Literature Report VIII

Enantioselective Intramolecular Ring Opening of Cyclobutanones

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Checker：Zi-Biao Zhao

Date：2019-01-14

Xu, L.-W. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 897.
Cramer, N. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9640.

Contents

CV of Li-Wen Xu

Xu, Li-Wen

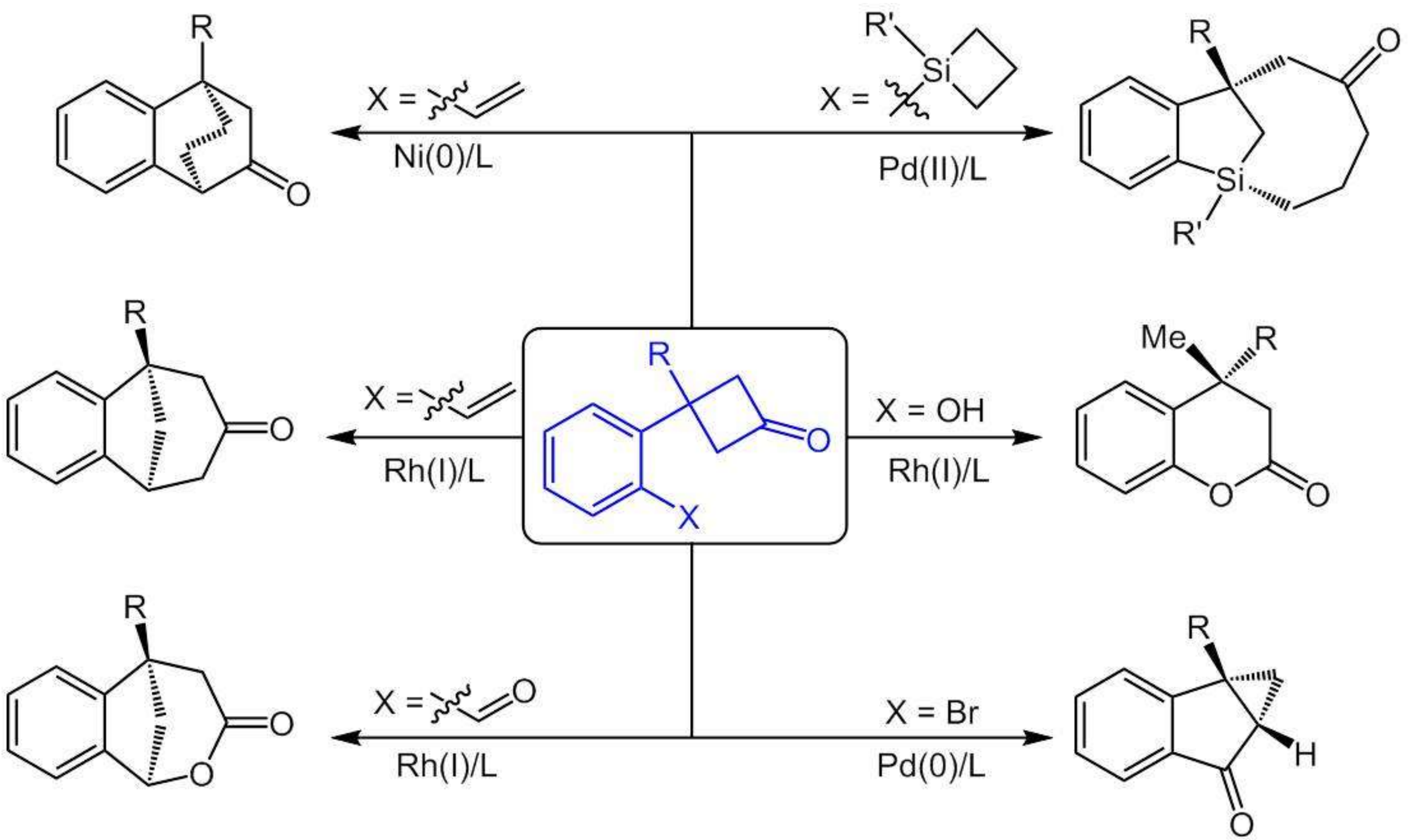
Education:

- **1994–1998** B.S., Anhui Normal University
- **1998–2004** Ph.D., LICP (Prof. Chun-Gu Xia)
- **2004–2006** Associate professor, LICP
- **2005–2006** Postdoc., CNRS UMR6011 (Prof. Jacques Mortier)
- **2007–2008** Research Fellow, NUS (Prof. Yixin Lu)
- **2008–2009** Postdoc., The University of Tokyo (Prof. Masakatsu Shibasaki)
- **2006–Present** Professor, Hangzhou Normal University

Research:

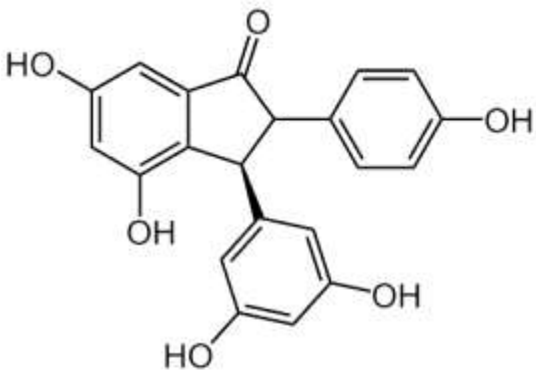
★ Organosilicon chemistry, asymmetric catalysis, and organic synthesis.

Catalytic Ring Opening of Cyclobutanones

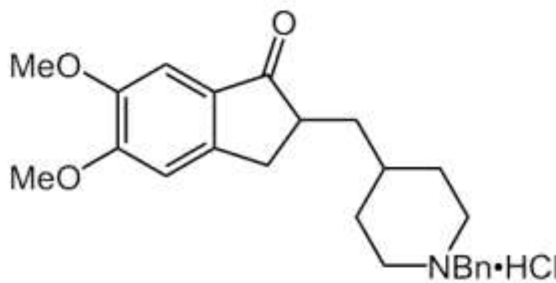


Cramer, N. *et al. Chem. Rev.* **2015**, *115*, 9410.
Murakami, M. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 2485.
Cramer, N. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9640.

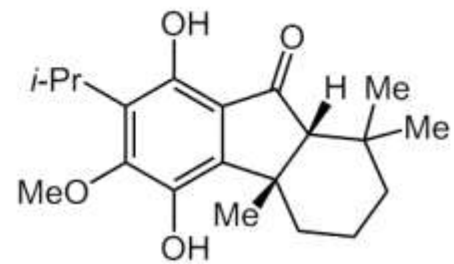
Biologically Active Molecules



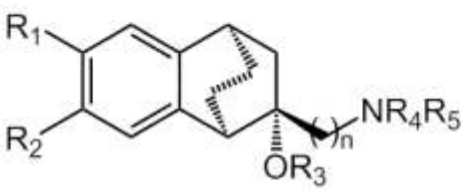
Pauciflorol F



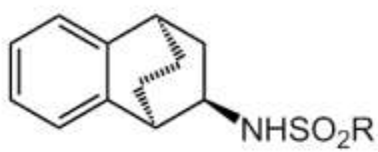
Donepezil hydrochloride



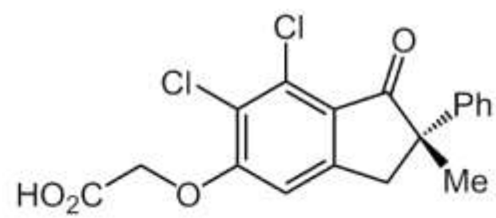
Taiwaniaquinol B



Calcium channel blocker



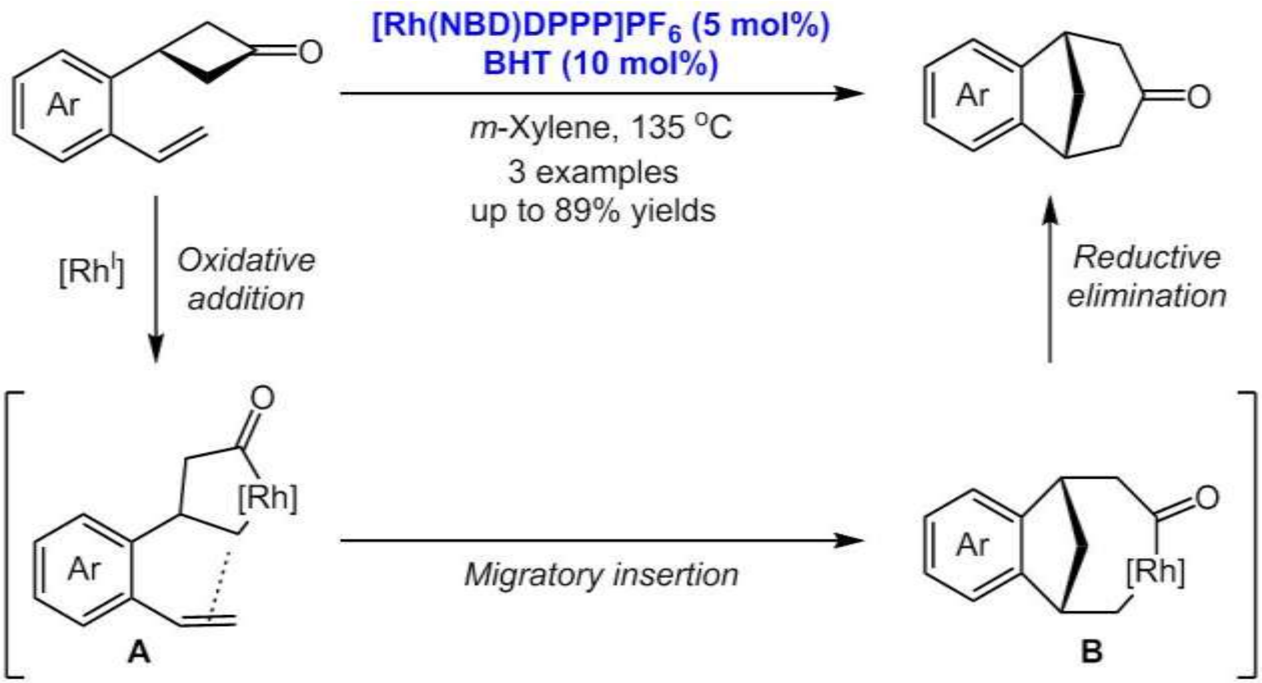
γ-Secretase inhibitor



(+)-Indacrinone

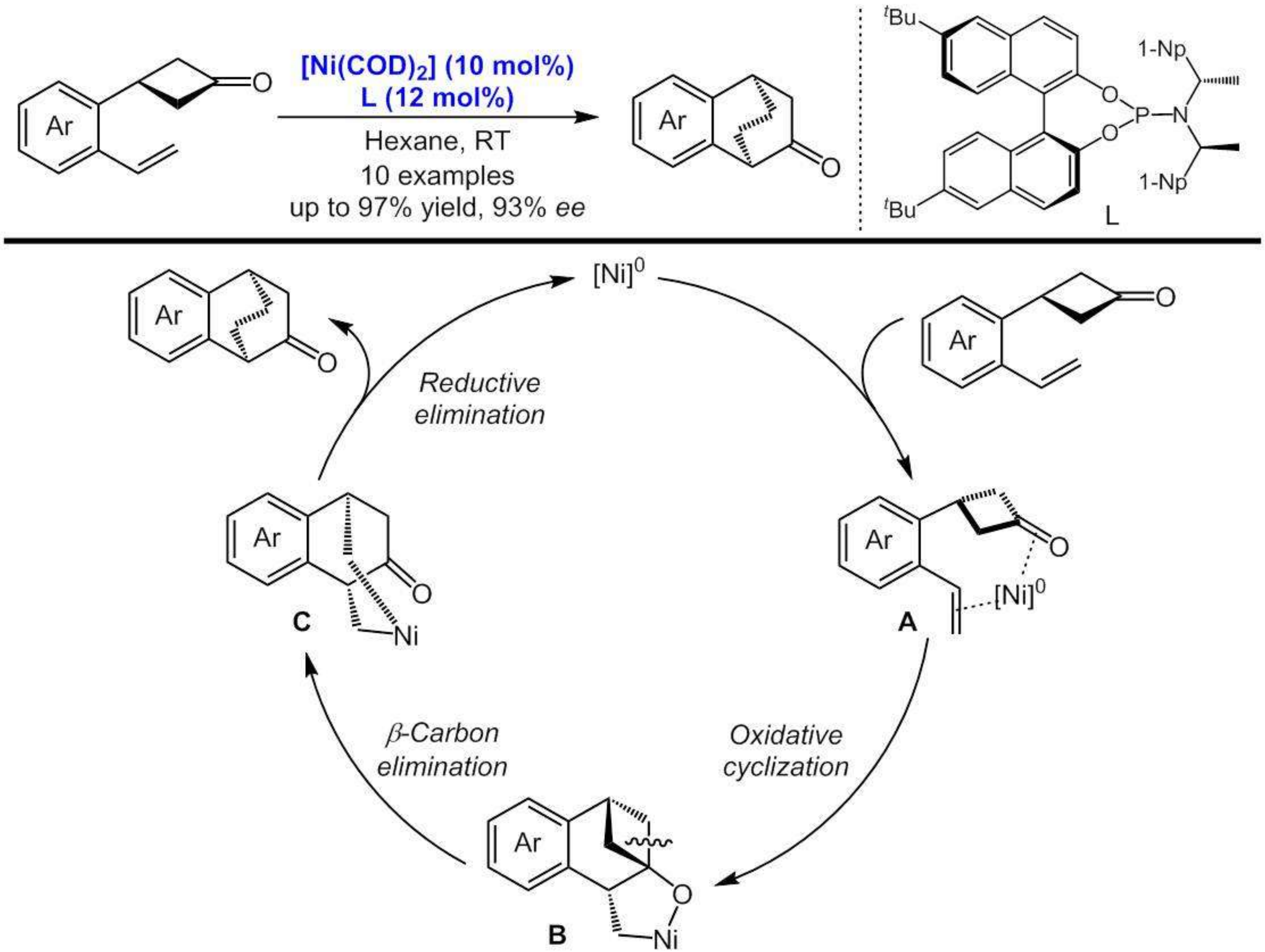
Balme, G. *et al. Org. Lett.* **2003**, *5*, 2055.
Darnaedi, D. *et al. J. Nat. Prod.* **2004**, *67*, 932.
Goll, J. M. *et al. J. Org. Chem.* **2005**, *70*, 1316.
Murakami, M. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 2485.

Ring Opening of Cyclobutanones with Alkene



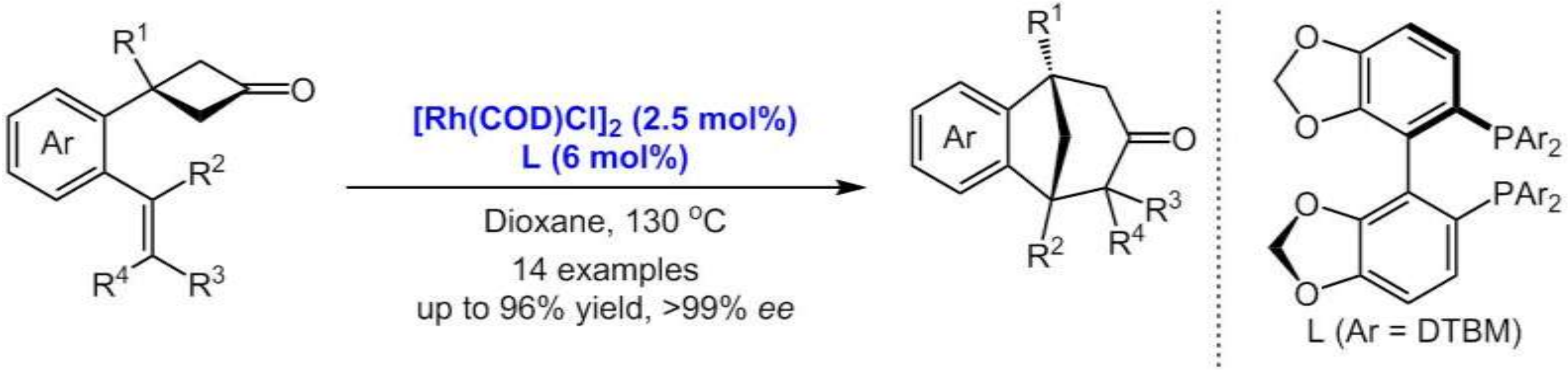
Murakami, M. *et al. J. Am. Chem. Soc.* **2002**, *124*, 13976.

Ring Opening of Cyclobutanones with Alkene

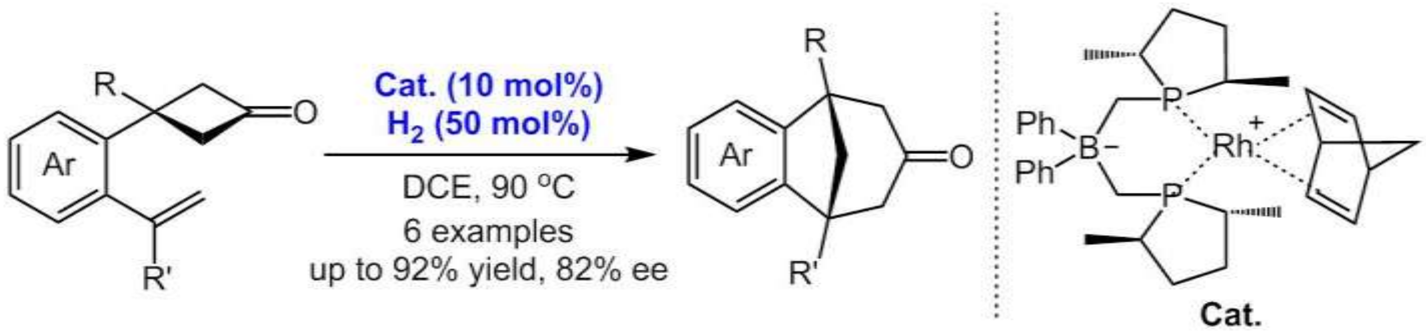


Murakami, M. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 2485.

Ring Opening of Cyclobutanones with Alkene

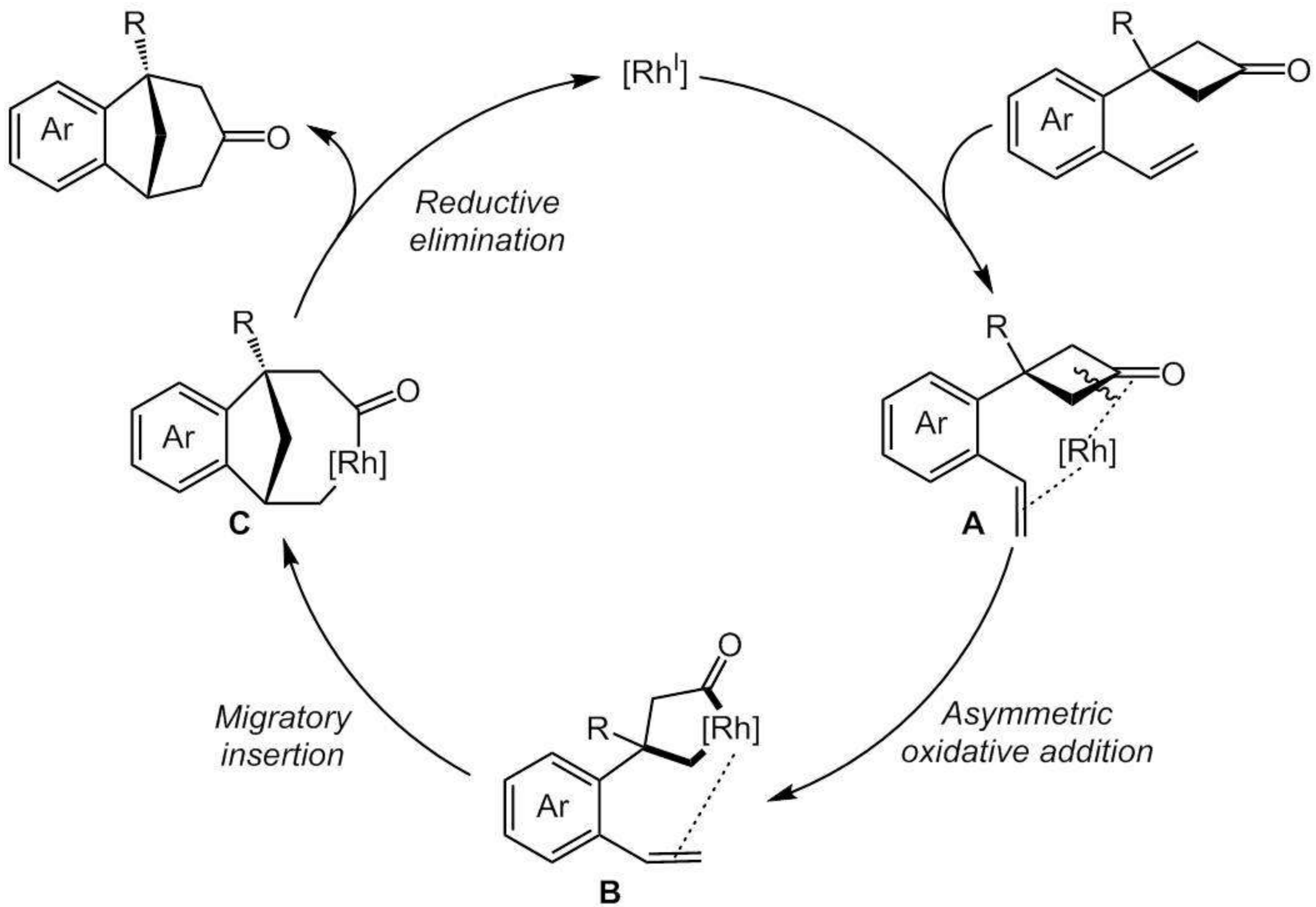


Cramer, N. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 3001.



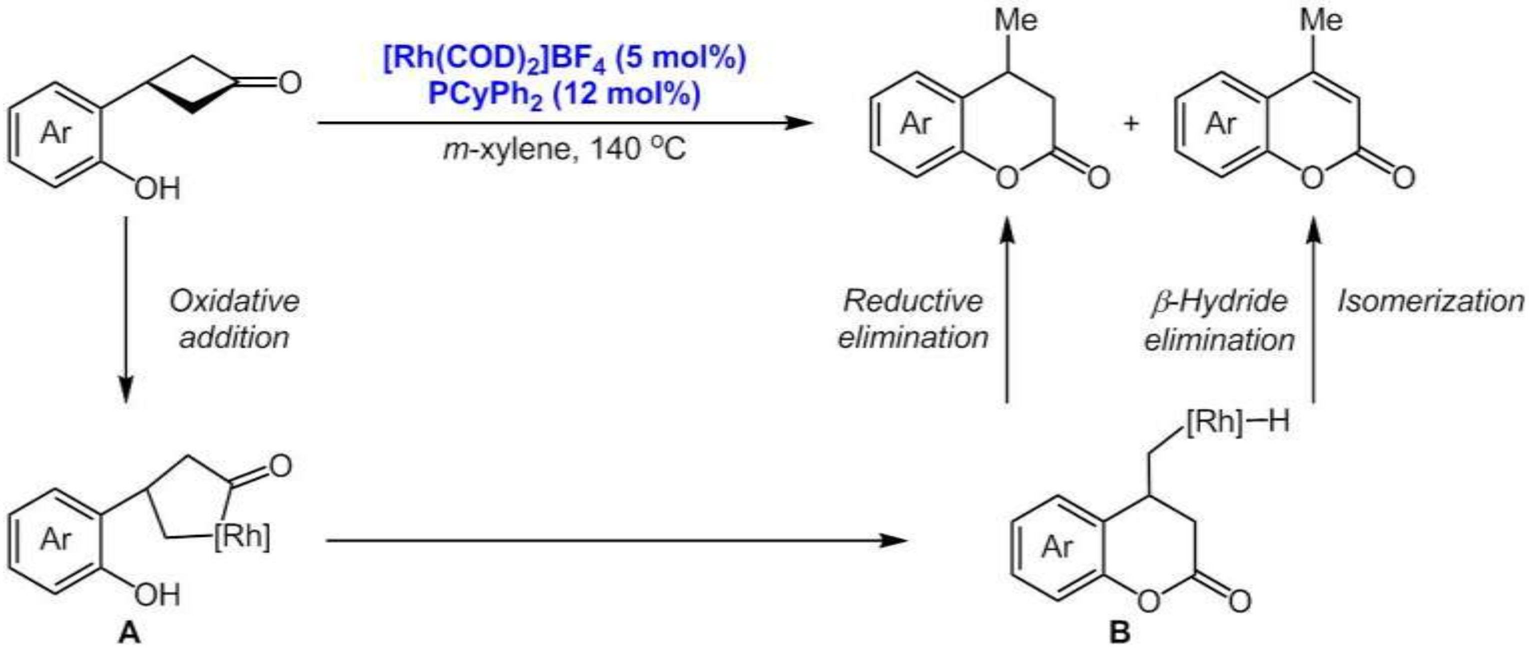
Cramer, N. *et al*. *Organometallics* **2014**, *33*, 780.

Ring Opening of Cyclobutanones with Alkene

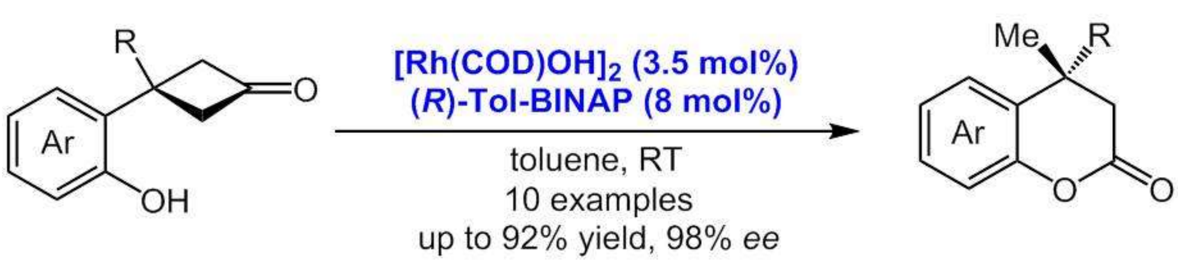


Cramer, N. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 3001.

Ring Opening of Cyclobutanones with Phenol

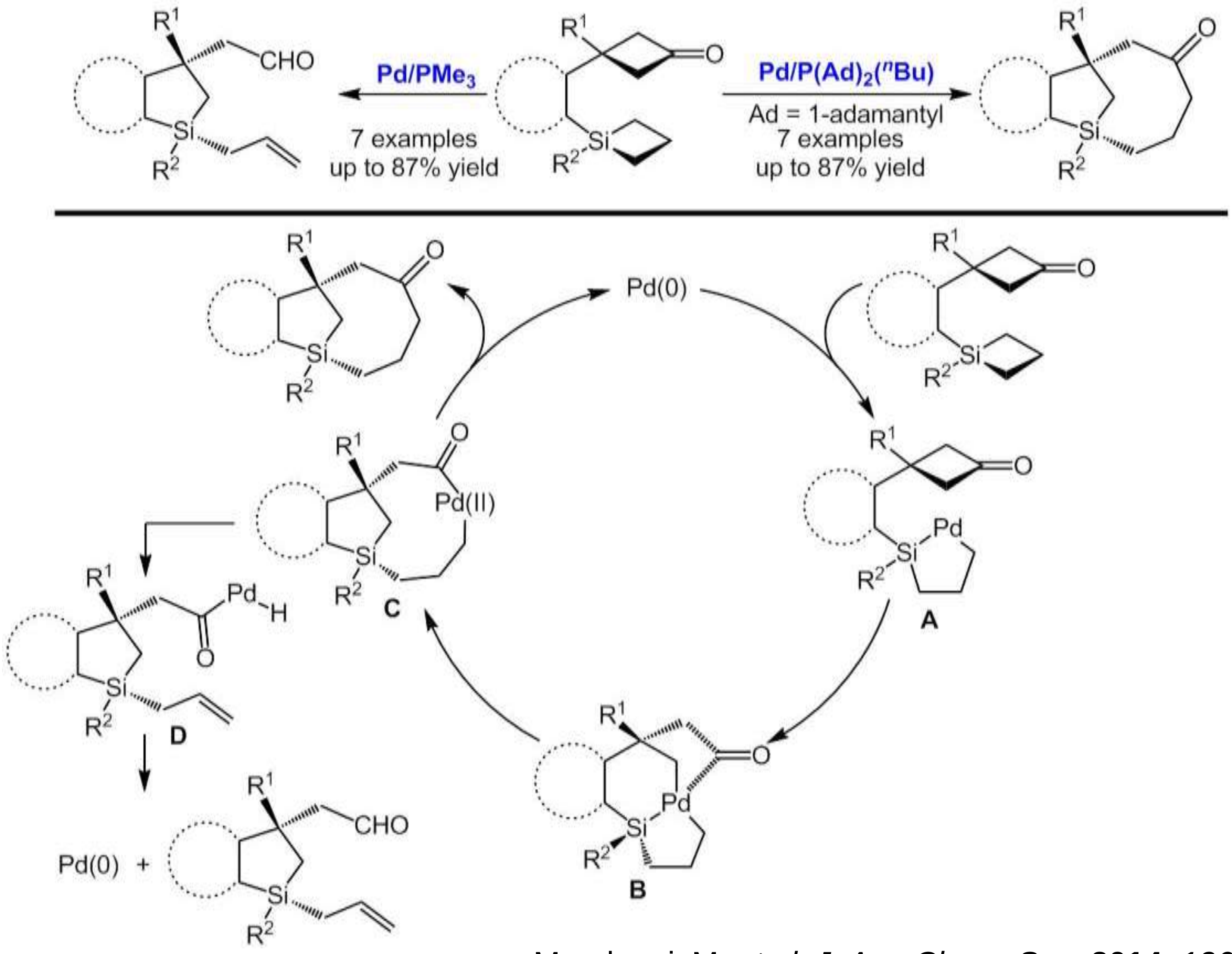


Murakami, M. *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2484.



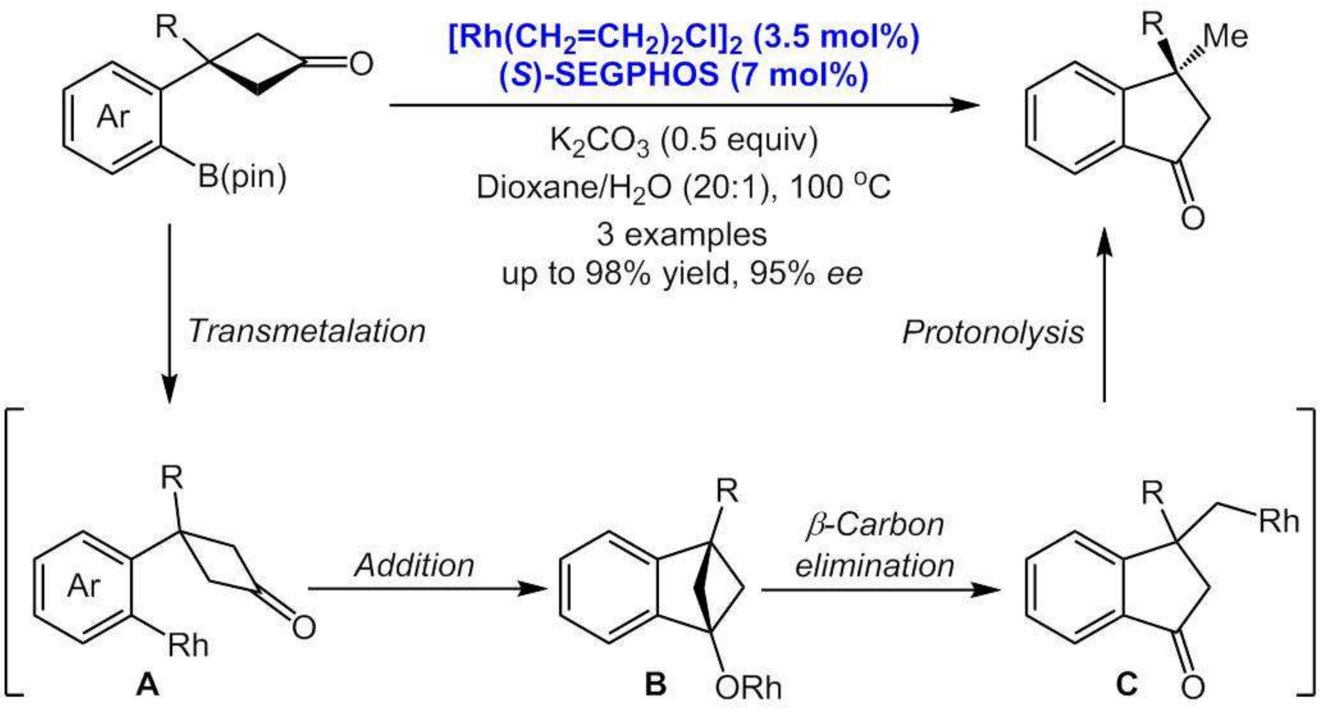
Murakami, M. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12086.

Ring Opening of Cyclobutanones with Silacyclobutane



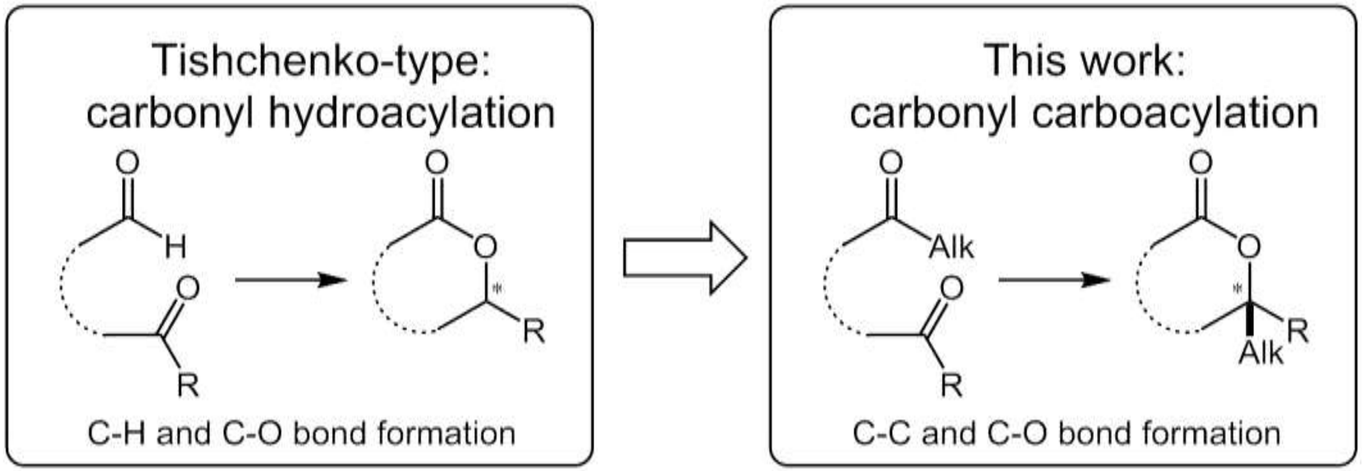
Murakami, M. *et al. J. Am. Chem. Soc.* **2014**, *136*, 5912.

Ring Opening of Cyclobutanones with ArB(pin)

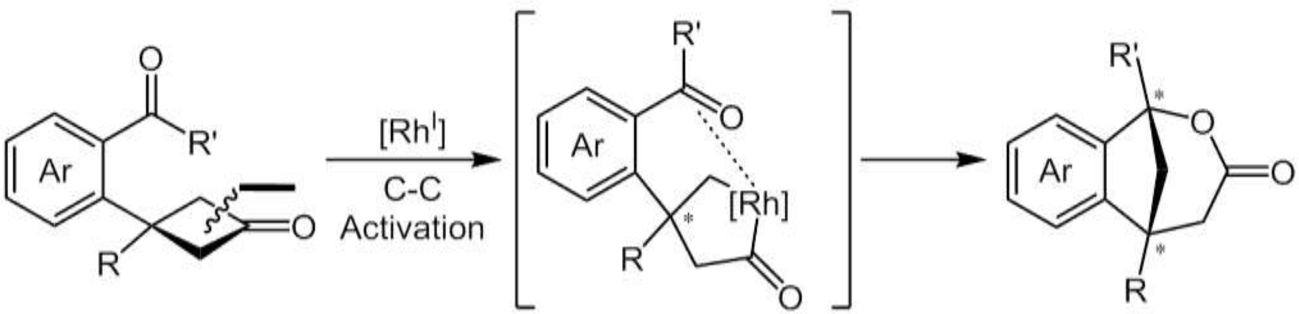


Murakami, M. *et al. Org. Lett.* **2006**, *8*, 3379.

Rh-Catalyzed Ring Opening of Cyclobutanones

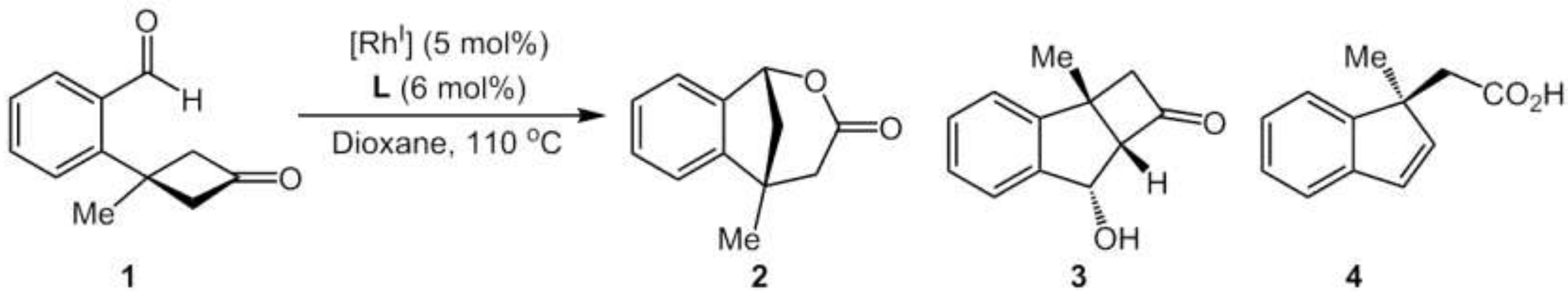


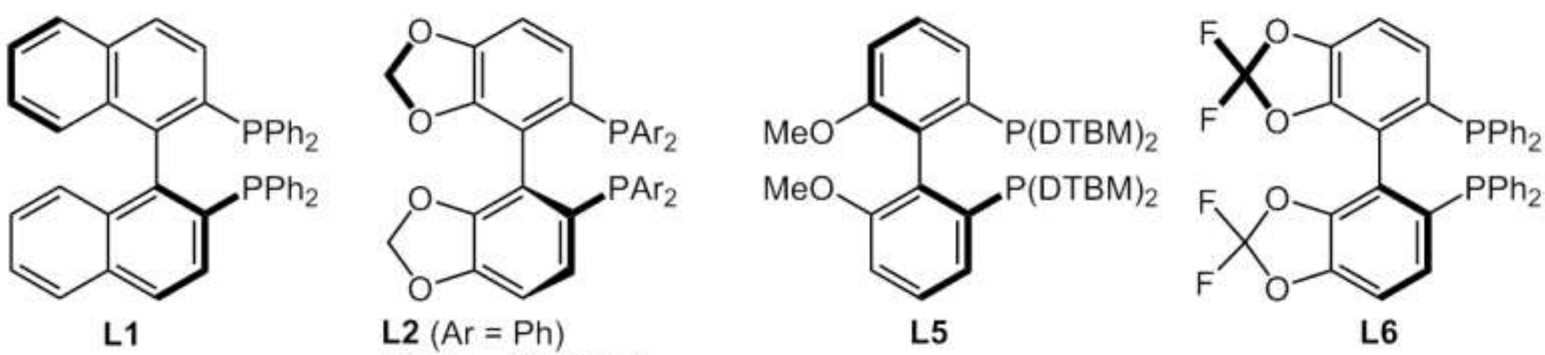
Carbonyl hydroacylation: First step (ketone C-C activation)



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9640.

Condition Optimization





L2 (Ar = Ph)
L3 (Ar = 3,5-Xylyl)
L4 (Ar = DTBM)

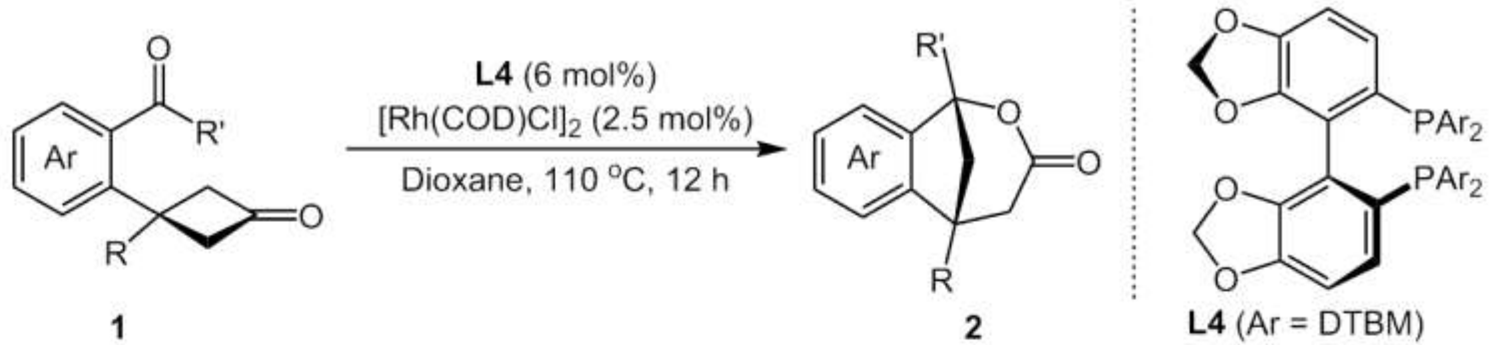
DTBM = 3,5-^{t}Bu-4-MeO-C_6H_2

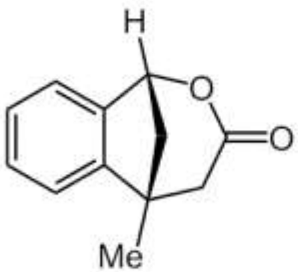
Condition Optimization

Entry[a]	[Rh[I]]	L	Temp (°C)	Yield (%) [b]	*Ee* [c]
1	$[Rh(COD)Cl]_2$	**L1**	110	8	86.4
2	$[Rh(COD)Cl]_2$	**L2**	110	30	98.4
3	$[Rh(COD)Cl]_2$	**L3**	110	45	99.0
4	$[Rh(COD)Cl]_2$	**L4**	110	94(89)	98.8
5	$[Rh(COD)Cl]_2$	**L5**	110	65	99.0
6	$[Rh(COD)Cl]_2$	**L6**	110	15	99.6
7	$[Rh(COD)OH]_2$	**L4**	110	0	ND
8	$[Rh(COD)_2]BF_4$	**L4**	110	25	ND
9	$[Rh(COD)I]_2$	**L4**	110	81 (**3**)	0
10	$[Rh(COD)Cl]_2$	**L4**	90	25	ND
11	$[Rh(COD)Cl]_2$	**L4**	130	90 (**4**)	ND

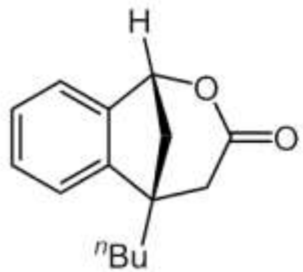
[a] Reaction conditions: **1** (0.05 mmol), [Rh[I]] (5 mol%), L (6 mol%), 0.25 M in 1,4-Dioxane at 110 °C for 12 h. [b] Yield of **2a** determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

Substrate Scope

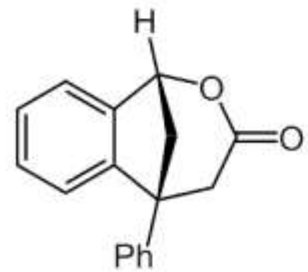




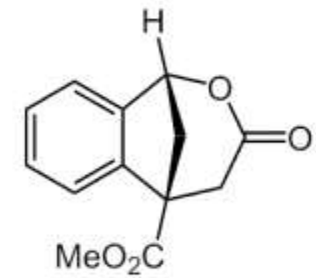
2a, 89% yield, 99% ee



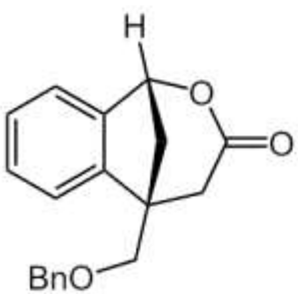
2b, 76% yield, 99% ee



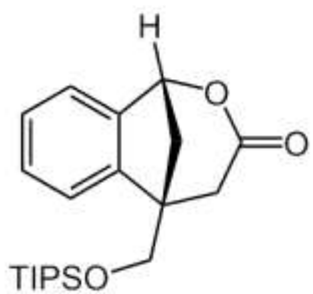
2c, 80% yield, 99% ee



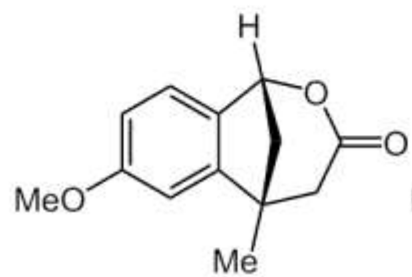
2d, 78% yield, 99% ee



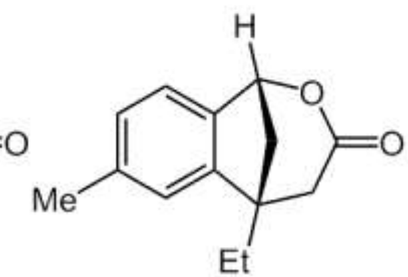
2e, 89% yield, 98% ee



2f, 64% yield, 94% ee

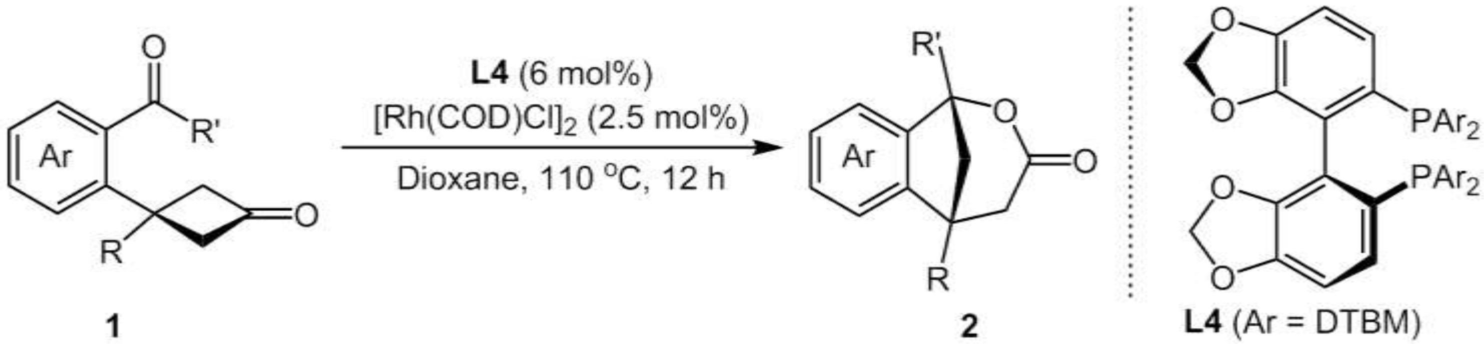


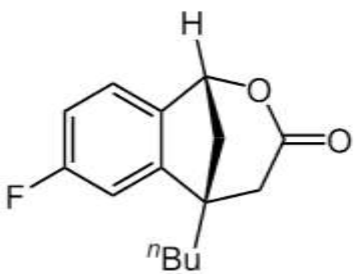
2g, 83% yield, 99% ee



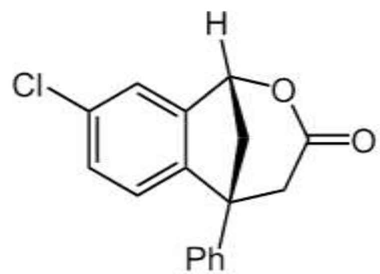
2h, 83% yield, 99% ee

Substrate Scope

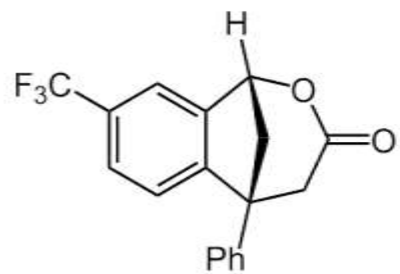




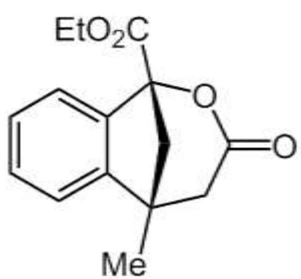
2i, 69% yield, 99% ee



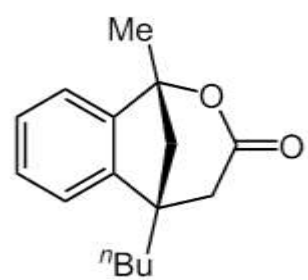
2j, 86% yield, 99% ee



2k, 85% yield, 99% ee

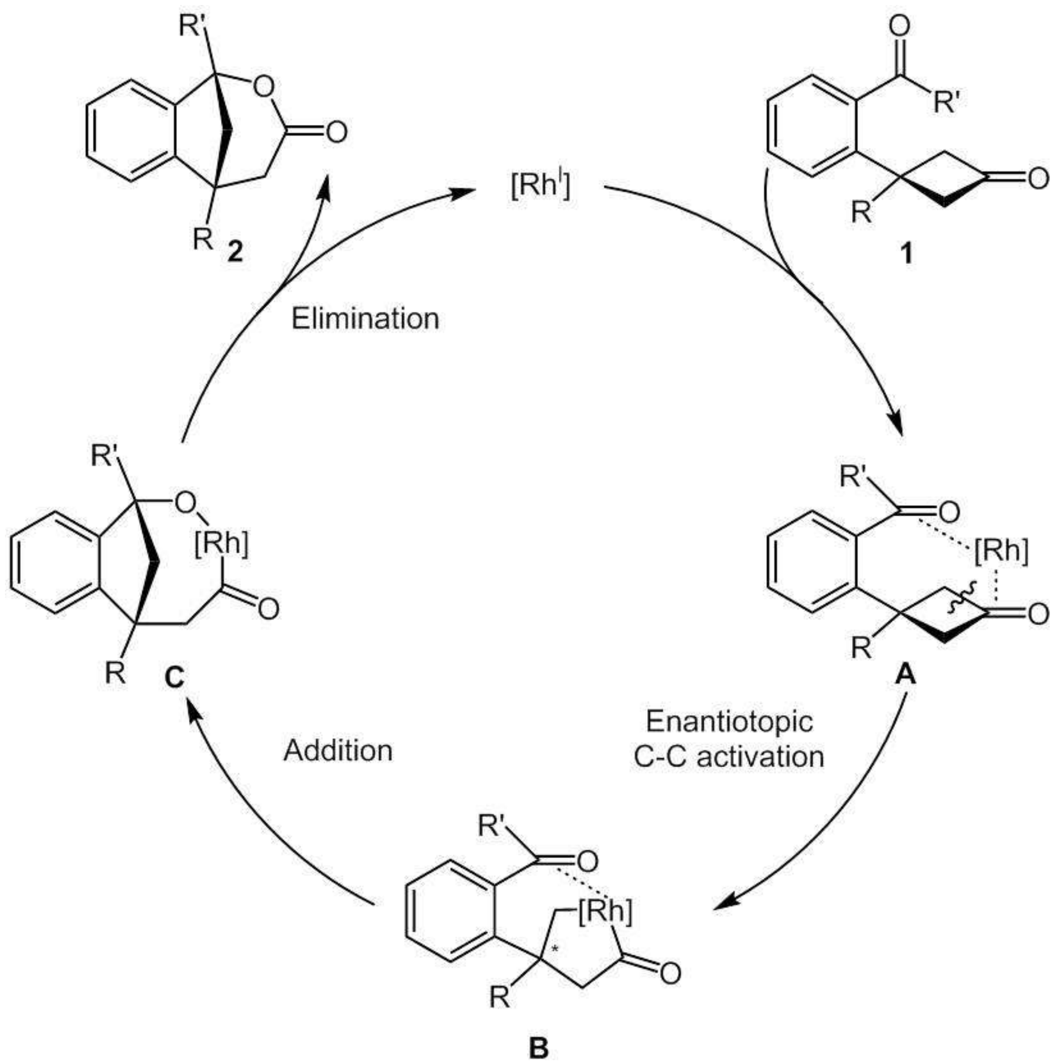


2l, 80% yield, 99% ee



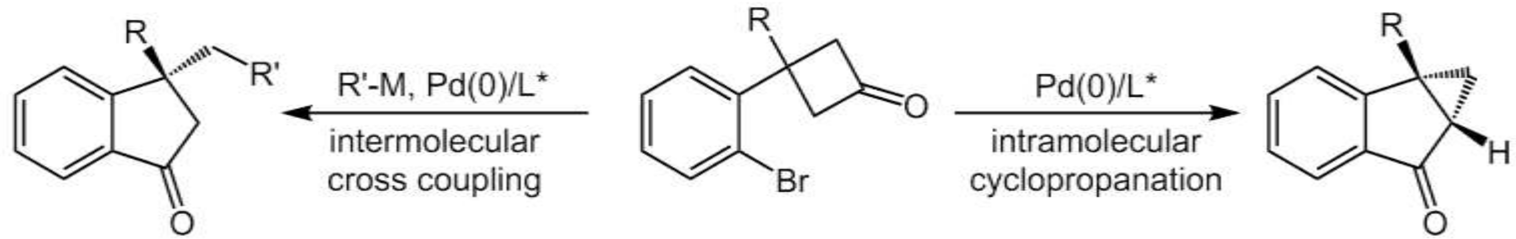
2m, 81% yield, 99% ee

Proposed Mechanism

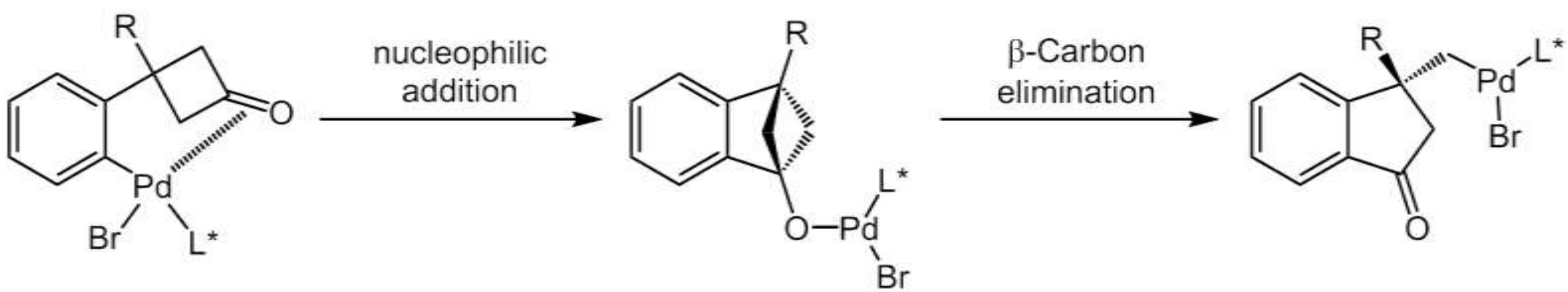


Pd-Catalyzed Ring Opening of Cyclobutanones

Enantioselective ring-opening/cyclopropanation and intermolecular capture



Proposed enantioselective ring-opening process



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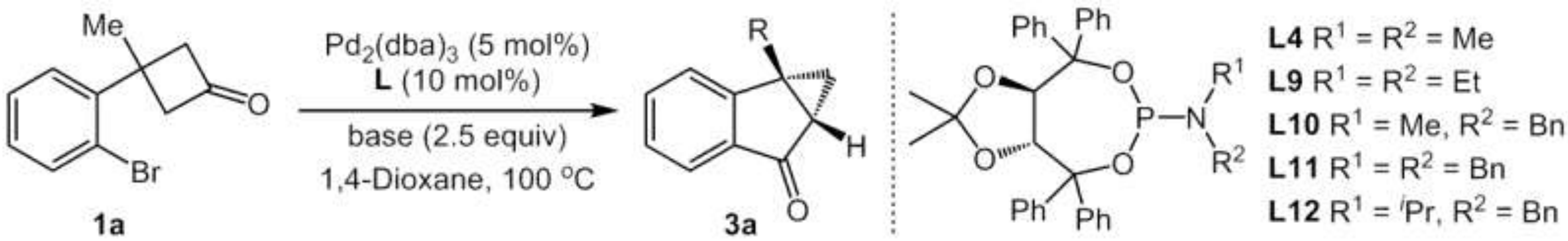
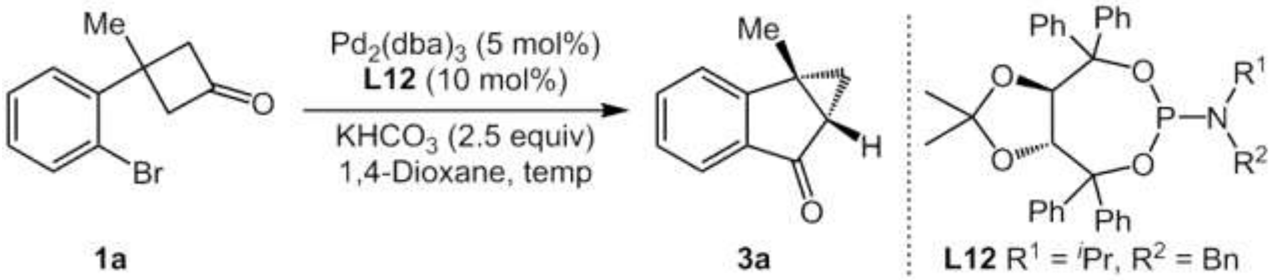
Condition Optimization



Entry[a]	L	Base	Yield (%) [b]	ee [c]
1	**XPhos**	K_2CO_3	9	-
2	**XPhos**	K_2CO_3+TsOH	49	-
3	**XPhos**	$KHCO_3$	96	-
4	**L4**	$KHCO_3$	94	32
5	**L9**	$KHCO_3$	92	80
6	**L10**	$KHCO_3$	96	78
7	**L11**	$KHCO_3$	94	75
8	**L12**	$KHCO_3$	91	93
9	**L12**	$NaHCO_3$	92	93
10	**L12**	Na_2CO_3	22	90
11	**L12**	$AgCO_3$	16	93

[a] Reaction conditions: **1** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), L (10 mol%), Base (2.5 equiv), 1,4-Dioxane (2 mL), 100 °C, 24 h.

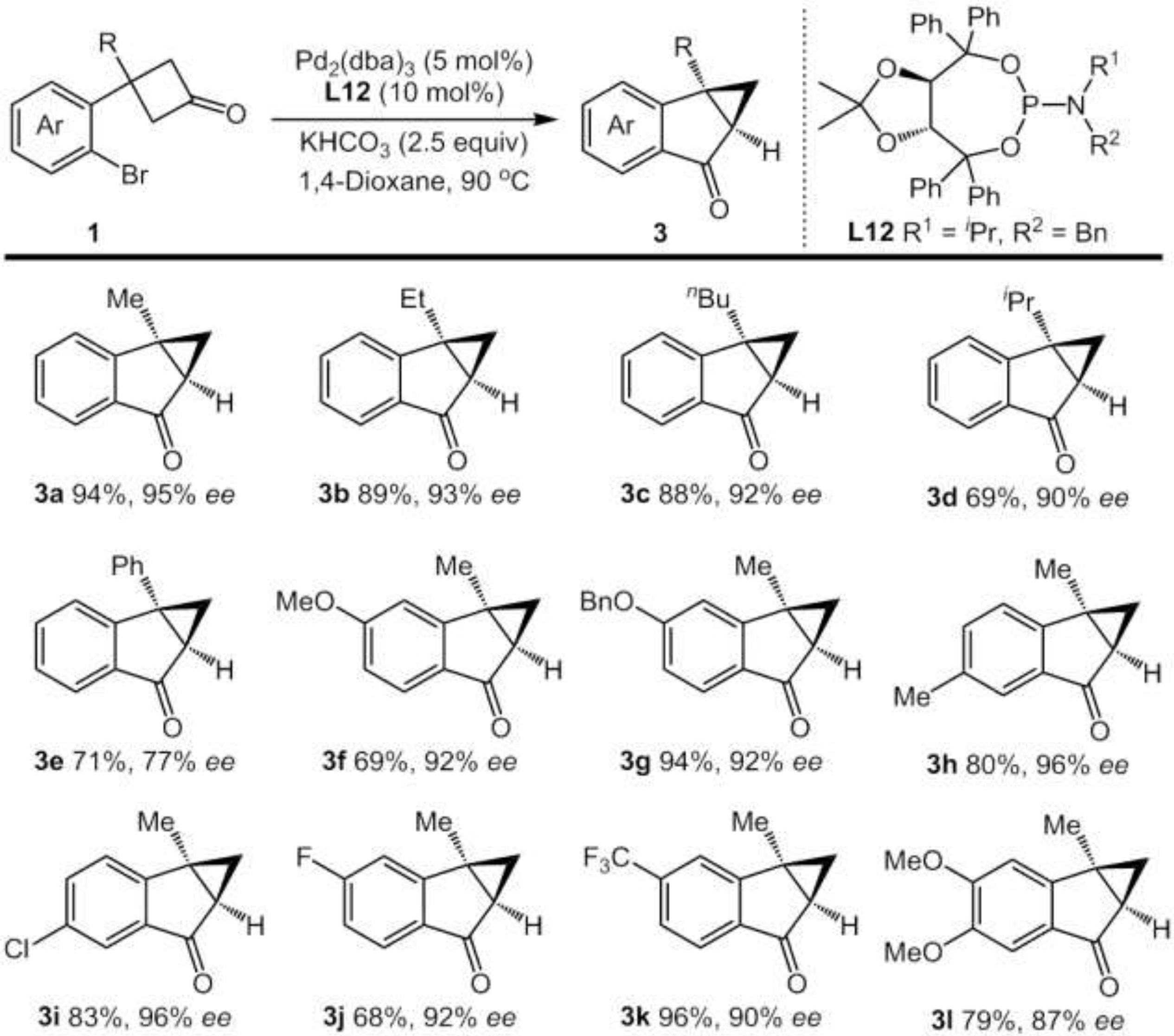
Condition Optimization



Entry[a]	Solvent	Temp (°C)	Yield (%) [b]	ee [c]
1	1,4-Dioxane	100	91	93
2	1,4-Dioxane	90	94	95
3	1,4-Dioxane	80	26	94
4	Toluene	90	70	92
5	CH_3CN	90	20	30
6	DCE	90	94	93
7	DMF	90	90	24
8	$CHCl_3$	90	85	94

[a] Reaction conditions: **1** (0.2 mmol), $Pd_2(dba)_3$ (5 mol%), **L12** (10 mol%), $KHCO_3$ (2.5 equiv), 1,4-Dioxane (2 mL), 100 °C, 24 h.

Substrate Scope



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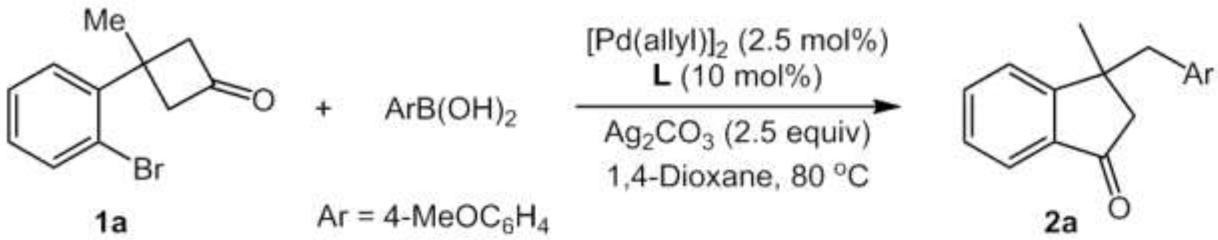
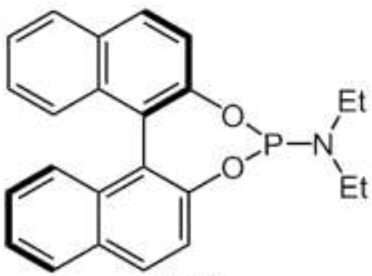
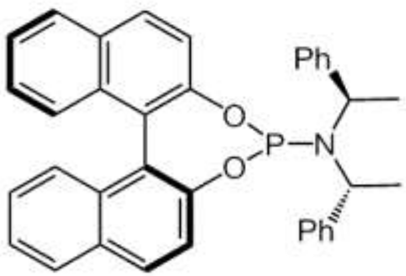
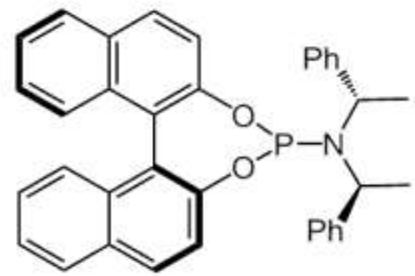




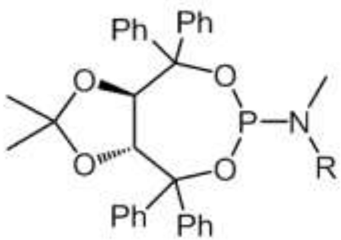
L1 (R)
19%, 46% *ee*



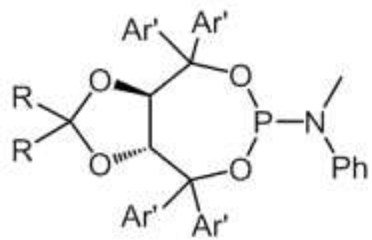
L2 (*S*,*R*,*R*)
35%, 31% *ee*



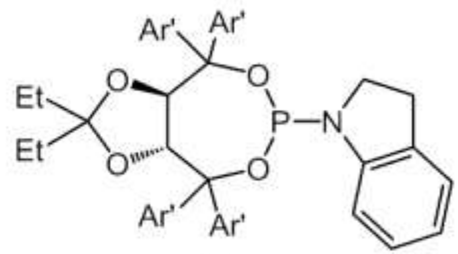
L3 (*S*,*S*,*S*)
34%, 54% *ee*



L4 (*R*,*R*) R = Me
31%, -11% *ee*
L5 (*R*,*R*) R = Ph
11%, 25% *ee*

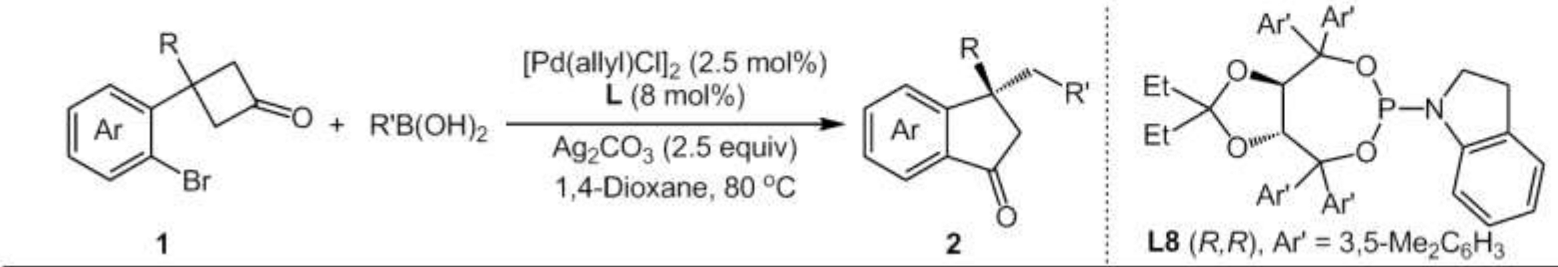


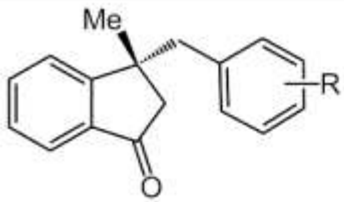
L6 (*R*,*R*) R = Me
42%, 72% *ee*
L7 (*R*,*R*) R = Et
90%, 86% *ee*



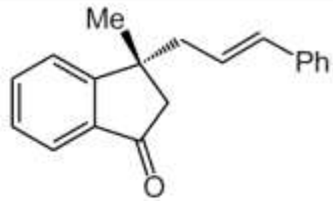
L8 (*R*,*R*)
91%, 87% *ee*
Ar' = 3,5-$Me_2C_6H_3$

Substrate Scope

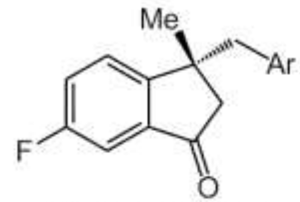




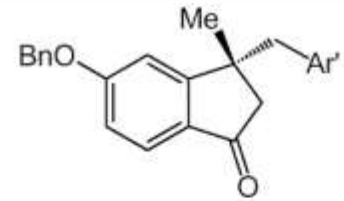
2a R = 4-MeO 91%, 87% *ee*
2b R = 3-F 50%, 91% *ee*
2c R = 4-CO_2Me 72%, 88% *ee*



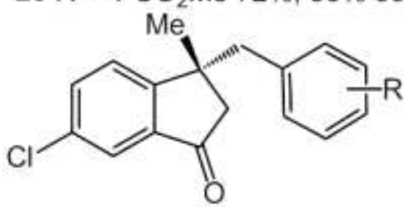
2m 64%, 88% *ee*



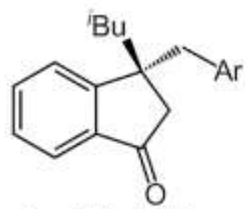
2t 70%, 91% *ee*



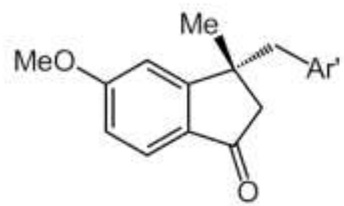
2u 58%, 90% *ee*



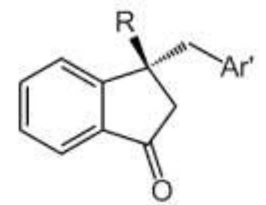
2d R = 4-MeO 68%, 95% *ee*
2e R = 3-MeO 55%, 88% *ee*
2f R = 4-MeS 62%, 86% *ee*
2g R = 4-Phent 57%, 92% *ee*
2h R = 3,5-Me_2 63%, 91% *ee*
2i R = H 87%, 92% *ee*
2j R = 4-CF_3O 67%, 93% *ee*
2k R = 4-Cl 76%, 92% *ee*
2l R = 4-CO_2Me 71%, 92% *ee*



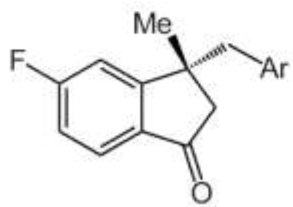
2q 40%, 90% *ee*



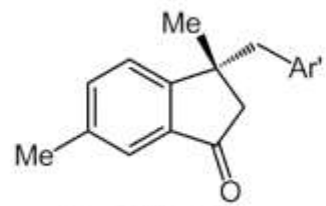
2r 83%, 90% *ee*



2n R = Et 64%, 92% *ee*
2o R = ^{n}Bu 73%, 91% *ee*
2p R = Ph(CH_2)$_2$ 76%, 90% *ee*



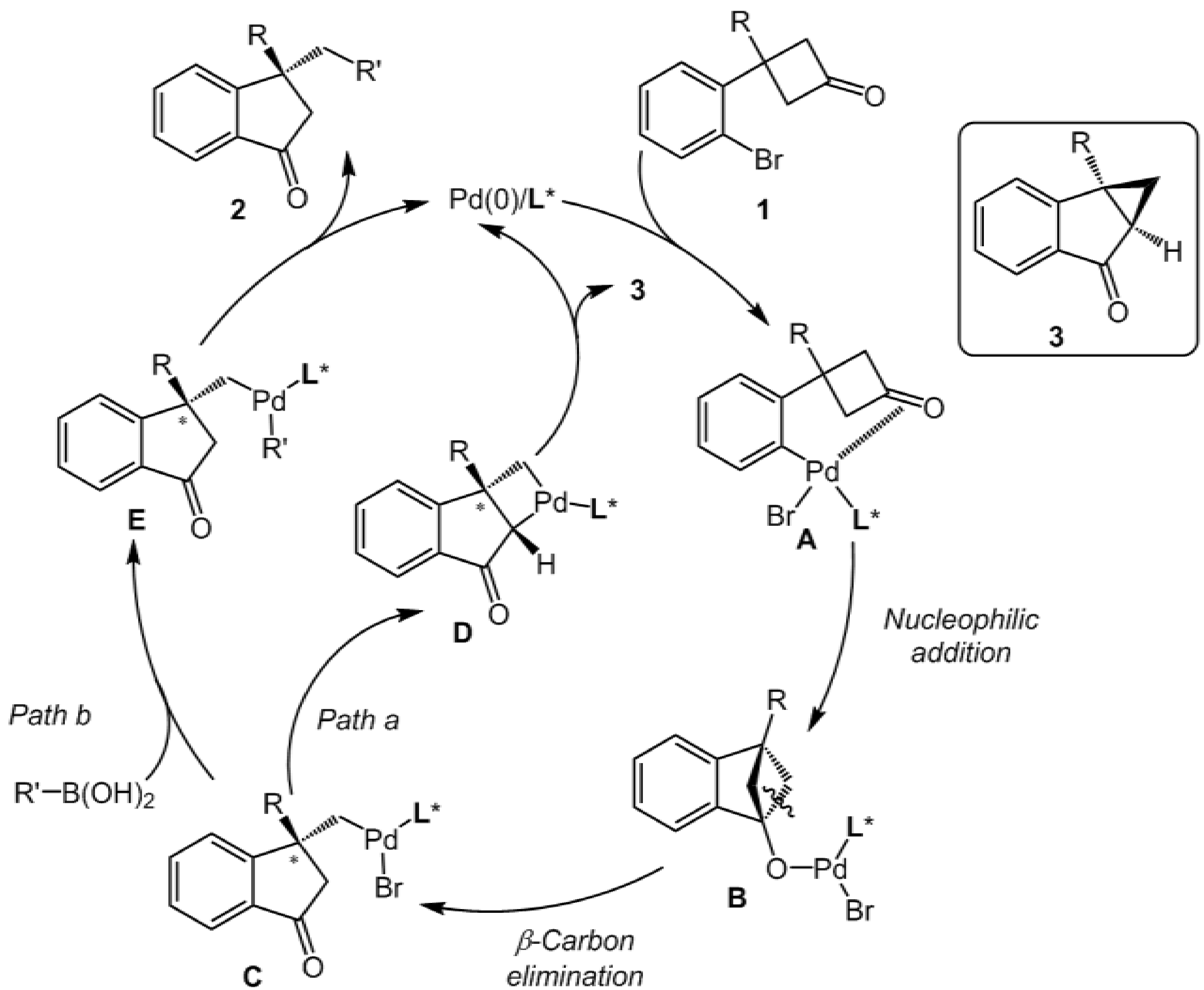
2v 65%, 92% *ee*



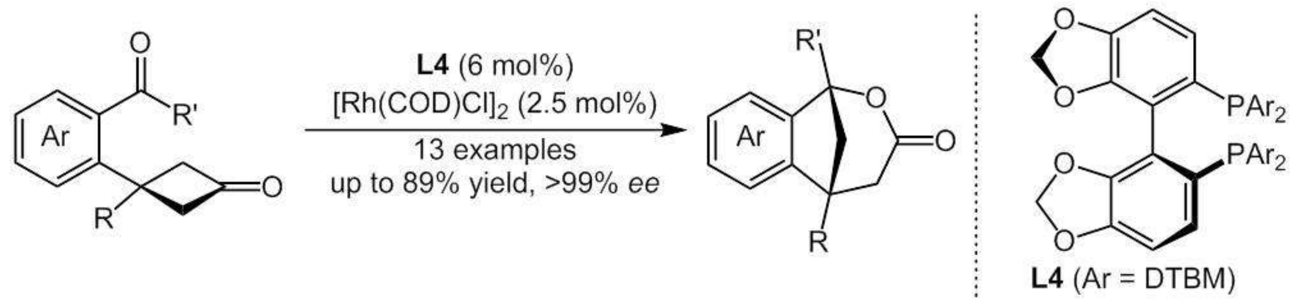
2s 63%, 88% *ee*

Ar = 4-MeOC_6H_4
Ar' = 4-(MeOCO)C_6H_4

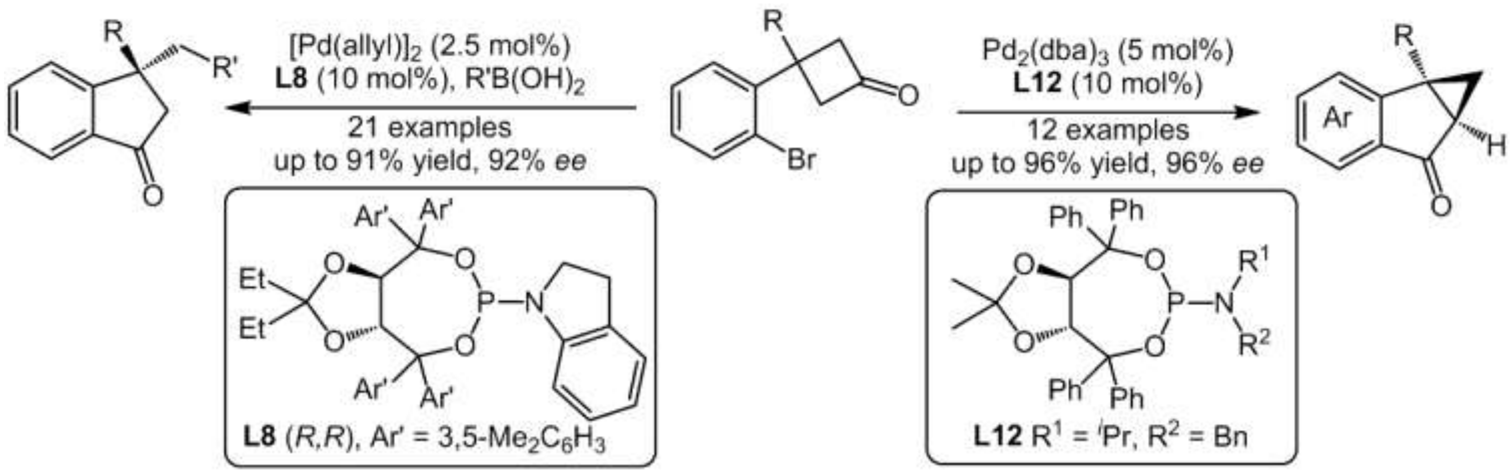
Proposed Catalytic Cycle



Summary



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 9640.



Xu, L.-W. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 897.

The First Paragraph

Quaternary carbon stereocenters, bonded by four different carbon substituents, are omnipresent in natural products and pharmaceuticals. Catalytic enantioselective creation of quaternary stereocenters is a long term challenge. In this respect, enantioselective desymmetrization of prochiral small-ring compounds has emerged as a powerful tool for creating quaternary carbon stereocenters. For example, enantioselective desymmetrization of prochiral cyclobutanones through Rh- and Ni catalyzed ring opening and ring expansion has been achieved by the groups of Murakami, Cramer, and Dong. In addition, Pd-catalyzed racemic ring-opening and ring-expansion reaction patterns of cyclobutanones were established by Murakami and co-workers with achiral catalyst systems.

The First Paragraph

Recently, Lu and co-workers reported a Pd-catalyzed asymmetric intramolecular α-arylation of prochiral cyclobutanones and aryl halides to form chiral cyclobutanones containing quaternary carbon stereocenters.

The Last Paragraph

In conclusion, we have developed a tandem nucleophilic addition/β-carbon elimination reaction between cyclobutanones and intramolecular aryl halides, which generates σ-alkylpalladium species bearing β-quaternary carbon stereocenters. When using boronic acids as external nucleophilic trapping reagents, an enantioselective domino ring-opening/cross-coupling reaction was achieved for the construction of 1-indanones bearing C3-quaternary stereocenters. In addition, a ring opening/cyclopropanation sequence was realized in the absence of external nucleophiles, affording chiral cyclopropane-fused indanones in good yields and enantioselectivity.

Thanks

for your attention