylic alkylation



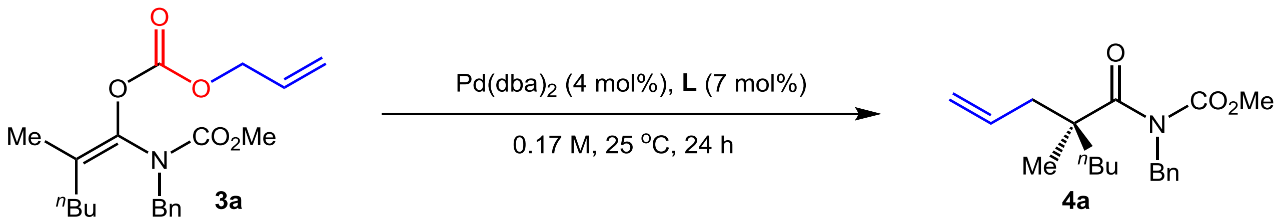


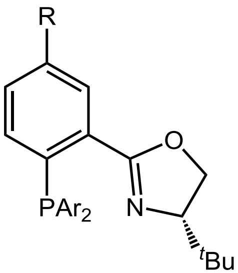
Marek, I. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 9615

Preparation of Stereodefined Substrates

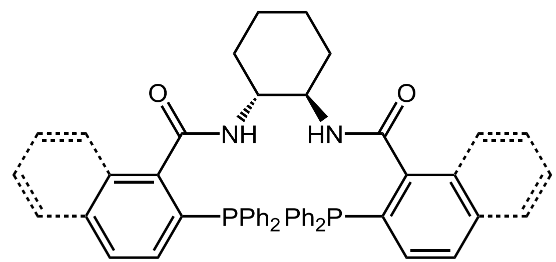


Optimization of DAA

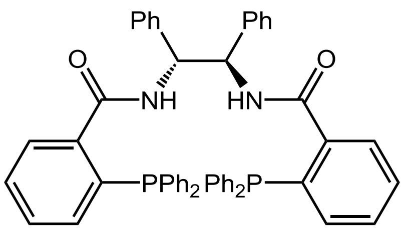




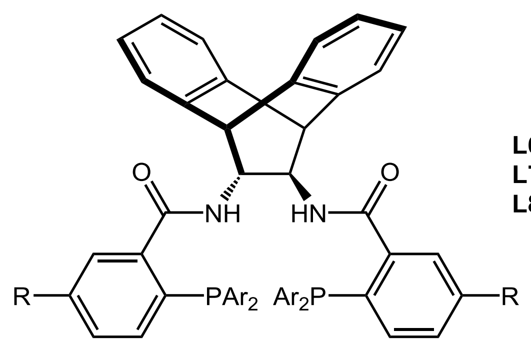
L1 R = H, Ar = Ph
L2 R = CF_3, Ar = 4-$CF_3C_6H_4$



L3 Phenyl
L4 Naphthyl

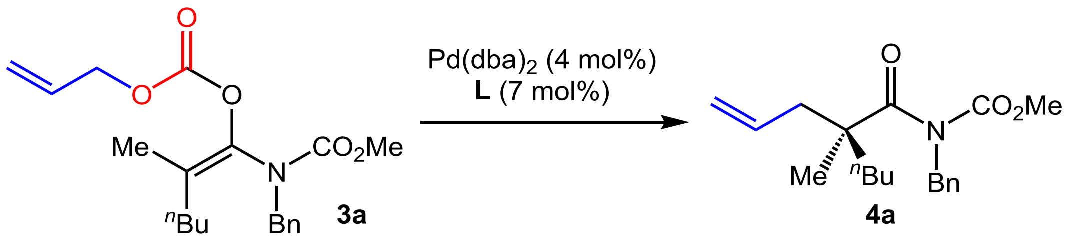


L5



L6 R = H, Ar = Ph
L7 R = CF_3, Ar = 4-$CF_3C_6H_4$
L8 R = H, Ar = 2-$CH_3C_6H_4$

Optimization of DAA

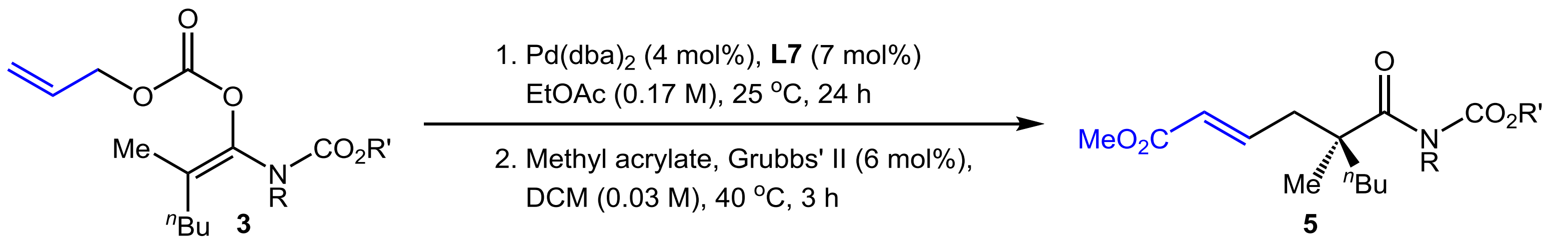


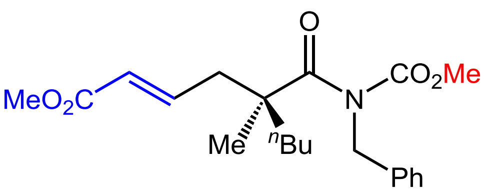
3a → **4a**

Entry[a]	L	Solvent	Ee [%][b]
1	**L1**	THF	4
2	**L2**	THF	24
3	**L3**	THF	-72
4	**L4**	THF	-74
5	**L5**	THF	60
6	**L5**	EtOAc	68
7	**L6**	THF	-85
8	**L6**	EtOAc	-84
9	**L7**	THF	-85
10	**L7**	EtOAc	-94
11	**L8**	THF	NR

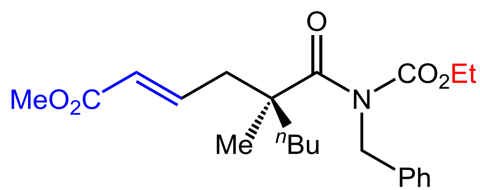
[a] Conditions: polysubstituted amide (1.0 eq), Pd(dba)$_2$ (5 mol%), **L** (7 mol%) in solvent (0.17 M) at 25 ^{o}C for 24 h in glovebox. [b] Determined by chiral SFC.

Substrate Scope

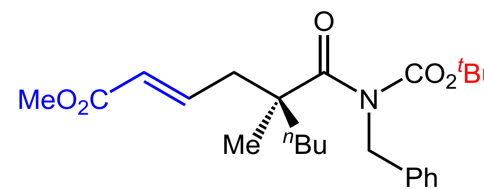




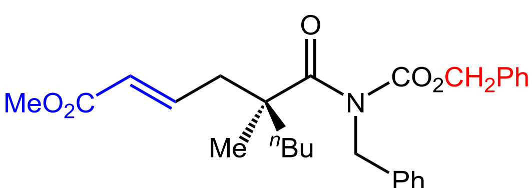
5a
85% and 80% yield
68% yield (2 steps)
94% ee



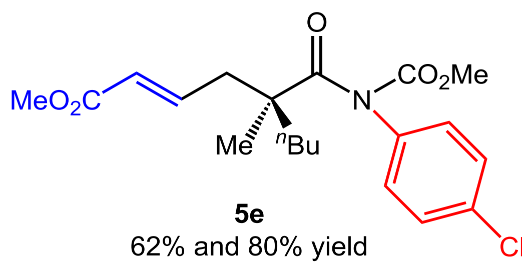
5b
62% and 85% yield
53% yield (2 steps)
94% ee



5c
88% and 79% yield
70% yield (2 steps)
90% ee

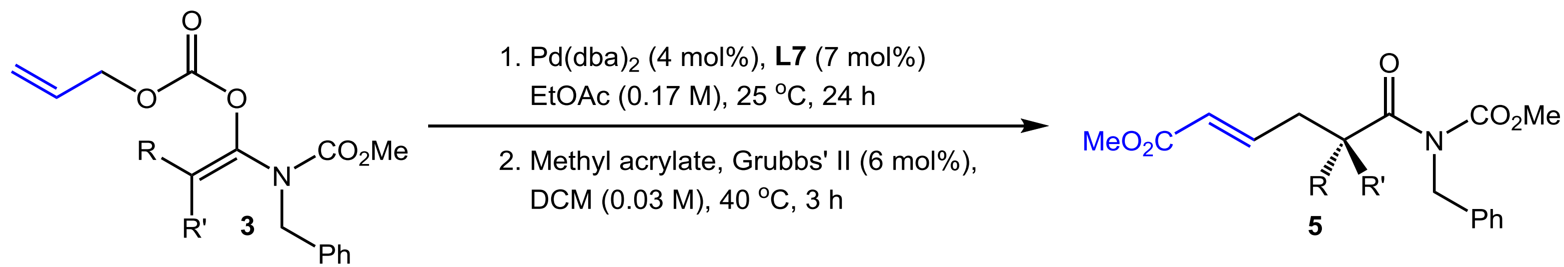


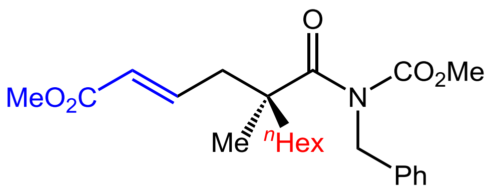
5d
53% and 76% yield
40% yield (2 steps)
94% ee



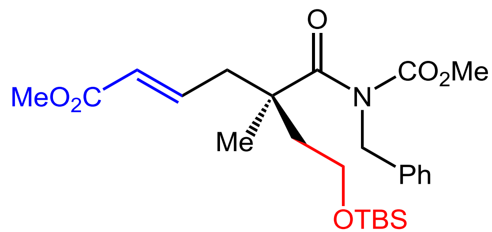
5e
62% and 80% yield
50% yield (2 steps)
90% ee

Substrate Scope

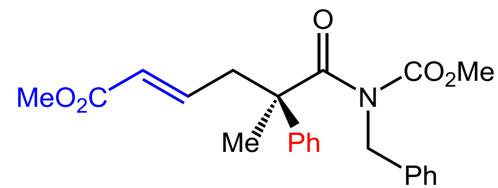




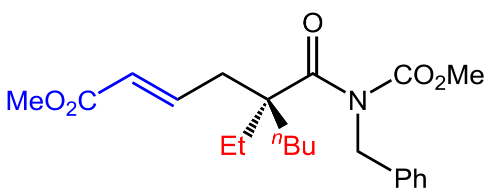
5f
69% and 84% yield
58% yield (2 steps)
94% ee



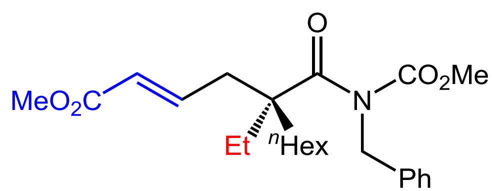
5g
76% and 79% yield
60% yield (2 steps)
94% ee



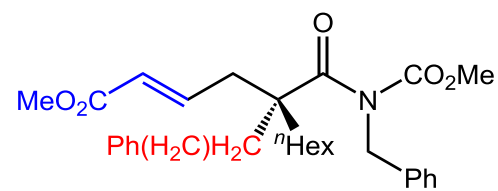
5h
77% and 78% yield
60% yield (2 steps)
76% ee



5i
76% and 85% yield
65% yield (2 steps)
82% ee

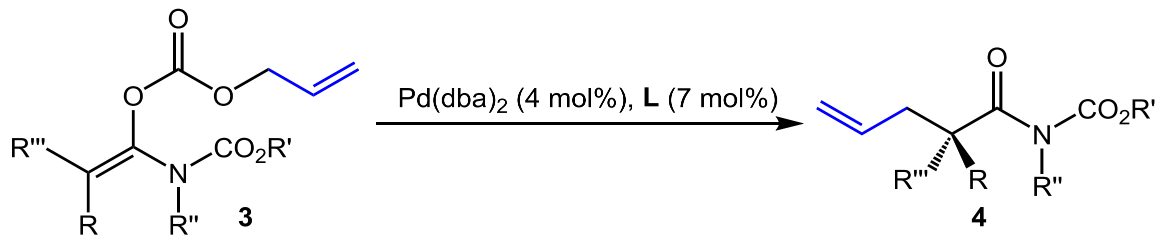


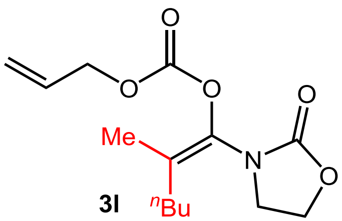
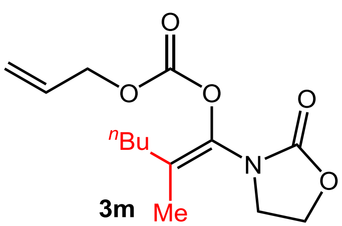
5j
64% and 85% yield
54% yield (2 steps)
94% ee



5k
56% and 84% yield
47% yield (2 steps)
76% ee

Mechanism Studies



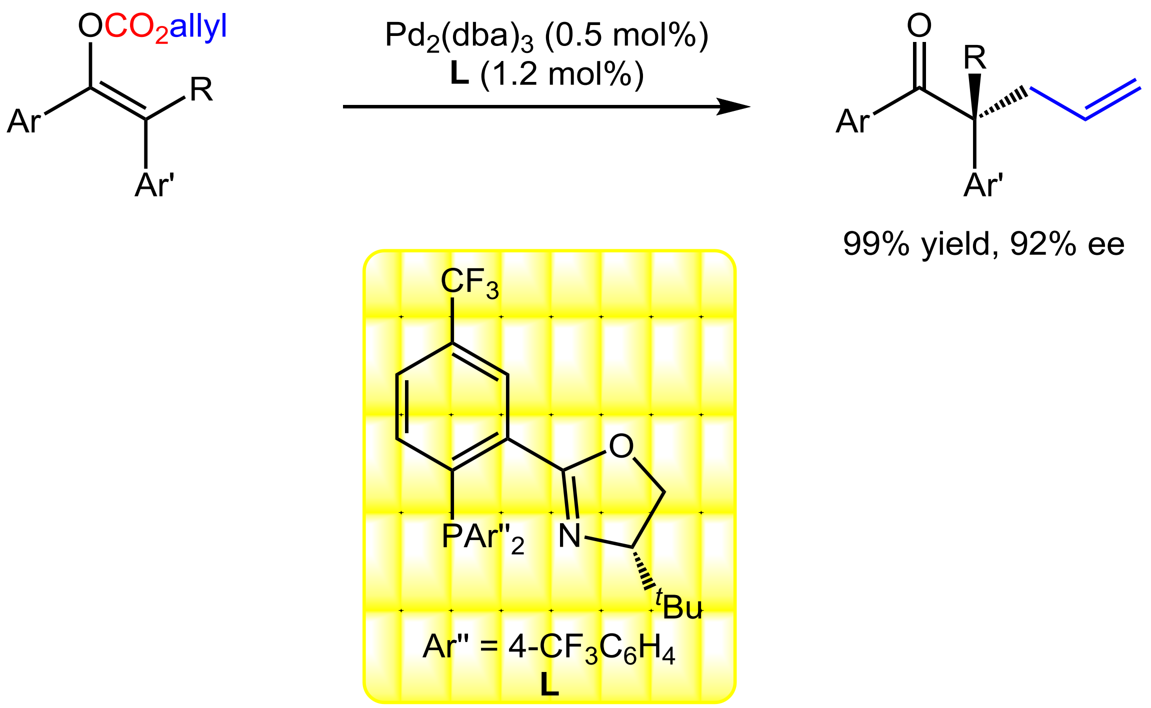
Entry[a]	Substrate	L	Ee [%][b]
1	 **3l**	**L5**	**-70**
2		**L6**	**70**
3	 **3m**	**L5**	**47**
4		**L6**	**-30**

[a] Conditions: polysubstituted amide (1.0 eq), Pd(dba)$_2$ (4 mol%), **L** (7 mol%) in THF (0.17 M) at 25 ^{o}C for 24 h in glovebox. [b] Determined by chiral SFC.

These observations suggest that the enolate geometry is likely conserved through the course of the reaction and that the highest enantioselectivities are obtained when the smallest substituent is syn to the allyloxycarbonyl group.

DAA of Enol Carbonates

Pd-catalyzed allylic alkylation



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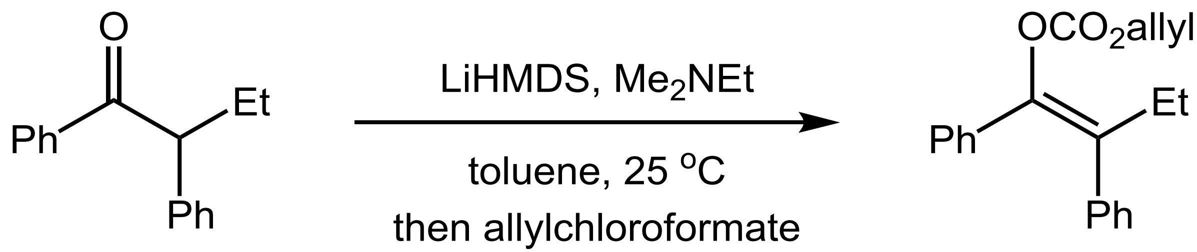
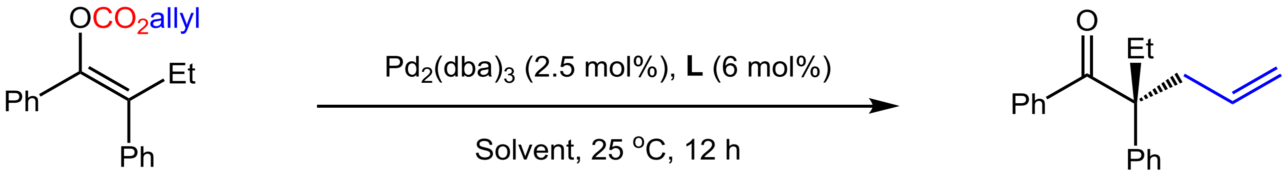
Preparation of Stereodefined Substrates



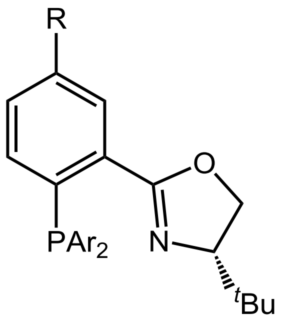
95% yield
>98:2 E/Z

Optimization of DAA

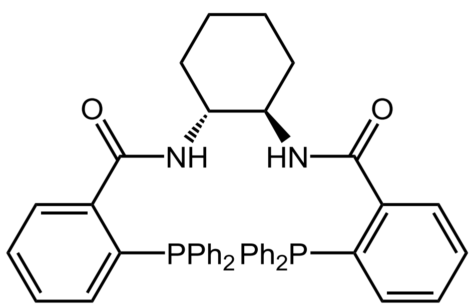


1 >98:2 E/Z

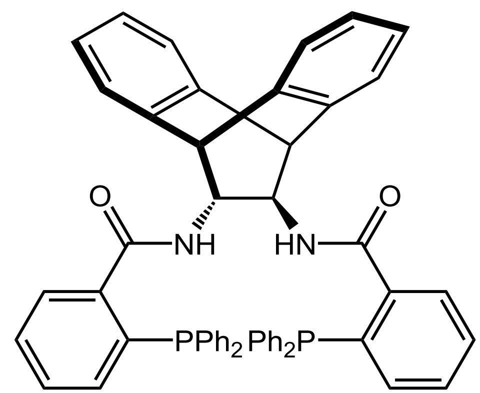
2a



L1 R = H, Ar = Ph
L2 R = CF_3, Ar = 4-$CF_3C_6H_4$

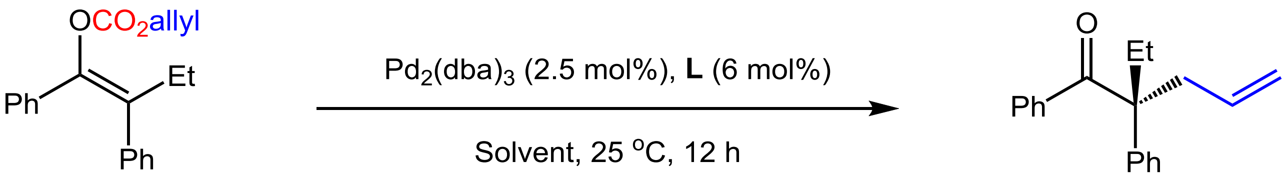


L3



L4

Optimization of DAA



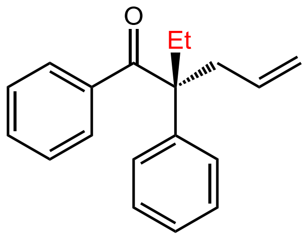
1 >98:2 E/Z

2a

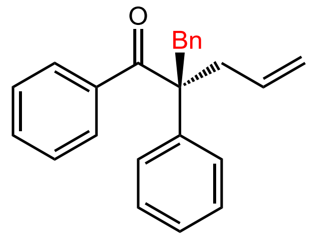
Entry[a]	L	Solvent	Yield[%][b]	Ee [%][c]
1	**L1**	THF	--	6
2	**L2**	THF	--	54
3	**L3**	THF	--	-45
4	**L4**	THF	42	-73
5	**L2**	MeCy	83	89
6	**L2**	3:1 hexane/PhMe	90	89
7	**L4**	3:1 hexane/PhMe	89	-86
8	**L2**	3:1 hexane/PhMe	98	90
9[e]	**L2**	3:1 hexane/PhMe	97	91

[a] Conditions: **1** (0.1 mmol), $Pd_2(dba)_3$ (2.5 mol%), **L** (6 mol%), solvent (1.0 mL). [b] Yield of isolated product. [c] Determined by chiral SFC. [e] **1** (0.2 mmol), $Pd_2(dba)_3$ (0.5 mol%), **L** (1.2 mol%), solvent (2.0 mL).

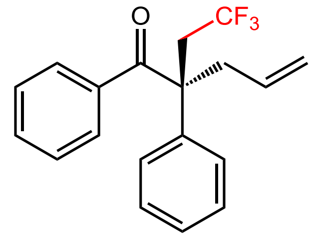
Substrate Scope



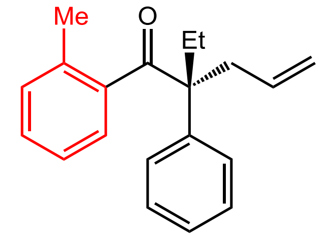
2a
97% yield, 91% ee



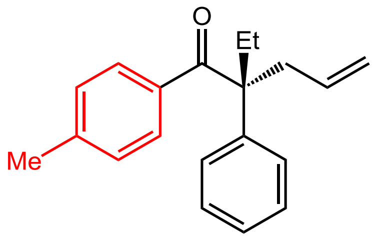
2b
99% yield, 76% ee



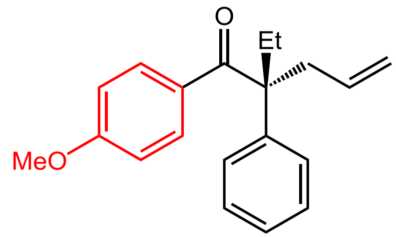
2c
90% yield, 86% ee



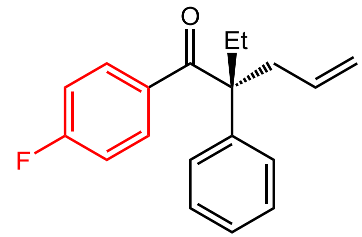
2d
95% yield, 72% ee



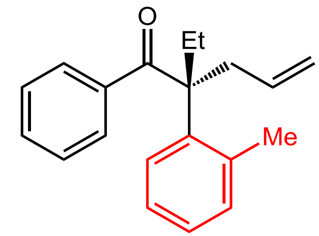
2e
99% yield, 92% ee



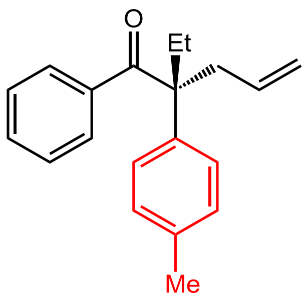
2f
99% yield, 92% ee



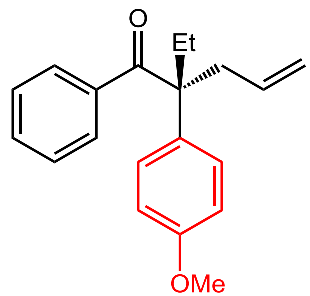
2g
96% yield, 91% ee



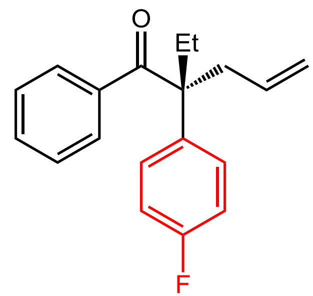
2h
99% yield, 90% ee



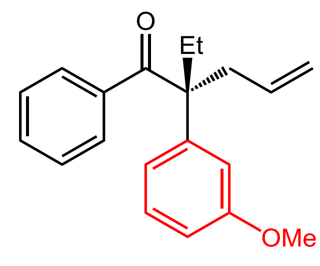
2i
96% yield, 91% ee



2j
99% yield, 92% ee

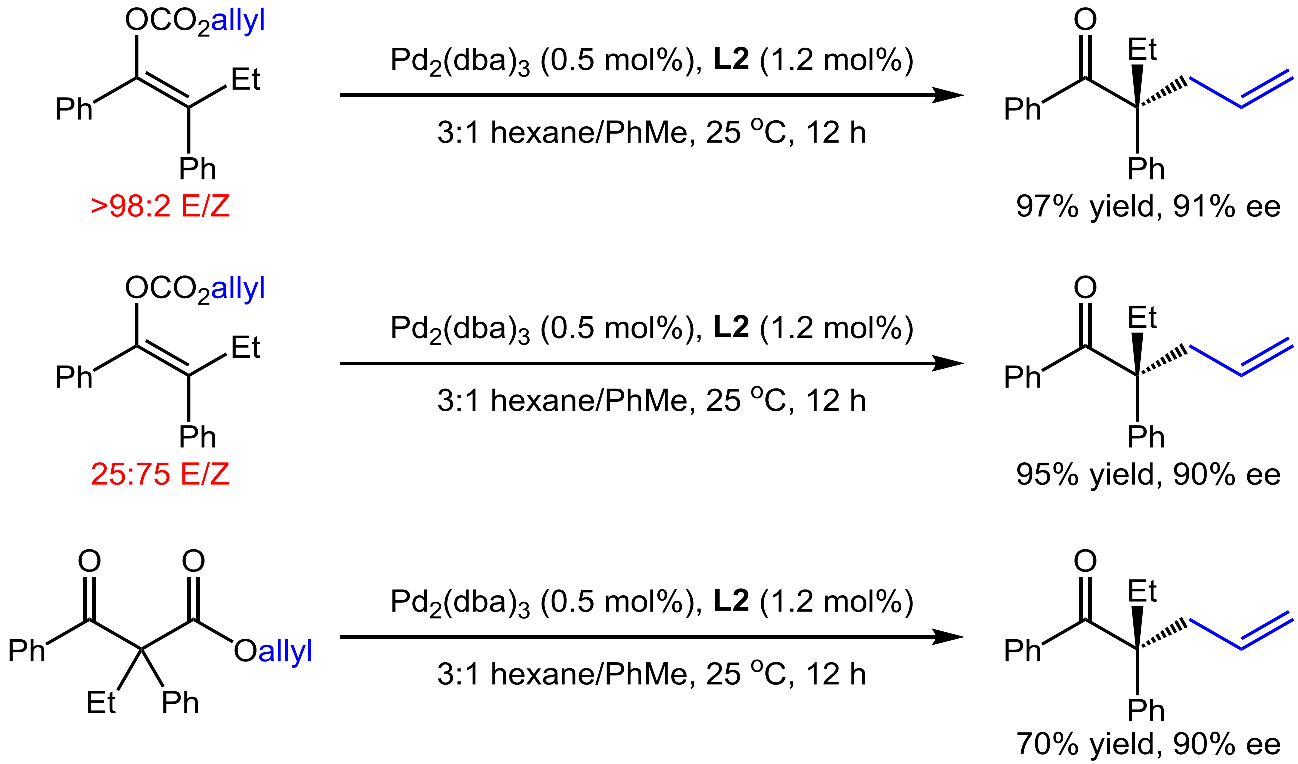


2k
98% yield, 90% ee



2l
95% yield, 90% ee

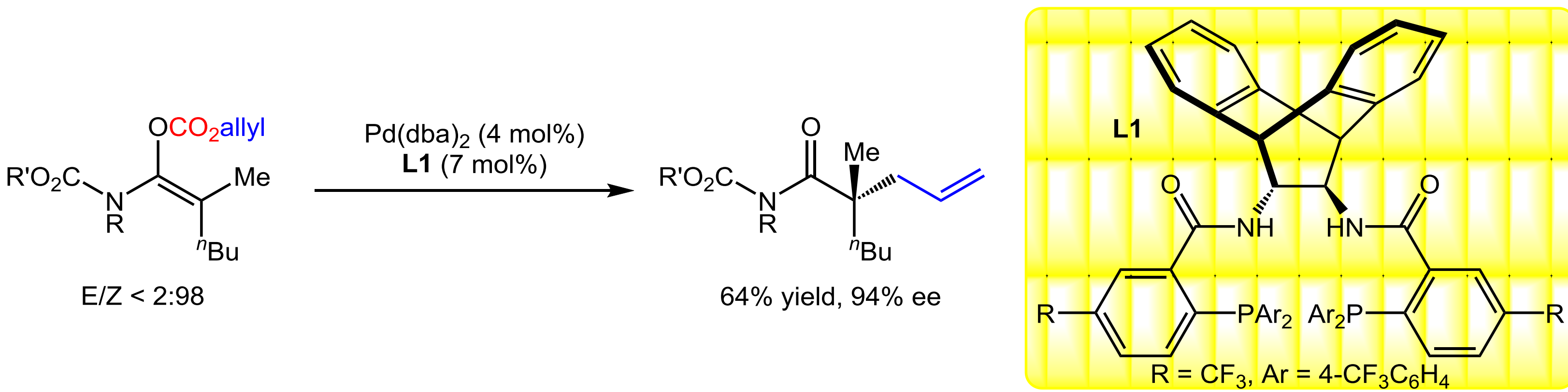
Mechanism Studies



we postulate that a dynamic kinetic resolution of the two enolate geometries occurs in the reaction when **L2** is used as the ligand, possibly due to facile equilibration between O-bound and C-bound palladium enolates.

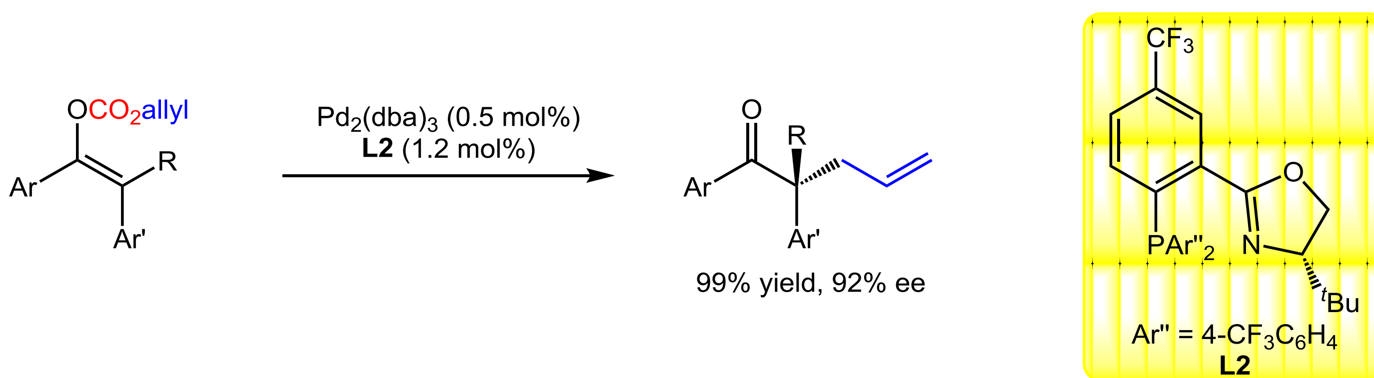
Summary

Decarboxylative Allylic Alkylation of Amide Enolates



Marek, I. *et al. J. Am. Chem. Soc.* **2017**, *139*, 9615

Decarboxylative Allylic Alkylation of Enol Carbonates



Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 10109

The First Paragraph

All-carbon quaternary stereocenters are prominent features in many natural products and can provide beneficial biochemical stability and three-dimensionality to molecules for medicinal chemistry applications. As a result, a number of methods to address their synthesis have been developed, particularly in cyclic systems. In acyclic systems, however, the synthesis of this motif is less explored. This is in part due to additional problems that often arise in acyclic systems such as reduced rigidity of particular substrates leading to lower levels of selectivity.

The First Paragraph

Additionally, selectively controlling the formation of fully substituted olefins/enolates is required for high selectivity in many catalytic processes. In the case of electrophilic functionalization of fully substituted enolates, the general and selective formation of such enolates as pure geometric isomers is highly challenging and has slowed progress. Although selective enolizations have been reported, these typically require highly specialized substrates, often incorporating chiral auxiliaries to impart selectivity in the enolate formation step.

The Last Paragraph

In conclusion, we have developed the first enantioselective palladium-catalyzed decarboxylative allylic alkylation toward the synthesis of chiral acyclic α-quaternary ketones. The use of electron-deficient phosphinooxazoline ligand is critical to achieve high yields and enantioselectivity. The allyl enol carbonate substrates could be prepared in high levels of E/Z geometrical selectivity, however a proposed dynamic kinetic enolate equilibration during the palladium catalyzed reaction allows the use of enolate mixtures and racemic β-ketoesters as substrates as well. Further exploration into the scope, mechanism, and applications of this process are underway.