Literature Report 3

Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted 1*H*-Indoles with Vinylcyclopropanes

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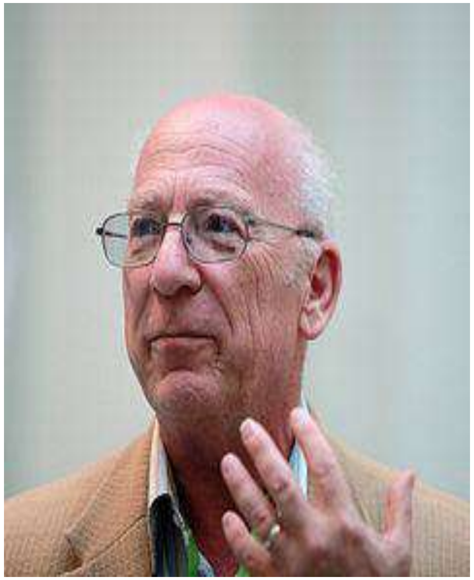
Checker: Xiao-Yong Zhai

Date: 2018-6-25

Trost, B. M.*; Bai, W.-J.; Hohn, C.; Bai, Y.; Cregg, J. J.
J. Am. Chem. Soc. **2018**, *140,* 6710-6717.

CV of Prof. Trost, B. M.



Background:

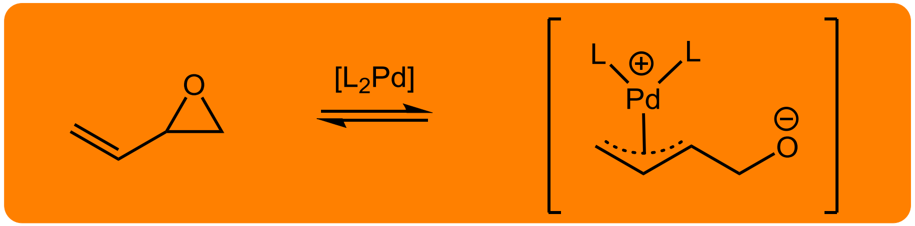
- **1962** B.S., University of Pennsylvania
- **1962-1965** Ph.D., Massachusetts Institute of Technology
- **1965-1968** Assistant Professor, University of Wisconsin
- **1968-1969** Associate Professor, University of Wisconsin
- **1969-1987** Professor, University of Wisconsin
- **1987-Now** Professor, Stanford University

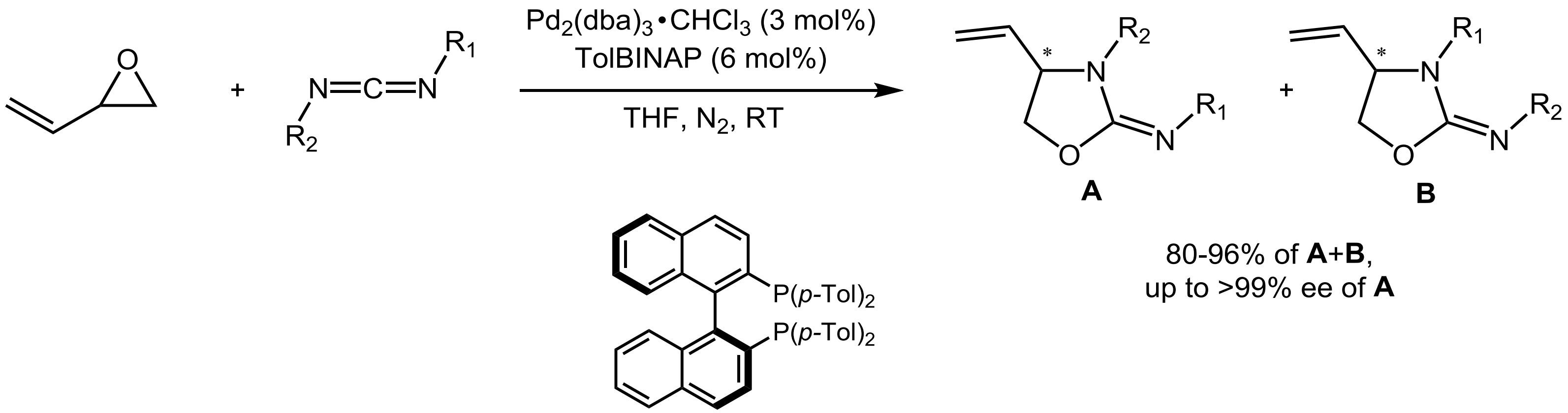
Research:

- Designing new reactions and reagent involves the development of transition metal based catalysts.
- Developing new synthetic strategies towards complex natural products.

Contents

"Three-carbon-atom" Precursors for Cycloadditions

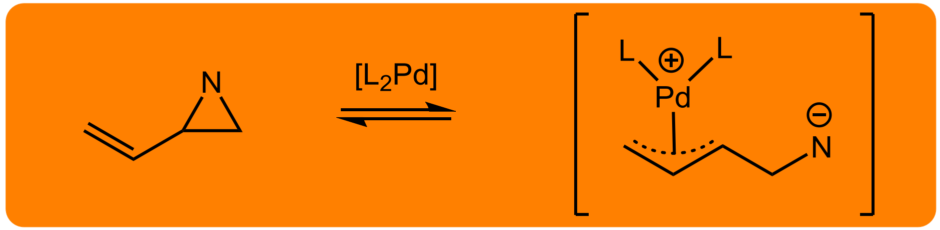


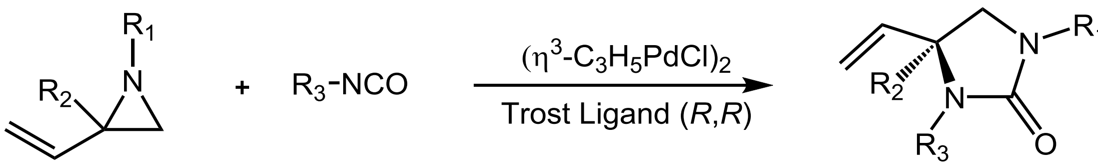


80-96% of **A**+**B**,
up to >99% ee of **A**

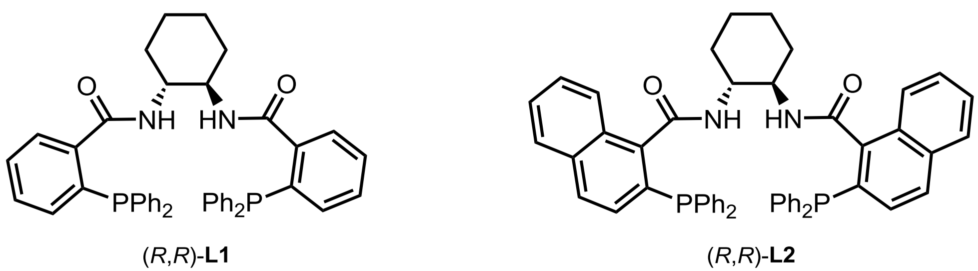
Larksarp, C.; Alper, H. *J. Org. Chem*. **1998**, *63*, 6229.

“Three-carbon-atom” Precursors for Cycloadditions



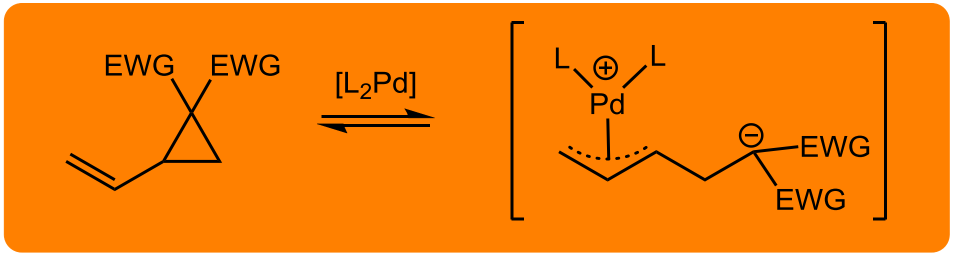


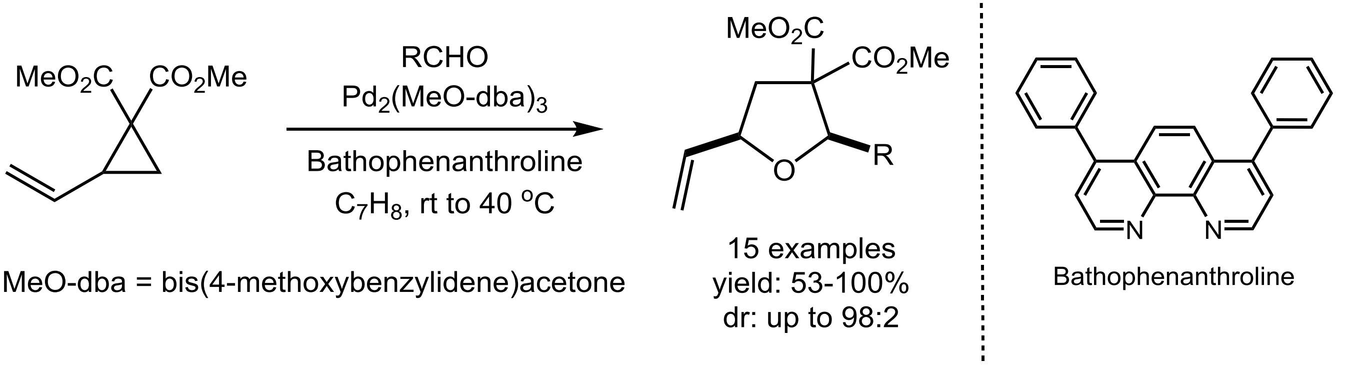
Up to 95% ee



Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836.

"Three-carbon-atom" Precursors for Cycloadditions



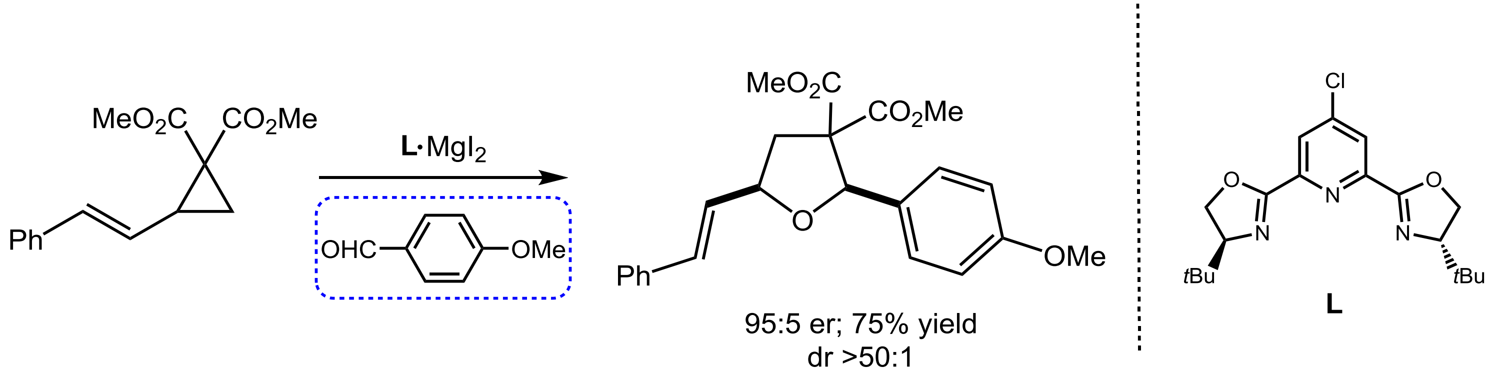


MeO-dba = bis(4-methoxybenzylidene)acetone

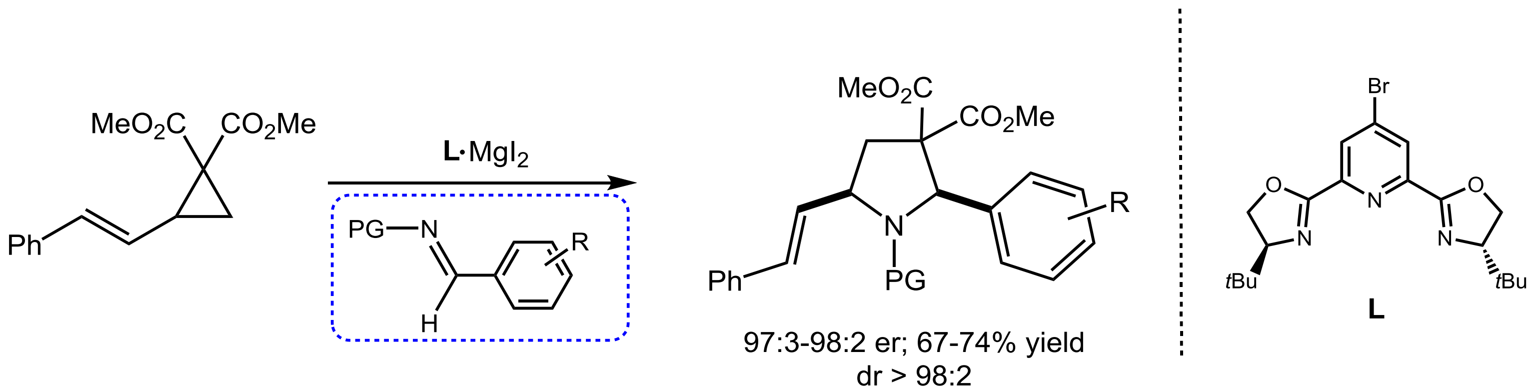
15 examples
yield: 53-100%
dr: up to 98:2

Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett*. **2008**, *10*, 2541.

Vinylcyclopentane Cycloaddition

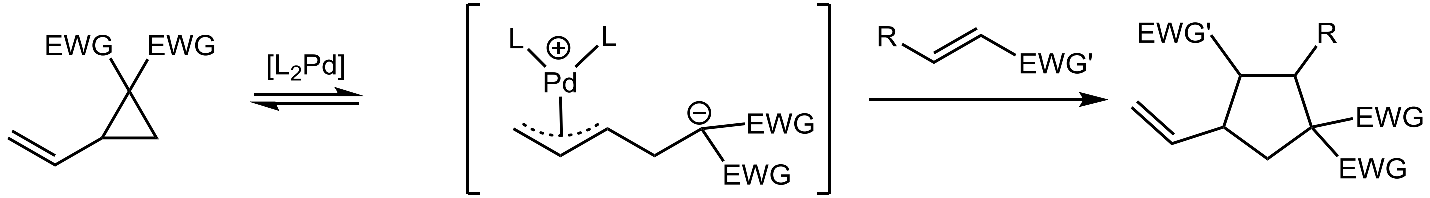


Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.



Parsons, A. T.; Smith, A. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688.

Pd-Catalyzed Vinylcyclopentane Cycloaddition

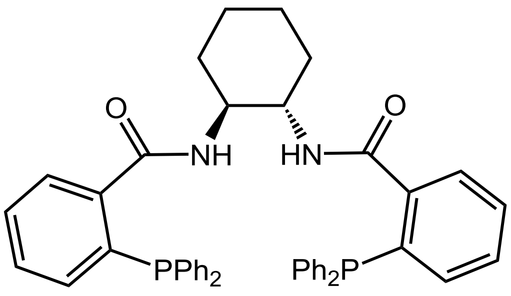


(±)-1 **2** **3**

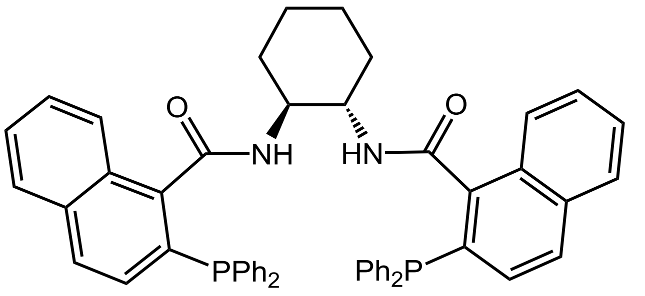
a) EWG = CO_2CH_3
b) EWG = $CO_2CH_2CF_3$

Trost, B. M.; Morris, P. J. *Angew. Chem. Int. Ed.* **2011**, 50, 6167.

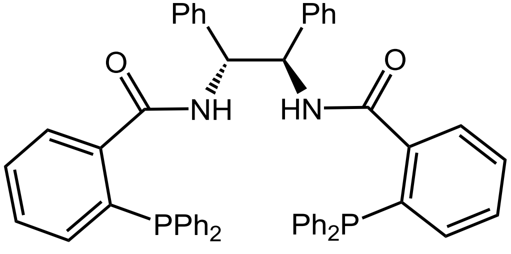
Trost Asymmetric Allylic Alkylation Ligands



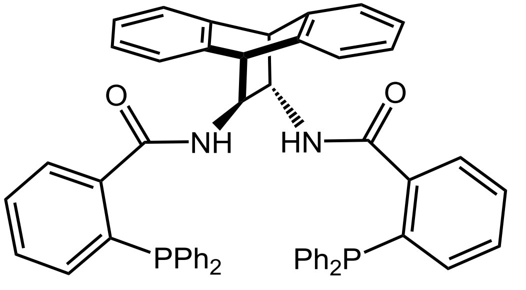
(*S*,*S*)-**L1:** standard



(*S*,*S*)-**L2:** naphthyl

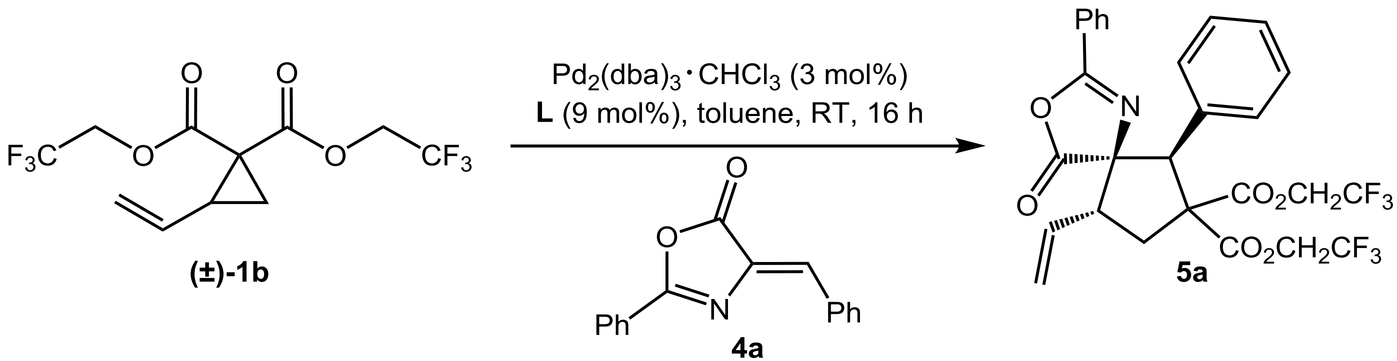


(*R*,*R*)-**L3:** stilbene



(*S*,*S*)-**L4:** anthracene

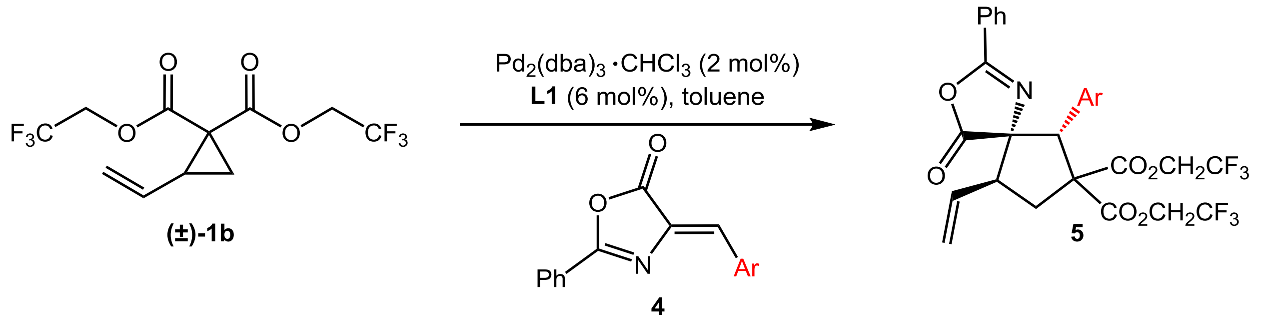
Optimization of The Reaction Conditions

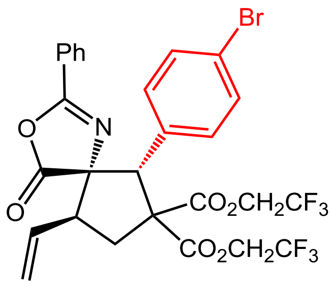


Entry	Ligand	Solvent	Yield(%)[a]	D.r.[b]	Ee(%)[c]
1	**L1**	toluene	64	19:1	96
2	**L2**	toluene	61	19:1	92
3	**L3**	toluene	66	15:1	-87
4	**L4**	toluene	21	4:1	23
5	**L1**	trifluorotoluene	69	4:1	83
6	**L1**	THF	14	15:1	89
7	**L1**	CH_2Cl_2	77	8:1	91
8	**L1**	dioxane	82	14:1	94

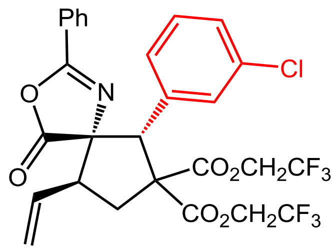
[a] Yields of isolated products. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC

Substrate Scope

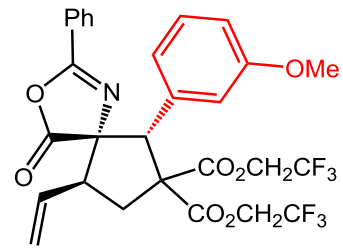




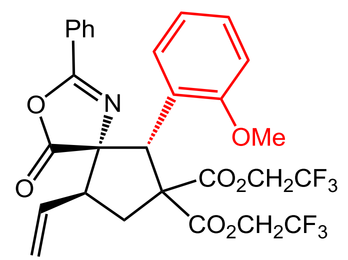
5b, 78%, 19:1 dr, 98% ee.



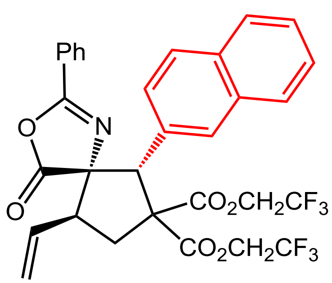
5c, 70%, >19:1 dr, 93% ee.



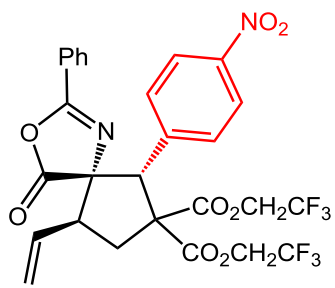
5d, 83%,19:1 dr, 94% ee.



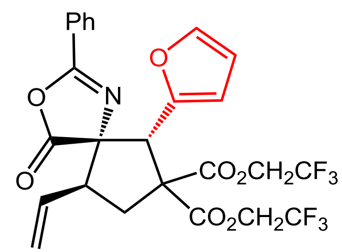
5e, 0%, n.d, n.d.



5f, 84%, >19:1 dr, 94% ee.

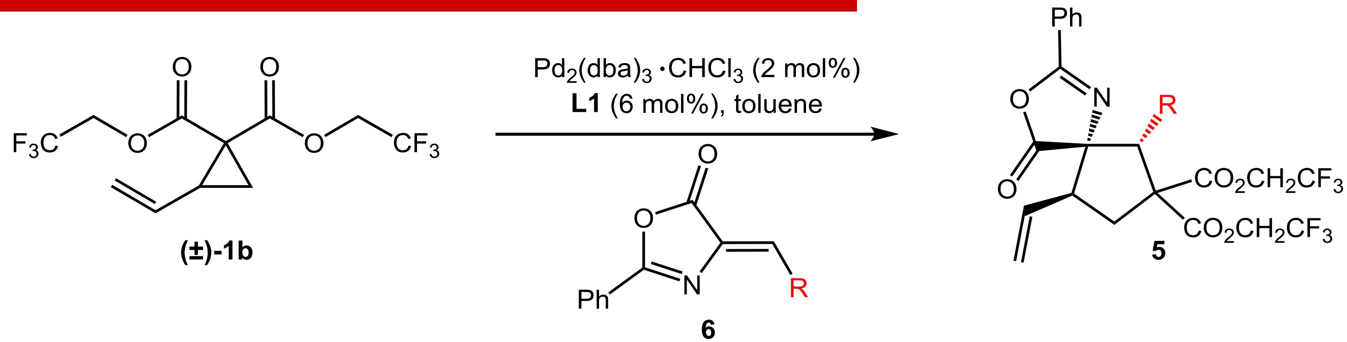


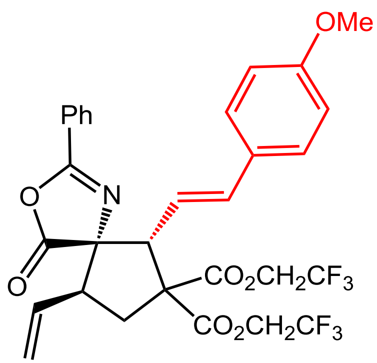
5g, 72%, 8:1 dr, 85% ee.



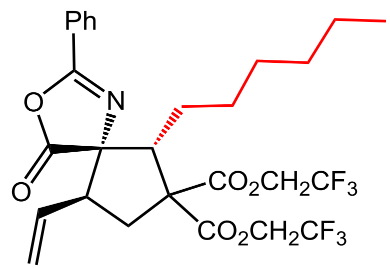
5h, 87%, >19:1 dr, 95% ee.

Substrate Scope

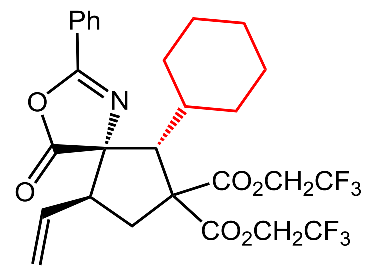




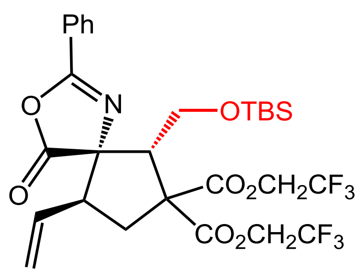
7a, 51%, >19:1 dr, 94% ee.



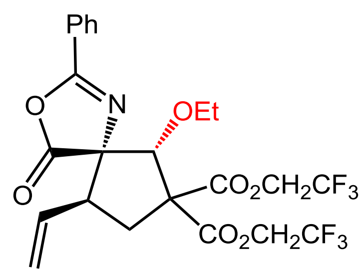
7b, 63%, 8:1 dr, 74% ee.



7c, 0%, n.d, n.d.

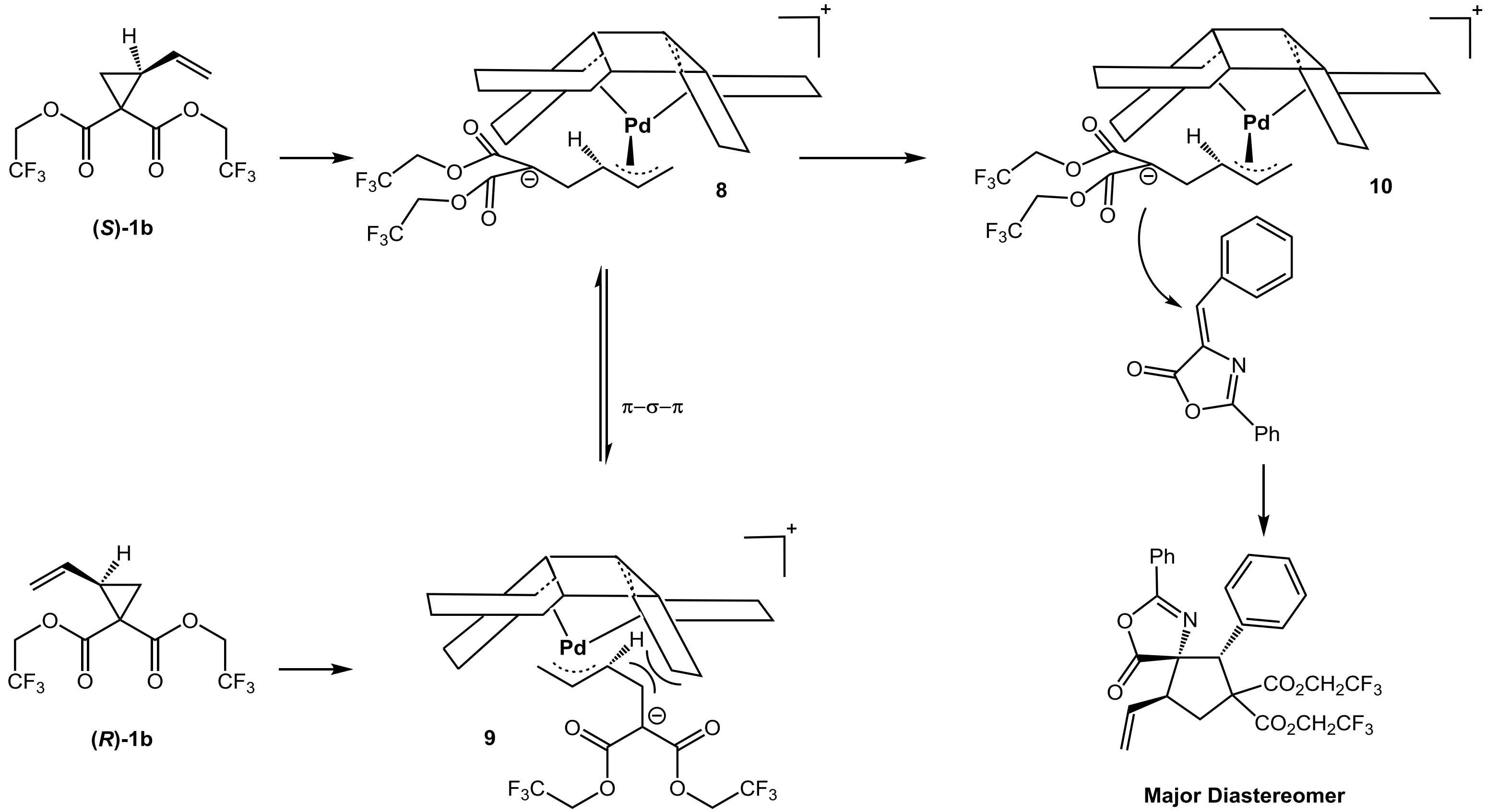


7d, 64%, 3:1 dr, 77% ee.

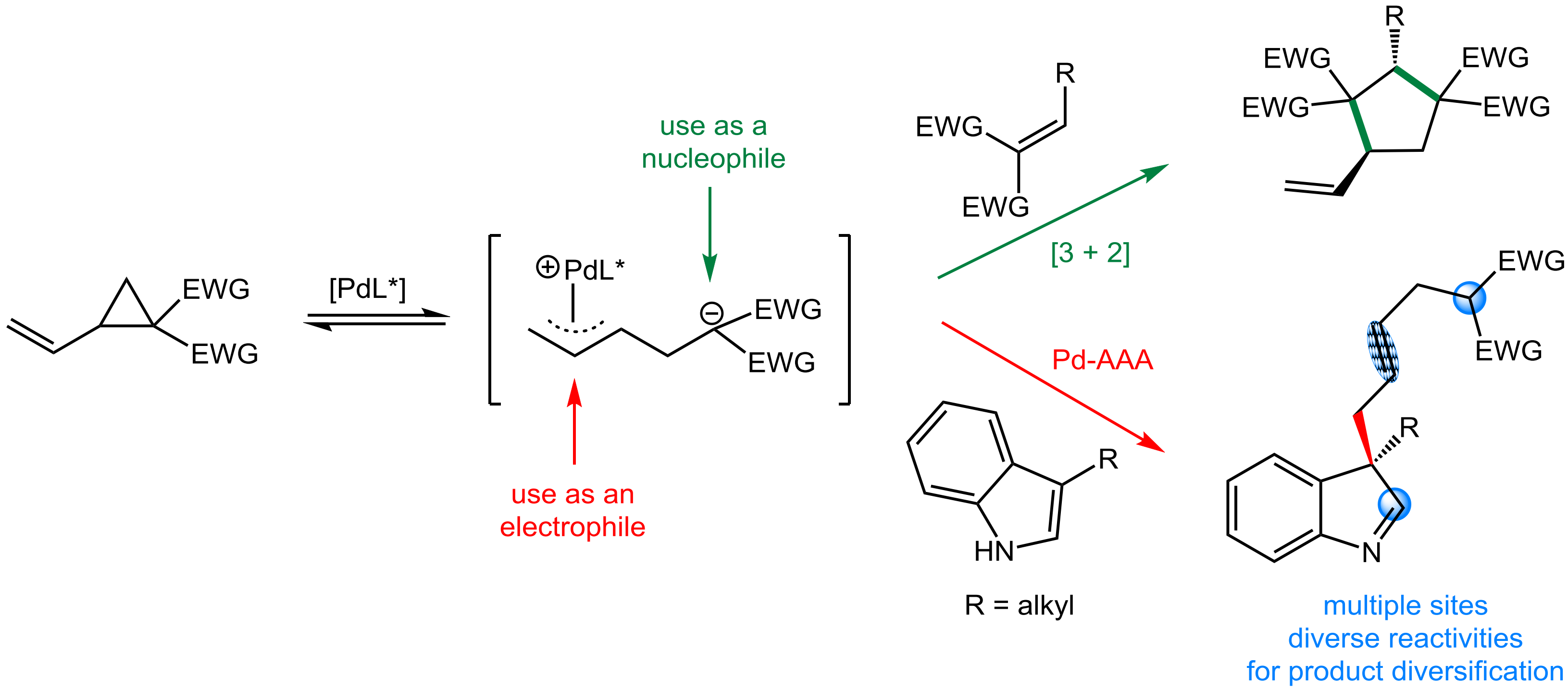


7e, 73%, 10:1 dr, 63% ee.

Mechanistic Rationale

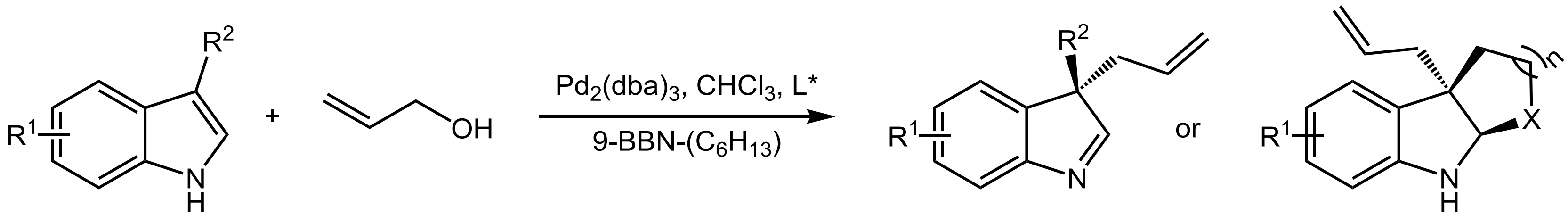


Asymmetric Allylic Alkylation of 3-Substituted 1*H*-Indoles



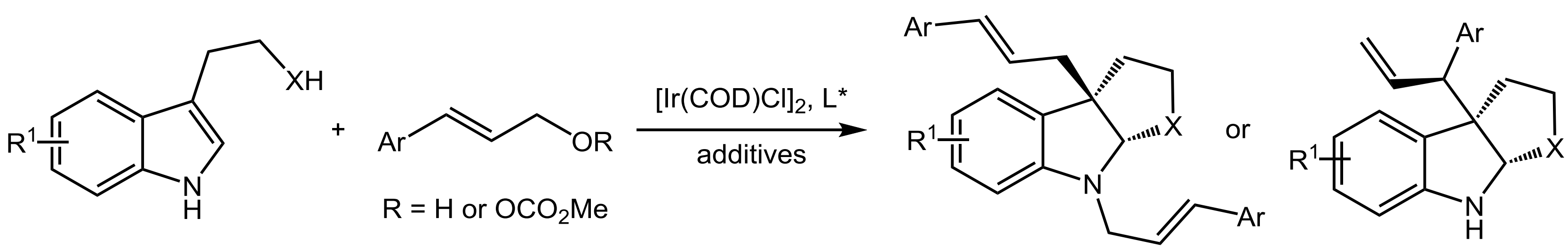
Trost, B. M.*; Bai, W.-J.; Hohn, C.; Bai, Y.; Cregg, J. J. *J. Am. Chem. Soc.* **2018**, *140,* 6710.

Pd-AAA of 3-Substituted Indoles



84-95% yield,
80:20 to 95: 5 er

Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.



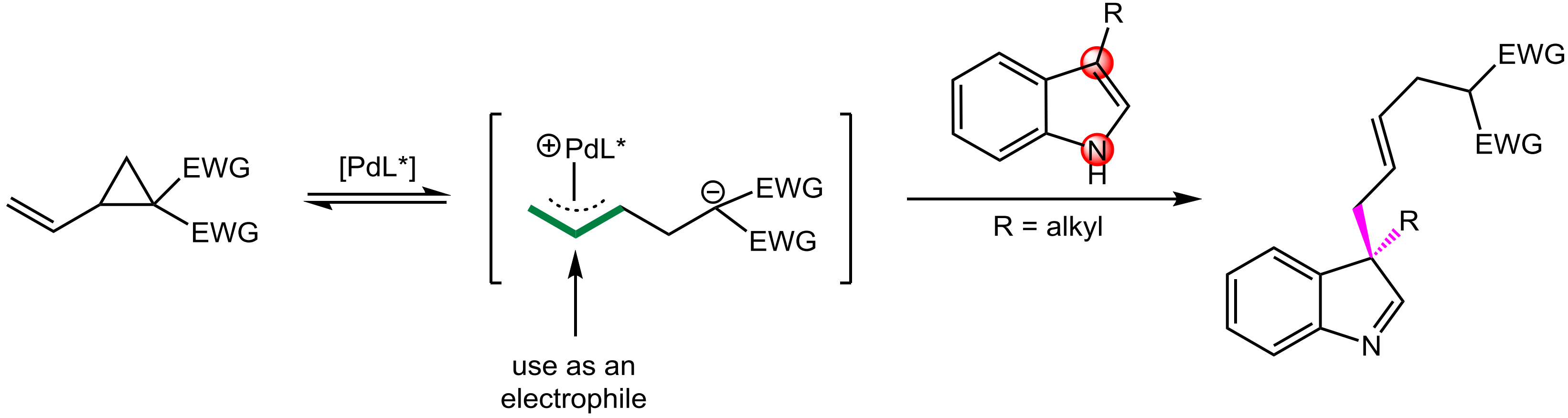
71-97% yield
92:8 to 99:1er
R = H

40-85% yield
96:4 to >99:1er
R = OCO_2Me

Zhang, X.; You, S.-L. *Chem. Sci.* **2014**, *5*, 1059.

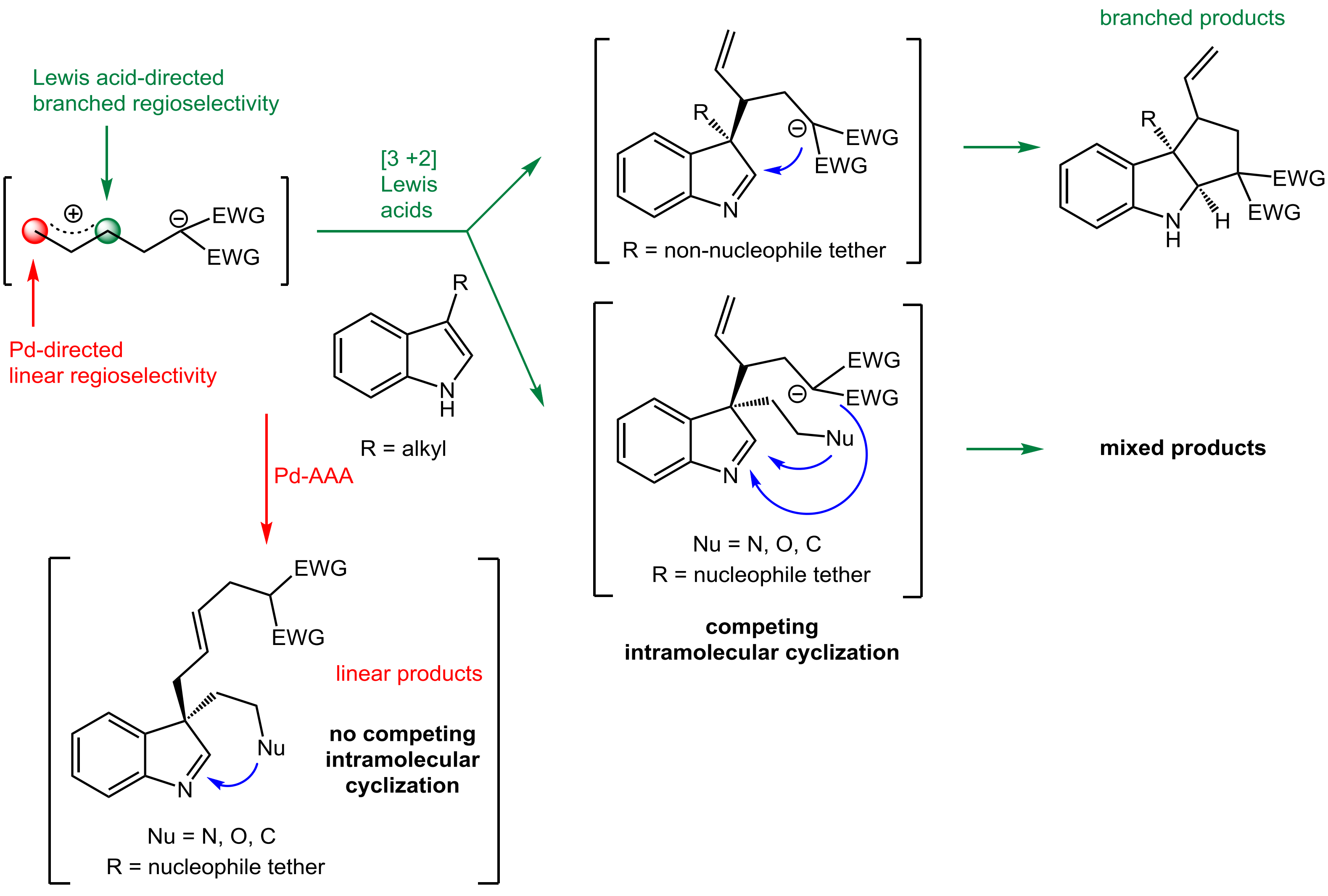
Zhang, X.; Liu, W.-B.; Tu, H.-F.; You, S.-L. *Chem. Sci.* **2015**, *6*, 4525.

Problems of Pd-AAA of 3-Alkylated 1*H*-Indoles

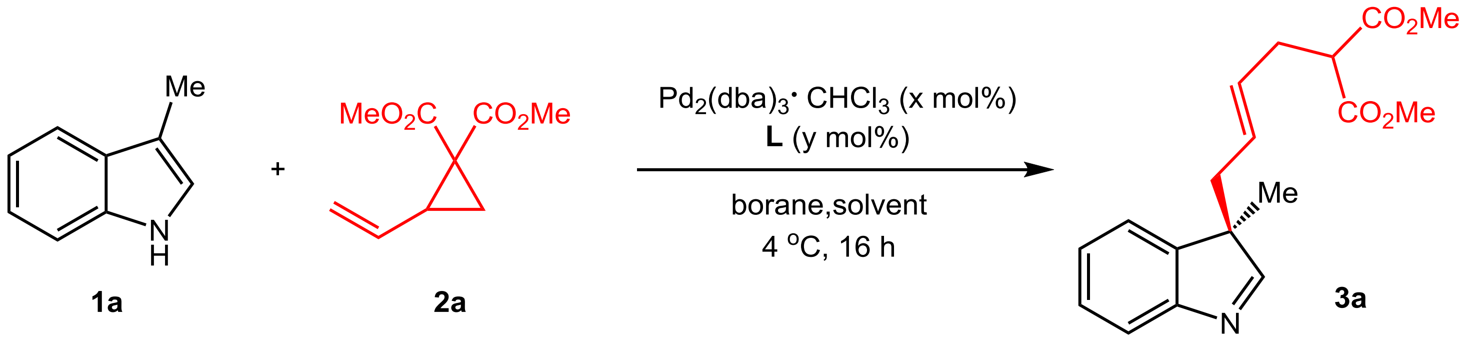


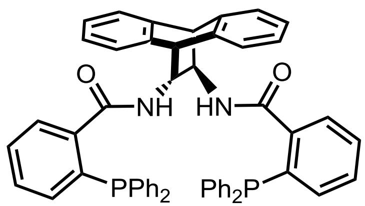
Problems: ♣ Chemoselectivity ♣ Regioselectivity ♣ Enantioselectivity

How To Solve Problems

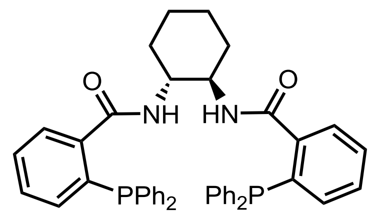


Pd-AAA of 3-Alkylated 1*H*-Indoles

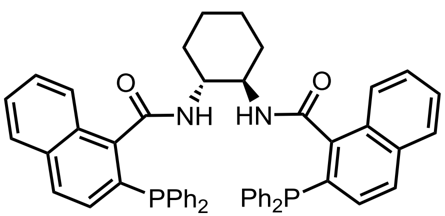




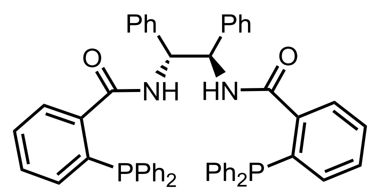
(*R*,*R*)-**L1**



(*R*,*R*)-**L2**



(*R*,*R*)-**L3**



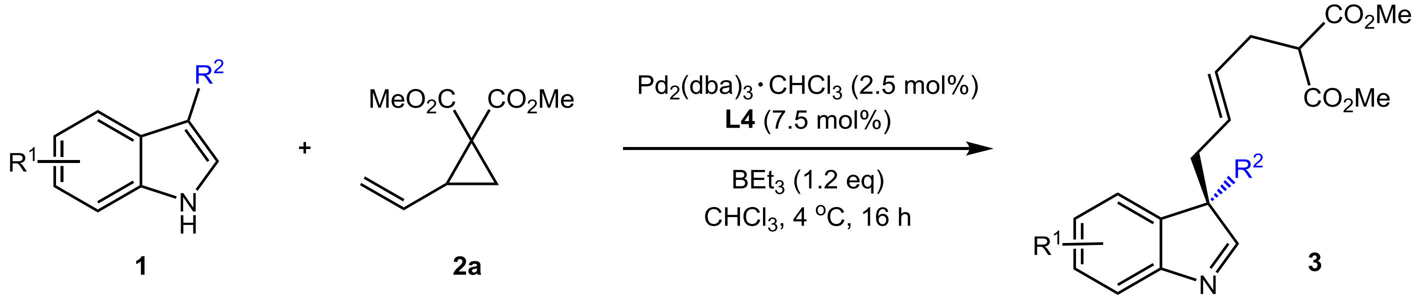
(*R*,*R*)-**L4**

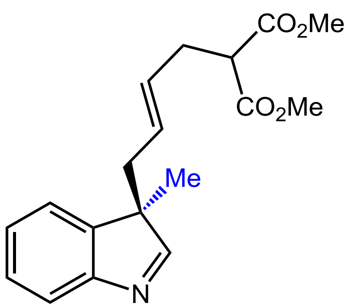
Optimization of The Reaction Conditions

Entry	Ligand	x/y	Borane	Solv.	Conv.[b]	Er[c]
1	**L1**	5/15	none	DCM	<5%	nd
2	**L1**	5/15	BEt_3	DCM	full	76:24
3	**L2**	5/15	BEt_3	DCM	full	92:8
4	**L3**	5/15	BEt_3	DCM	full	94:6
5	**L4**	5/15	BEt_3	DCM	full	95:5
6	**L4**	5/15	BEt_3	THF	66%	90:10
7	**L4**	5/15	BEt_3	MeCN	85%	95:5
8	**L4**	5/15	BEt_3	Tol	full	93:7
9	**L4**	5/15	BEt_3	$CHCl_3$	full	96:4
10	**L4**	5/15	9-BBN-(C_6H_{13})	$CHCl_3$	full	97:3
11	**L4**	5/15	Sia_2B-(C_6H_{13})	$CHCl_3$	<10%	nd
12	**L4**	2.5/7.5	BEt_3	$CHCl_3$	full	96:4
13	**L4**	1/3	BEt_3	$CHCl_3$	full	94:6
14[d]	**L4**	2.5/7.5	BEt_3	$CHCl_3$	75%	nd

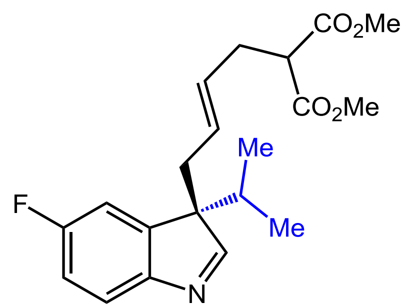
[a] Reaction conditions: 0.20 mmol of **1a**, x mol % of $Pd_2(dba)_3 \cdot CHCl_3$, y mol % of **L**, 0.24 mmol of BEt_3 and **2a**, in various solvents at 4 °C for 16 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC on a chiral stationary phase. [d] The reaction was performed with 0.2 equiv of BEt_3.

Scope of C3-Allylation of 3-Substituted 1*H*-Indoles

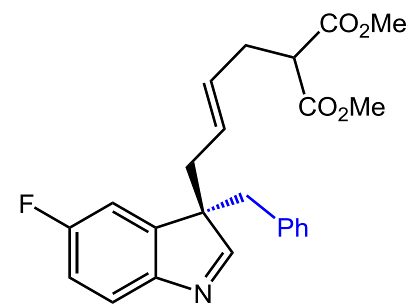




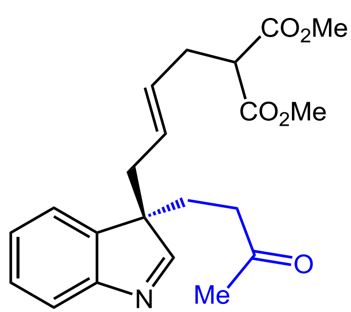
3a, 93% yield, 96:4 er



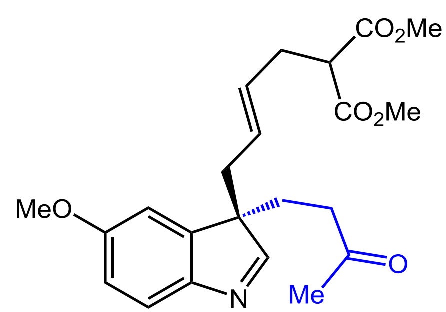
3b, 90% yield, 99:1 er



3c, 91% yield, 97:3 er

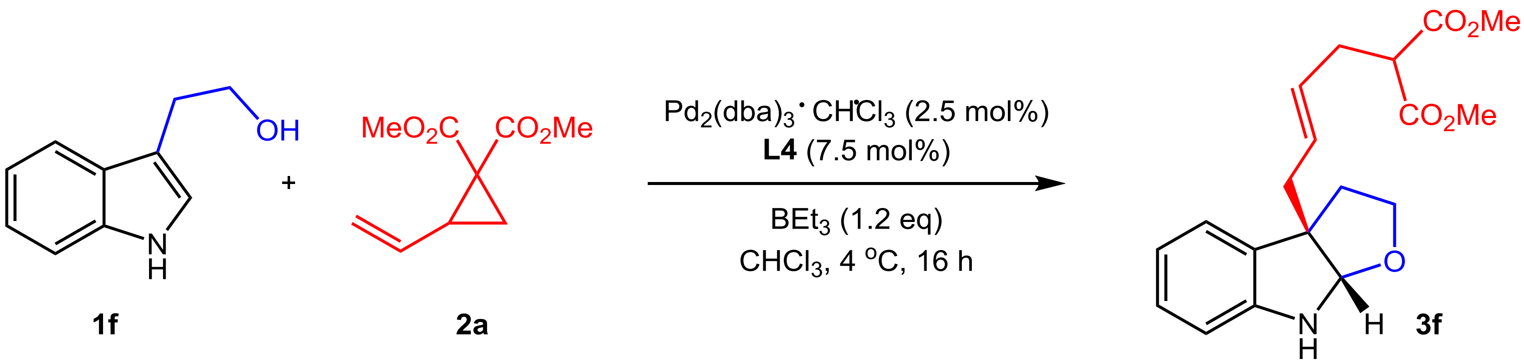


3d, 96% yield, 96:4 er



3e, 92% yield, 95:5 er

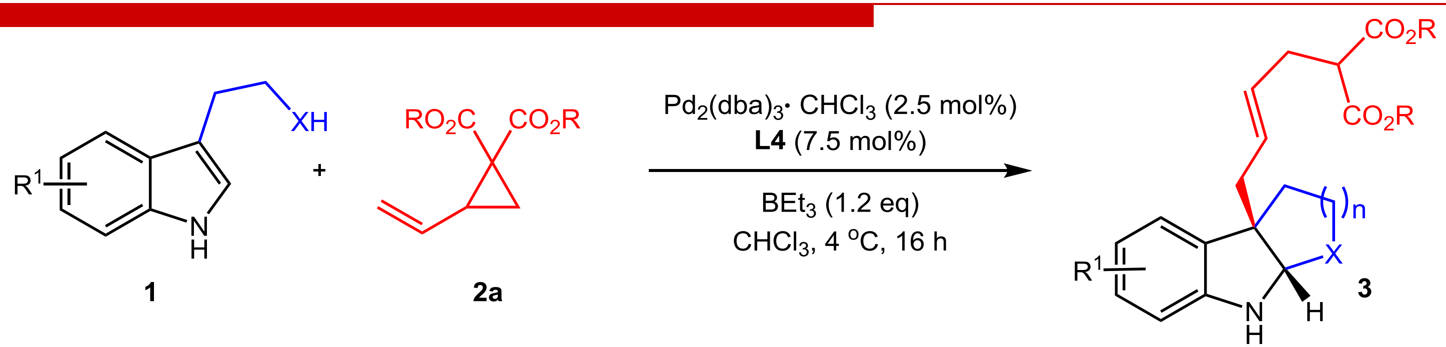
Optimization With Tryptophol 1f

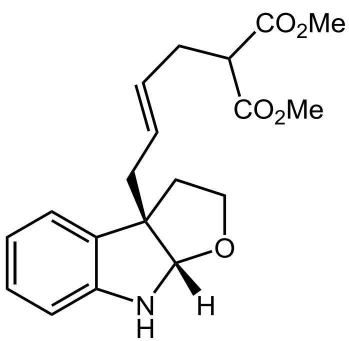


Entry	Deviation from standard conditions	Yield[b]	Er[c]
1	none	93	96:4
2	DCM as solvent	88	96:4
3	reaction at rt	91	94:6
4	9-BBN-(C_6H_{13}) as the borane	91	97:3
5	1 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 3 mol % of **L4**	88	94:6

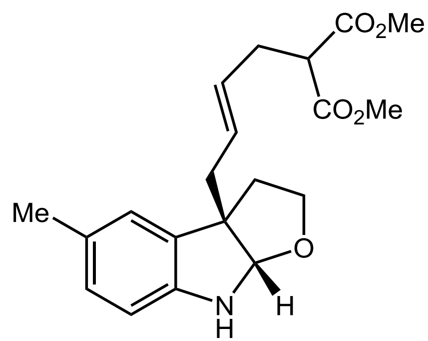
[a] Standard conditions: 0.20 mmol of **1f,** 2.5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 7.5 mol % of **L4**, 0.24 mmol of BEt_3 and **2a**, in $CHCl_3$ at 4 ° C for 16 h. [b] Isolated yield. [c] Determined by HPLC on a chiral stationary phase.

Scope of Tandem C3-Allylation/Cyclizations

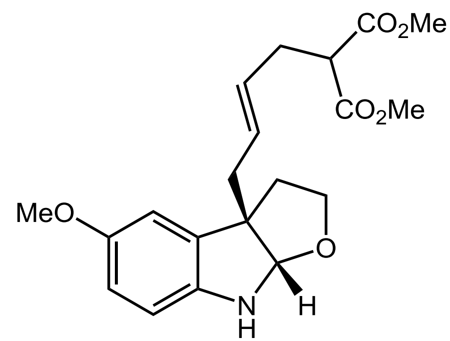




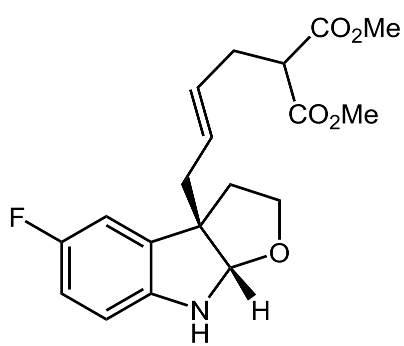
93% yield, 96:4 er



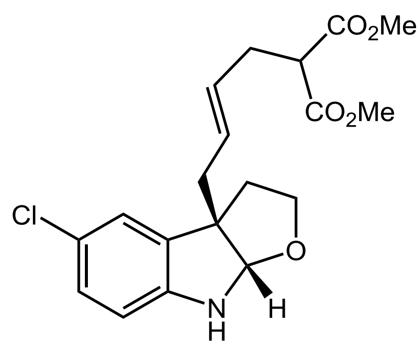
83% yield, 92:8 er



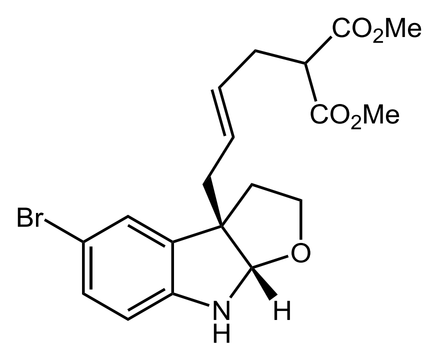
89% yield, 92:8 er



95% yield, 96:4 er

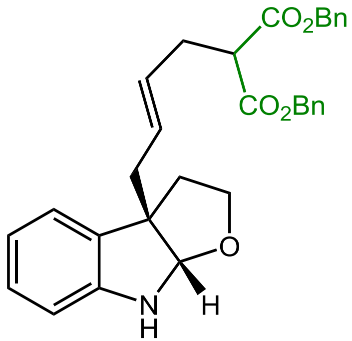


89% yield, 94:6 er

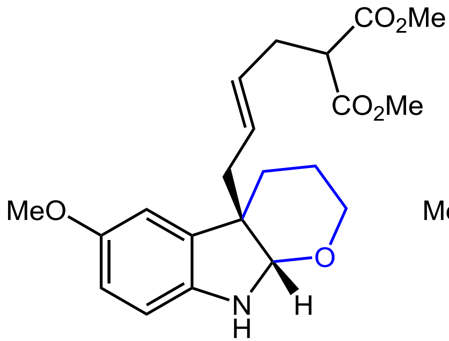


92% yield, 92:8 er

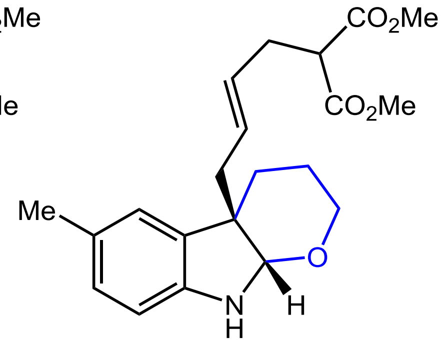
Scope of Tandem C3-Allylation/Cyclizations



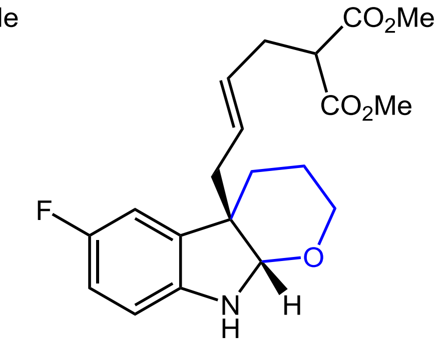
93% yield, 97:3 er



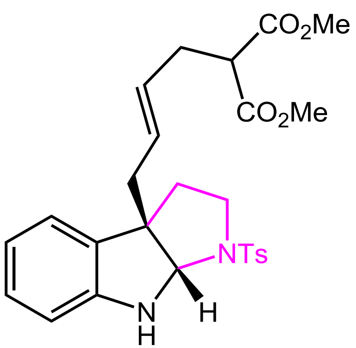
88% yield, 91:9 er



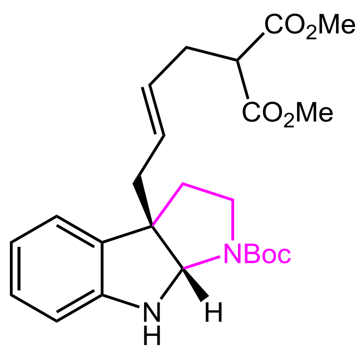
87% yield, 86:14 er



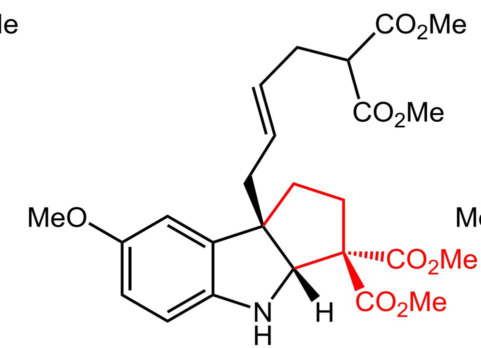
90% yield, 98:2 er



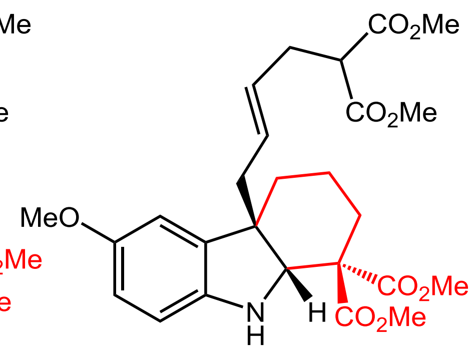
80% yield, 96:4 er



85% yield, 95:5 er

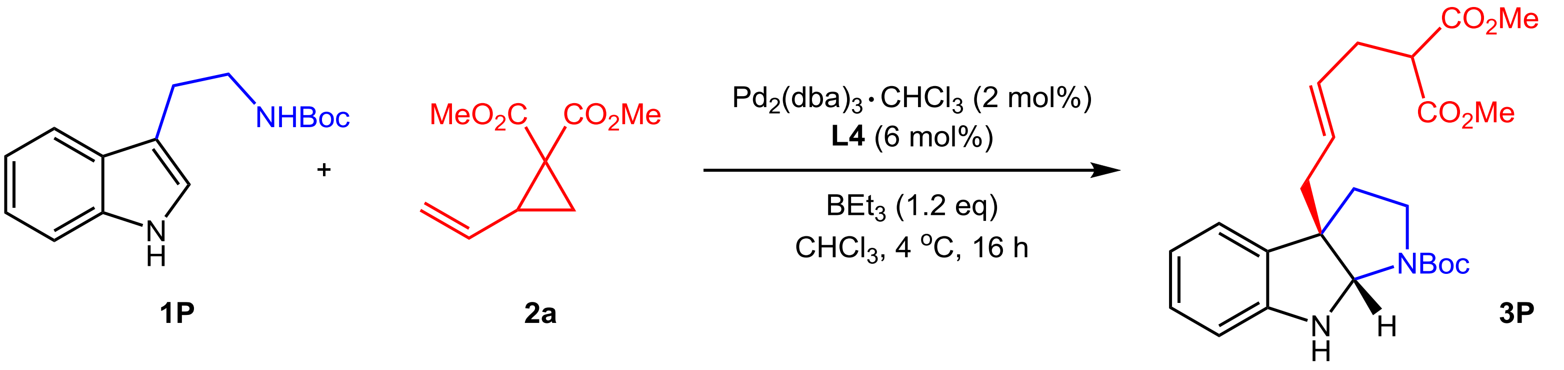


80% yield, 94:6 er



82% yield, 95:5 er

Gram Scale Experiment.

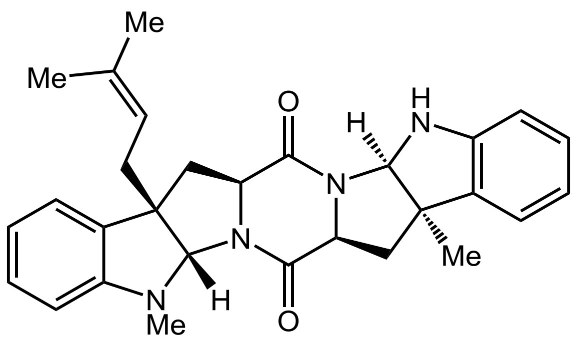


1 gram
(3.8 mmol)

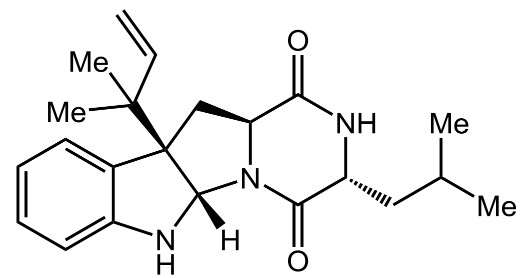
(1.2 eq)

1.57 g (3.4 mmol)
89% yield, 95:5 er

Bioactive Molecules Bearing DKP/DKM Motifs

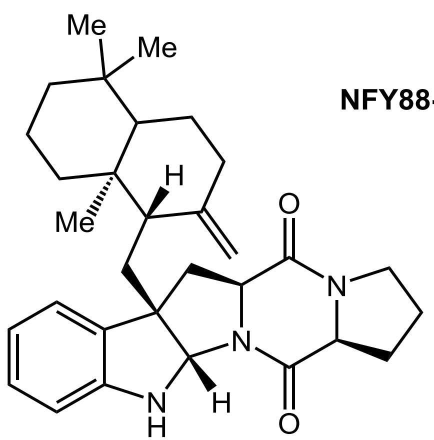


Nocardioazine B

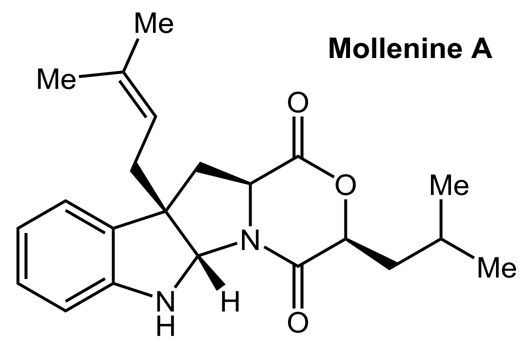


Brevicompanine B

NFY88-P



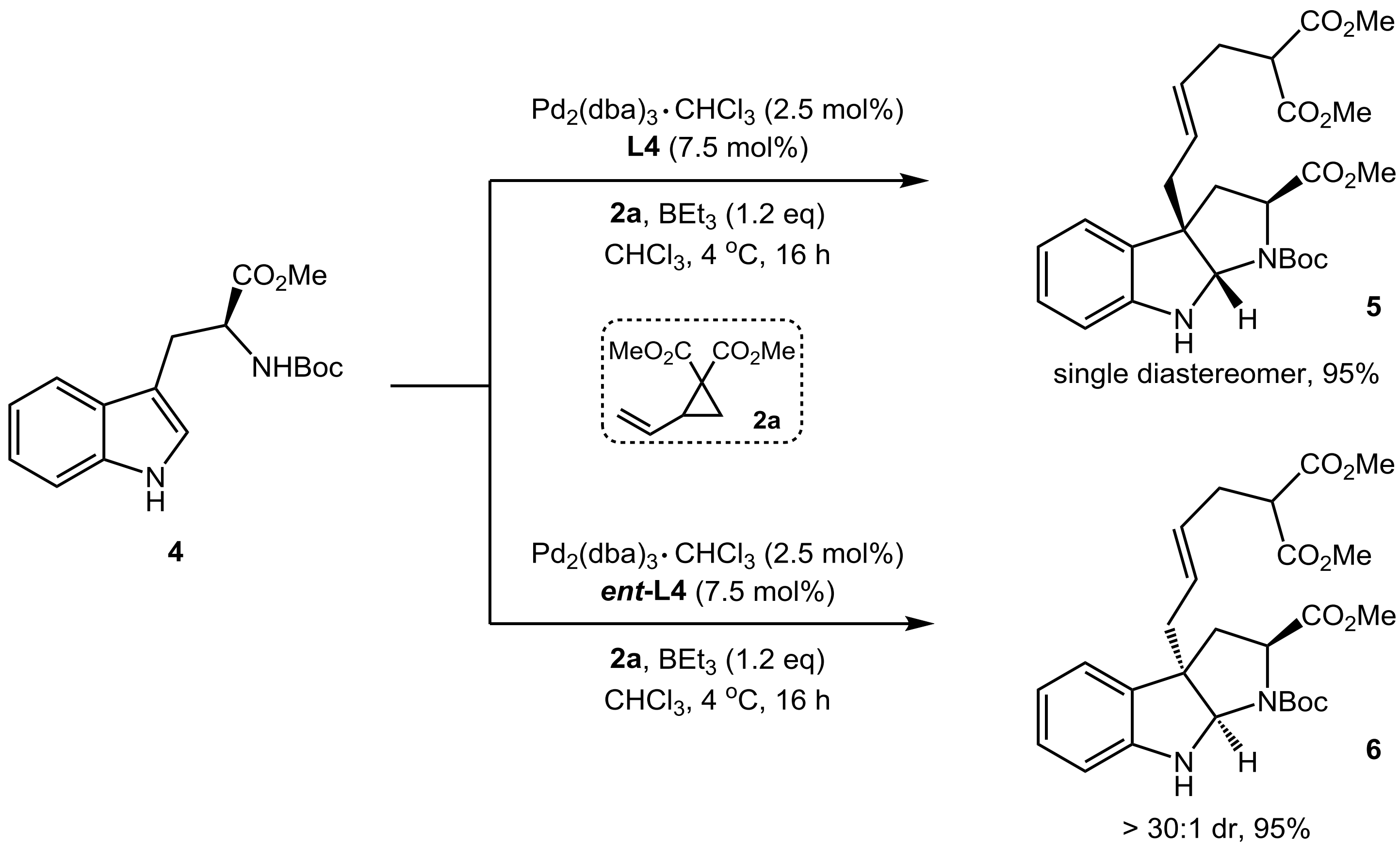
Mollenine A



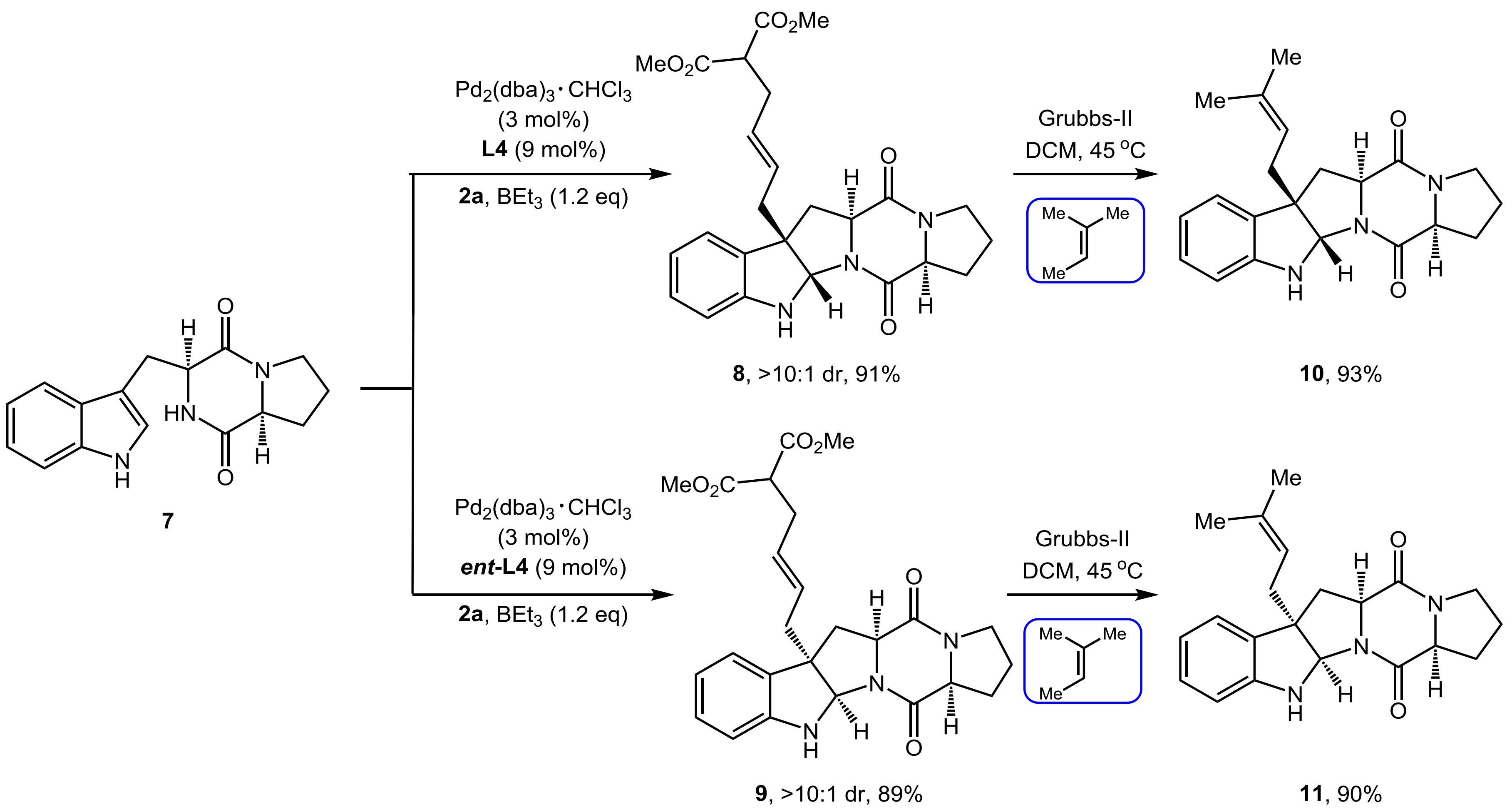
DKP (diketopiperazine)

DKM (diketomorpholine)

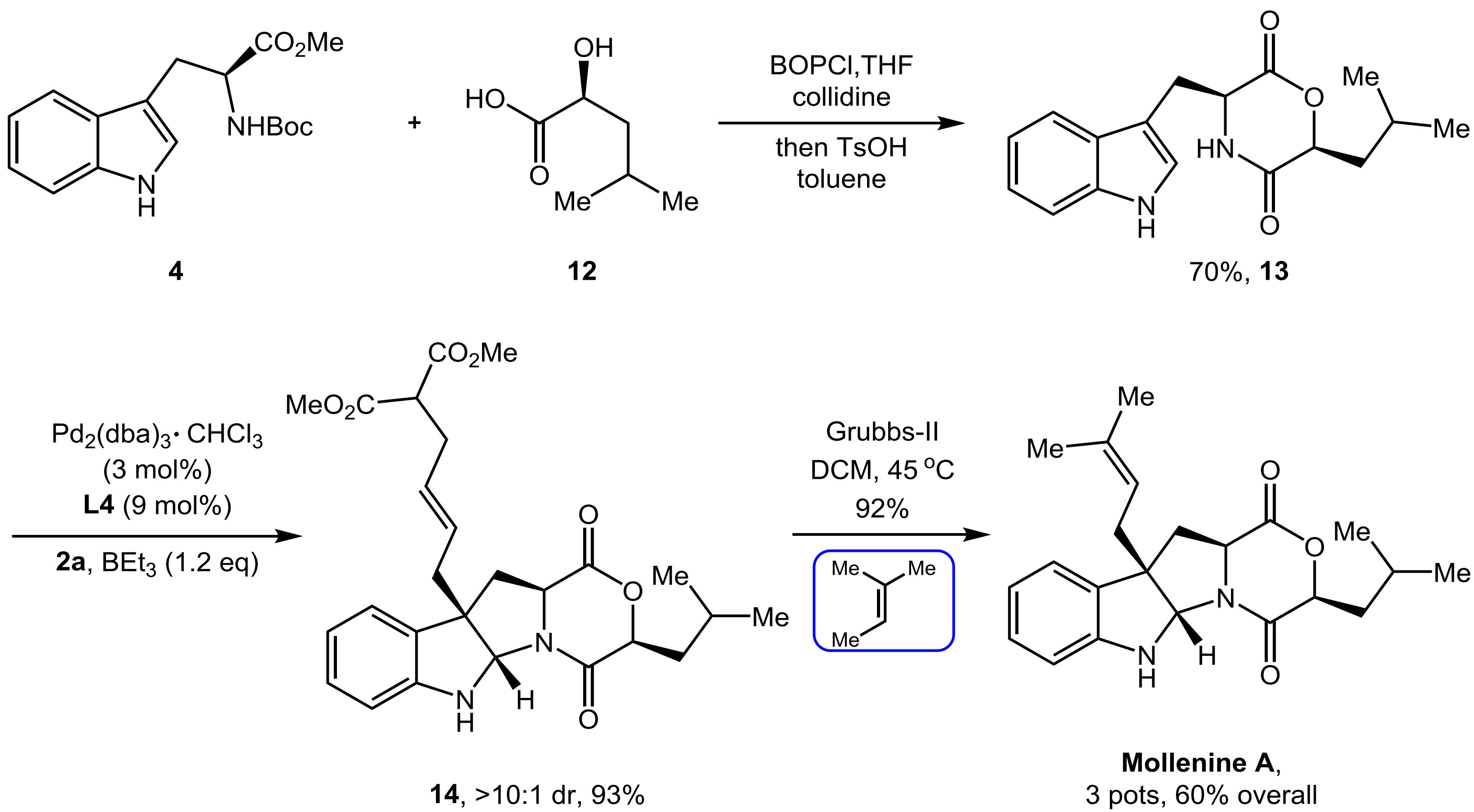
Pd-AAA of the N-Boc-*L*-Tryptophan Methyl Ester



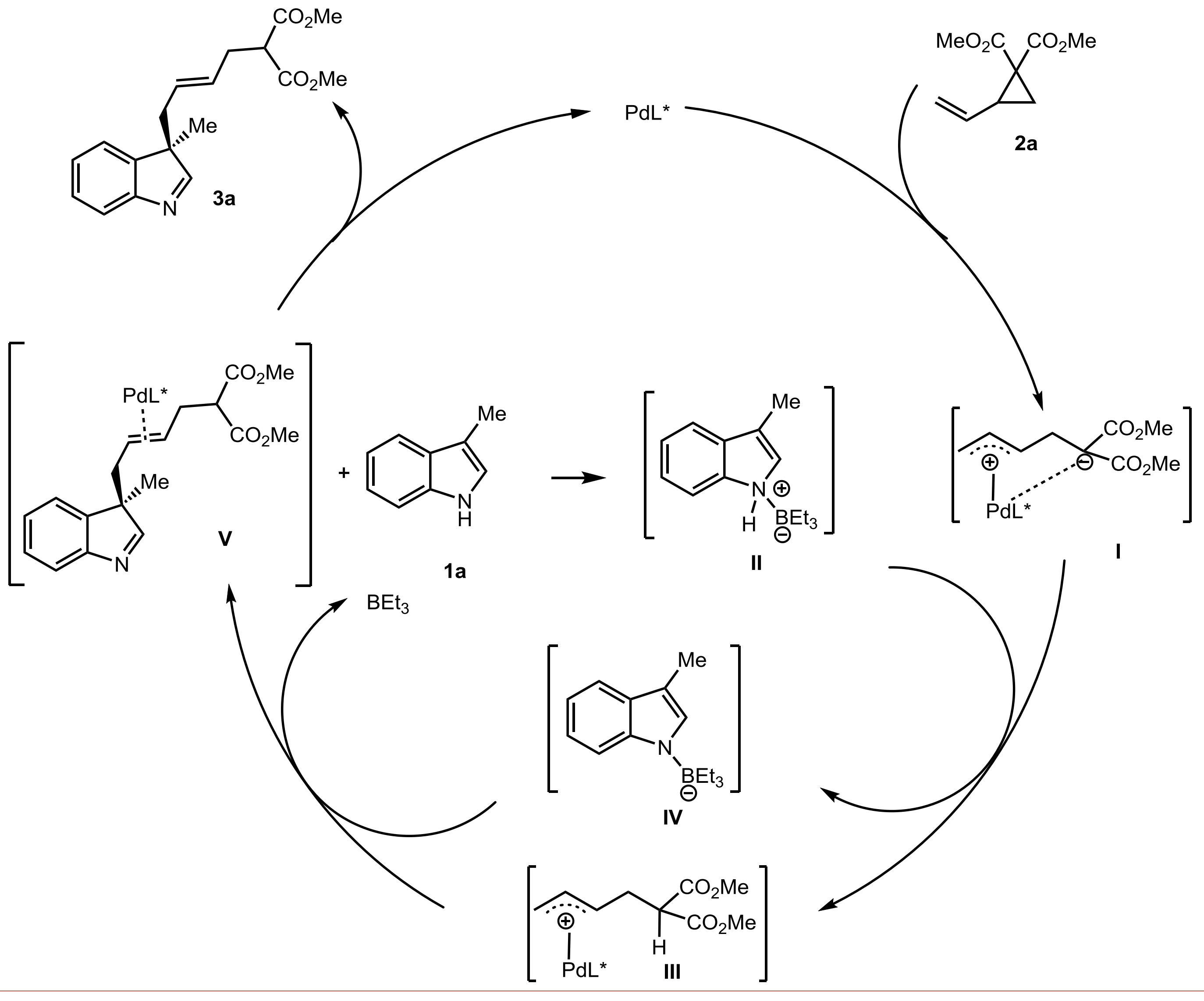
Pd-AAA of the Cyclo(*L*-Trp-*L*-Pro) (DKP Motif)



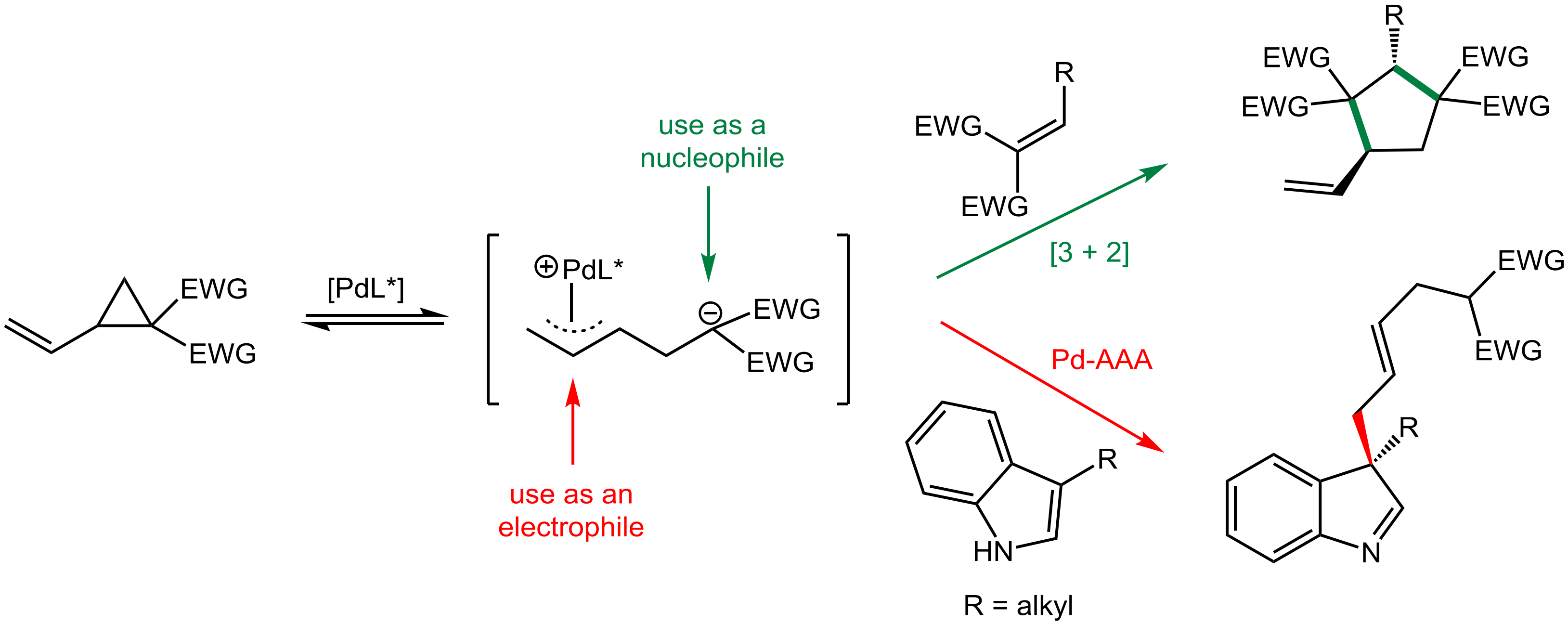
Pd-AAA of the Cyclo(*L*-Trp-*S*-HMA) (DKM Motif)



Proposed Catalytic Cycle



Summary



Trost, B. M.*; Morris, P. J. *Angew. Chem. Int. Ed.* **2011**, 50, 6167.

Trost, B. M.*; Bai, W.-J.; Hohn, C.; Bai, Y.; Cregg, J. J. *J. Am. Chem. Soc.* **2018**, *140,* 6710.

The First Paragraph

Naturally occurring indole alkaloids display a broad range of anticancer, antibacterial, and antifungal properties. For example, borreverine is strongly active against Grampositive bacteria. As a result, these molecules provide an attractive platform for structure-activity relationship studies and lead compound discovery in drug development. Their indoline cores usually fuse with other hetero- or carbocyclic backbones, creating marvelous structural complexity and diversity.

The Last Paragraph

In summary, we have reported the first use of VCP derivatives as electrophiles for the asymmetric allylation of C3-substituted 1H-indoles and tryptophan derivatives. Utilizing $Pd_2(dba)_3 \cdot CHCl_3$ and stilbene-derived Trost ligand L4, a broad range of 3,3-disubstituted indolenines and indolines has been prepared in a highly chemo-, regio-, and enantioselective fashion. This completely atom-economic transformation enables indoles bearing a pendant C3-nucleophile to cleanly react with VCPs, whereas employing a Lewis acid might be problematic. The reaction can be performed on the gram scale. The stereochemical

The Last Paragraph

outcomes of asymmetric functionalizations of tryptophan derivatives are well controlled by the chiral ligands, allowing us to expeditiously synthesize mollenine A. The indolenine products can be elaborated to intricate polycyclic compounds by making use of the newly installed imine and internal olefin motifs. More importantly, VCPs, like no other allylation reagents, introduce a nucleophilic malonate substituent through the Pd-AAA, providing an excellent handle for additional product derivatization.

Acknowledgement

Thanks for your attention