Literature Report VI

Palladium-Catalyzed Asymmetric Intramolecular Reductive Heck Desymmetrization of Cyclopentenes: Access to Chiral Bicyclo[3.2.1]octanes

Reporter: Xin-Wei Wang
Checker: Chang-Bin Yu
Date: 2019-6-3

Jia, Y.-X. *et al. J. Am. Chem. Soc*. **2015**, *137*, 4936.
Yao, H. *et al. Angew. Chem. Int. Ed.* **2019***, 58, 2884.*

CV of Professor Yao, H.

Yao, H.

Background:

- **1994-1998** B.S. in China Pharmaceutical University;
- **1998-2001** M.S. in China Pharmaceutical University;
- **2001-2004** Ph.D. in SIOC;
- **2004-2007** Postdoctoral, in Stanford University;
- **2008-Now** Professor, China Pharmaceutical University.

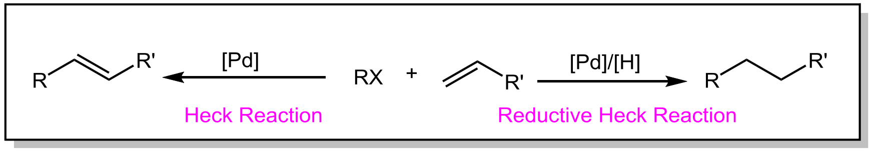
Research:

Total synthesis of biologically active natural products;

Catalytic organic reaction.

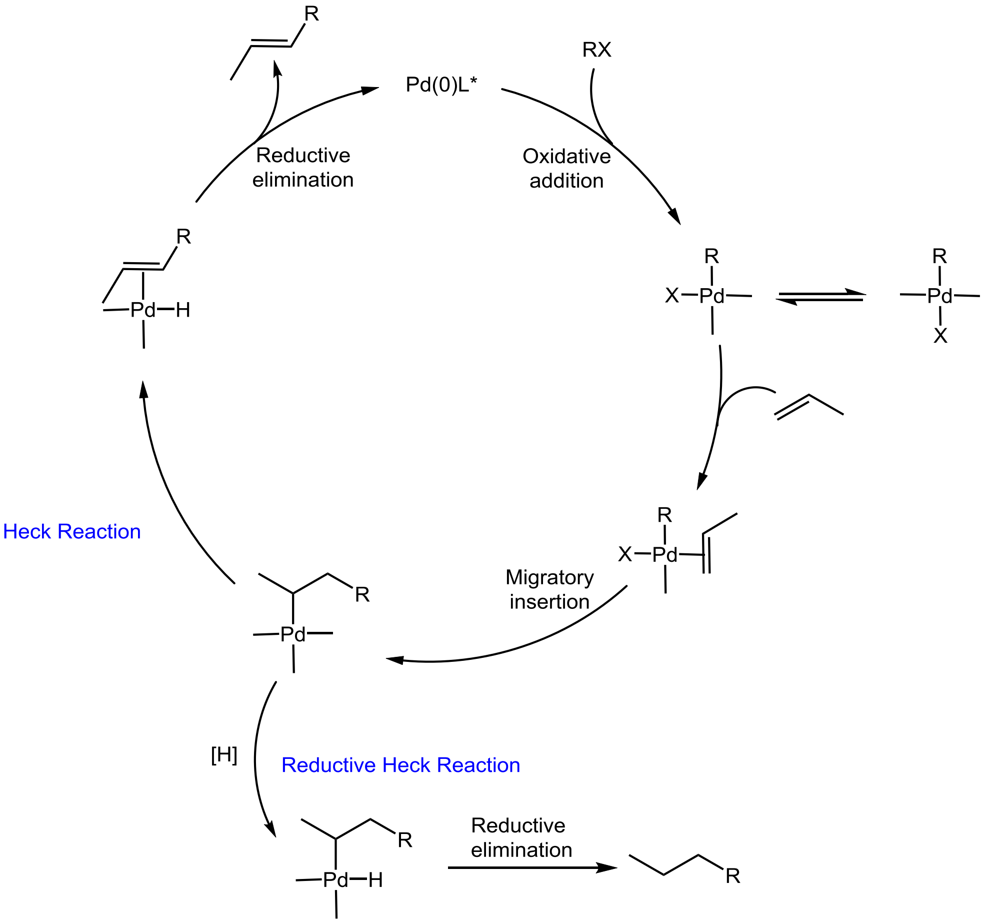
Contents

Introduction



Heck Reaction

Reductive Heck Reaction



Reductive elimination

Oxidative addition

Migratory insertion

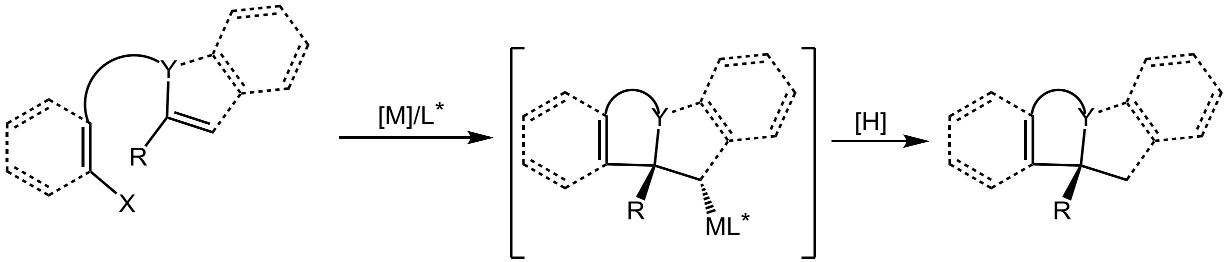
Heck Reaction

Reductive Heck Reaction

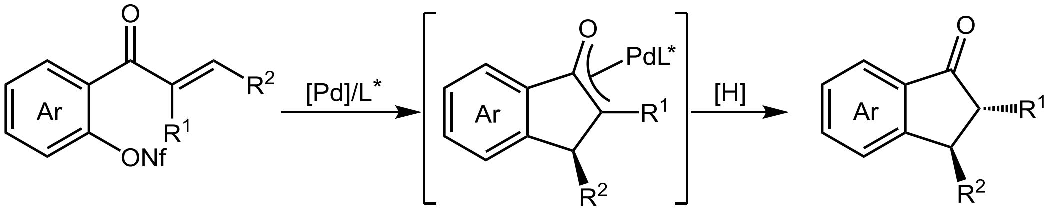
Reductive elimination

Present Works for Reductive Heck Reaction

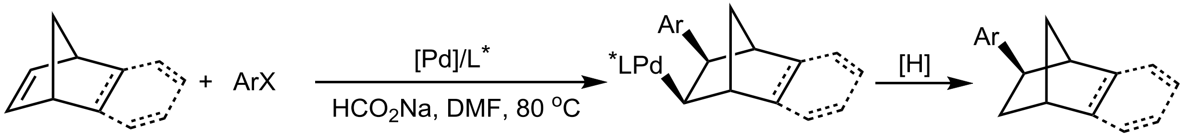
Intermediates Lacking β-Hydrogen



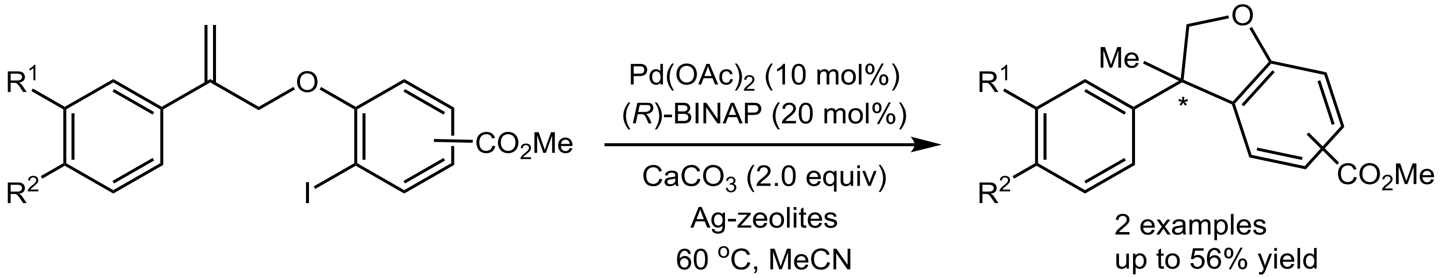
Stabilized Pd-enolate Intermediates



Geometrically Constrained Intermediates



First Asymmetric Reductive Heck Reaction

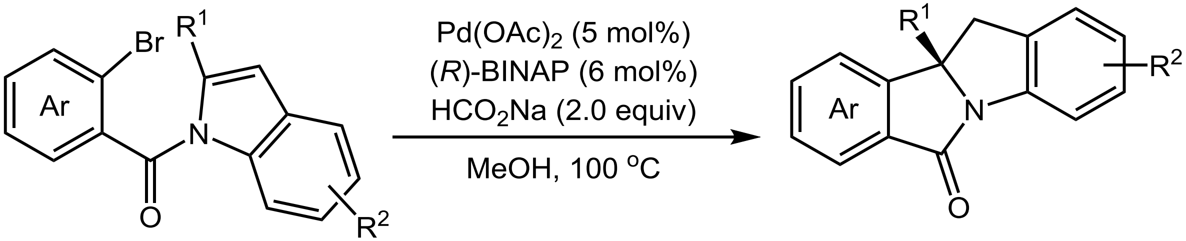


$Pd(OAc)_2$ (10 mol%)
(*R*)-BINAP (20 mol%)
$CaCO_3$ (2.0 equiv)
Ag-zeolites
60 °C, MeCN

2 examples
up to 56% yield
up to 81% ee

Diaz, P. *et al. Tetrahedron* **1998**, *54*, 4579.

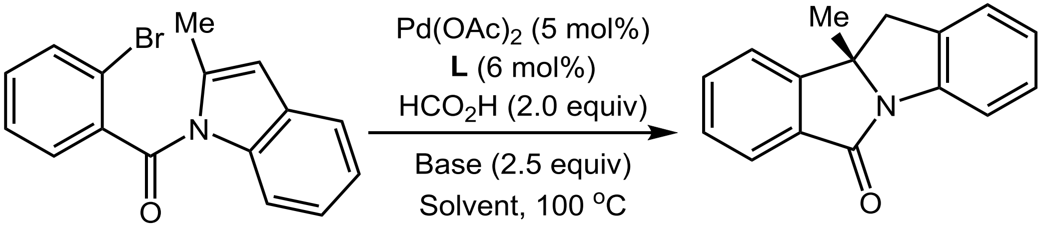
Enantioselective Reductive Heck Reaction



up to 89% yield
up to 99% ee

Jia, Y.-X. *et al. J. Am. Chem. Soc*. **2015**, *137*, 4936.

Optimization of the Reaction Conditions

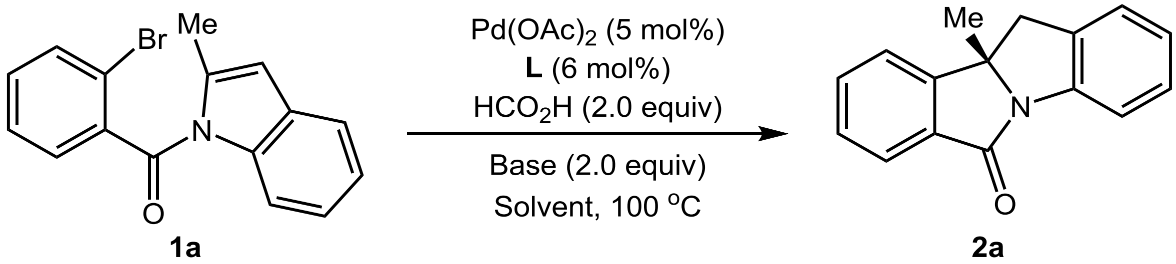


$Pd(OAc)_2$ (5 mol%)
L (6 mol%)
HCO_2H (2.0 equiv)
Base (2.5 equiv)
Solvent, 100 °C

1a **2a**

Entry[a]	**L**	Based	Solvent	Yield (%)[b]	Ee (%)[c]
1	(*R*)-BINAP	Et_3N	THF	<5	-
2	(*R*)-BINAP	Et_3N	toluene	<5	-
3	(*R*)-BINAP	Et_3N	MeCN	36	96
4	(*R*)-BINAP	Et_3N	DCE	35	96
5	(*R*)-BINAP	Et_3N	MeOH	79	97
6	(*R*)-BINAP	Et_3N	EtOH	75	97
7	(*R*)-BINAP	Et_3N	*i*PrOH	70	96
8	(*R*)-BINAP	TMEDA	MeOH	77	98
9	(*R*)-BINAP	DIPA	MeOH	80	97
10	(*R*)-BINAP	DABCO	MeOH	78	97

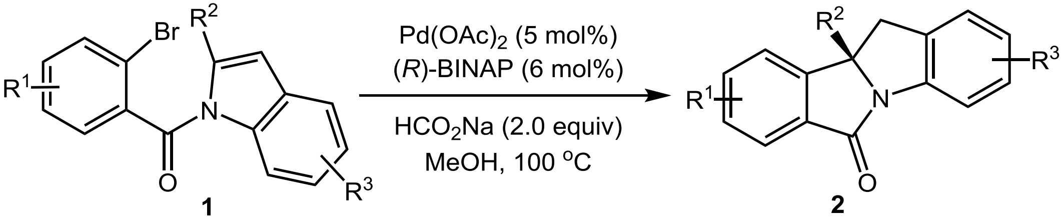
Optimization of the Reaction Conditions



Entry[a]	L	Based	Solvent	Yield (%)[b]	Ee (%)[c]
11	(*R*)-BINAP	DBU	MeOH	69	97
12[d]	(*R*)-BINAP	HCO_2NH_4	MeOH	80	93
13[d]	(*R*)-BINAP	HCO_2Na	MeOH	85	97
14[d]	(*R*)-Tol-BINAP	HCO_2Na	MeOH	82	97
15[d]	(*R*)-Segphos	HCO_2Na	MeOH	82	82
16[d]	(*R*)-Synphos	HCO_2Na	MeOH	81	98
17[d,e]	(*R*)-BINAP	HCO_2Na	MeOH	82	96

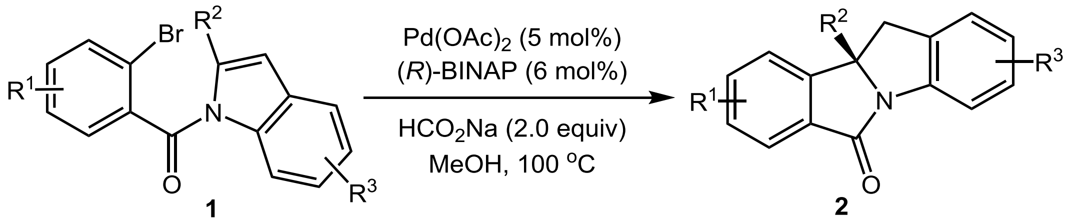
[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), **L** (6 mol %), and base (0.4 mmol) in the indicated solvent (2.0 mL) in a sealed Schlenk tube at 100 °C for 10 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] In the absence of HCO_2H. [e] At 80 °C for 36 h.

Substrate scope



Entry[a]	Product	R^1	R^2	R^3	Yield (%)[b]	Ee (%)[c]
1	**2a**	H	Me	H	85	97
2	**2b**	H	Bn	H	78	97
3	**2c**	H	CO_2Me	H	71	99
4	**2d**	H	Ph	H	81	97
5	**2e**	H	4-MeO-C_6H_4	H	88	92
6	**2f**	H	4-Me-C_6H_4	H	75	97
7	**2g**	H	4-Cl-C_6H_4	H	68	96
8	**2h**	H	4-CF_3-C_6H_4	H	64	98
9	**2i**	H	3-Me-C_6H_4	H	62	97
10	**2j**	H	2-Me-C_6H_4	H	15	94
11	**2k**	H	2-naphthyl	H	68	97
12	**2l**	H	2-furyl	H	67	98
13	**2m**	H	2-thienyl	H	62	99

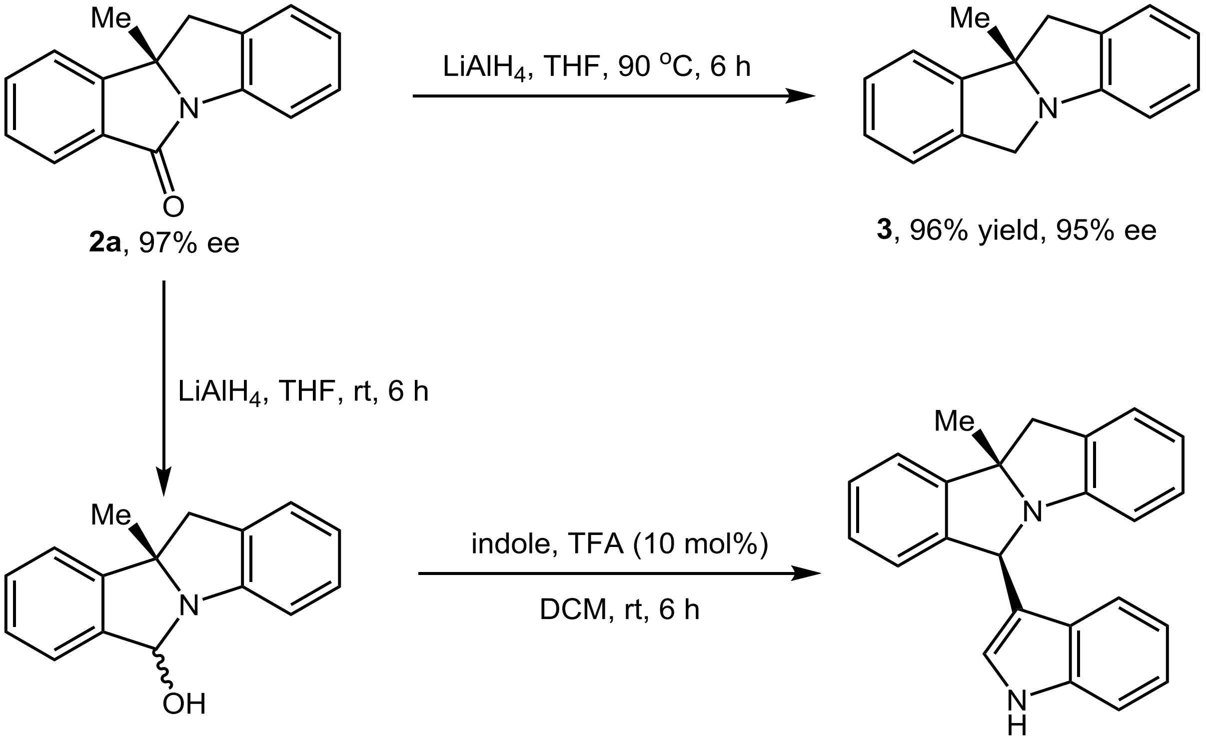
Substrate scope



Entry[a]	Product	R^1	R^2	R^3	Yield (%)[b]	Ee (%)[c]
14	**2n**	H	Ph	5-Me	76	98
15	**2o**	H	Ph	5-MeO	80	98
16	**2p**	H	Ph	5-Cl	46	98
17	**2q**	H	Ph	6-MeO	75	98
18	**2r**	H	Ph	6,7-$(CH)_4$	55	89
19[d]	**2s**	3-Me	Me	H	22	29
20	**2t**	4-Me	Me	H	85	98
21	**2u**	5-Me	Me	H	76	97
22	**2v**	5-Cl	Me	H	73	99
23	**2w**	5-F	Me	H	67	97

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (*R*)-BINAP (6 mol %), and HCO_2Na (0.4 mmol) in MeOH (2.0 mL) at 100 ºC for 10−36 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] At 120 ºC for 20 h.

Synthetic Transformations of Product 2a



$LiAlH_4$, THF, 90 °C, 6 h

$LiAlH_4$, THF, rt, 6 h

indole, TFA (10 mol%)

DCM, rt, 6 h

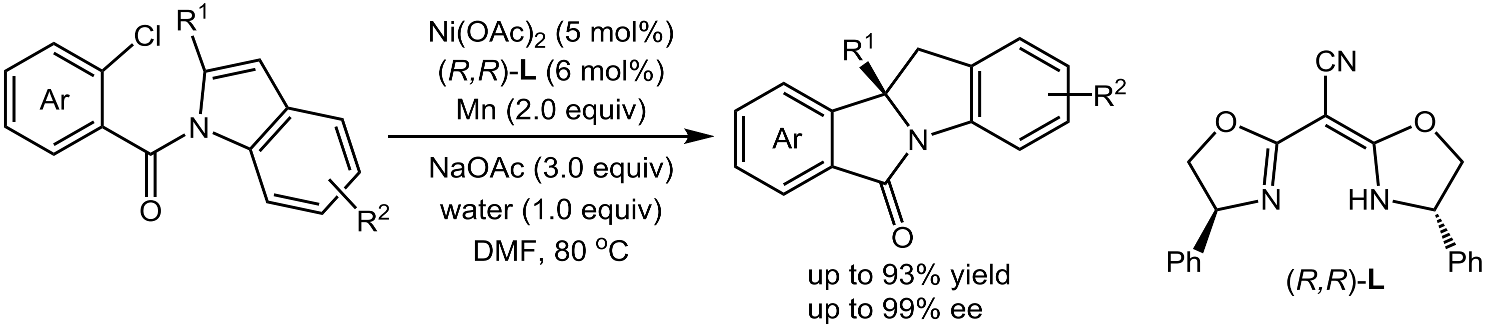
2a, 97% ee

3, 96% yield, 95% ee

4

5, 83% yield, 97% ee

Ni-Catalyzed Reductive Heck Cyclization



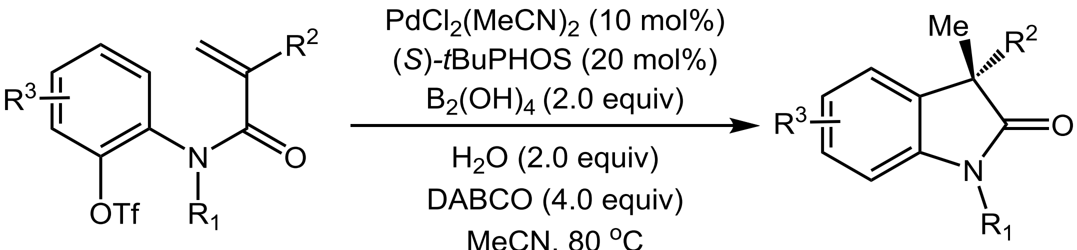
$Ni(OAc)_2$ (5 mol%)
(*R*,*R*)-**L** (6 mol%)
Mn (2.0 equiv)

NaOAc (3.0 equiv)
water (1.0 equiv)
DMF, 80 ^oC

up to 93% yield
up to 99% ee

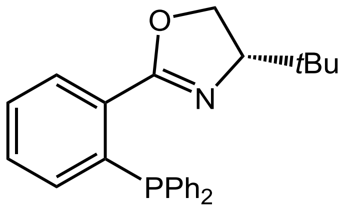
Zhou, J. S. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12727.

Asymmetric Synthesis of Oxindoles



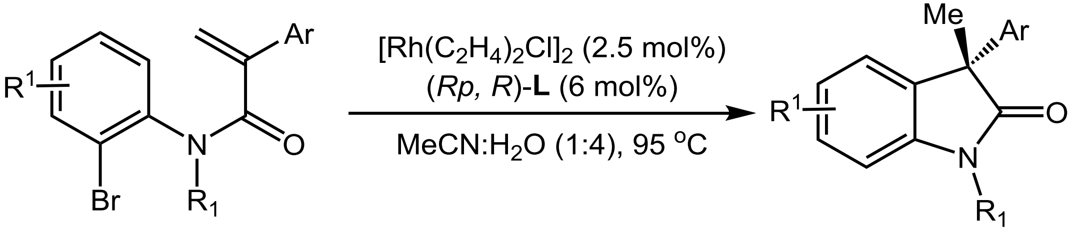
$PdCl_2(MeCN)_2$ (10 mol%)
(*S*)-*t*BuPHOS (20 mol%)
$B_2(OH)_4$ (2.0 equiv)
H_2O (2.0 equiv)
DABCO (4.0 equiv)
MeCN, 80 °C

up to 90% yield
up to 92% ee



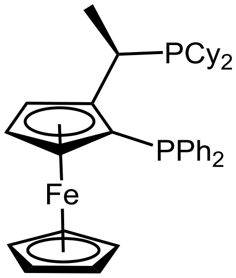
(*S*)-*t*BuPHOS

Zhu, J. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 3987.



$[Rh(C_2H_4)_2Cl]_2$ (2.5 mol%)
(*Rp, R*)-**L** (6 mol%)
$MeCN:H_2O$ (1:4), 95 °C

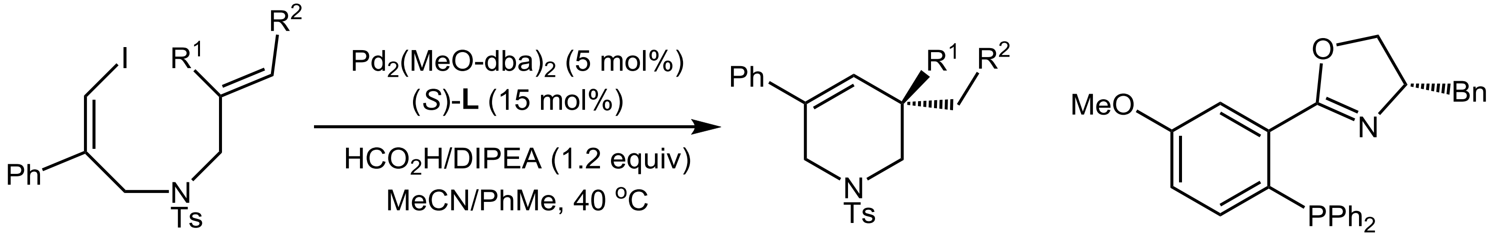
up to 99% yield
up to 96% ee



(*Rp, R*)-**L**

Lautens, M. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 11927.

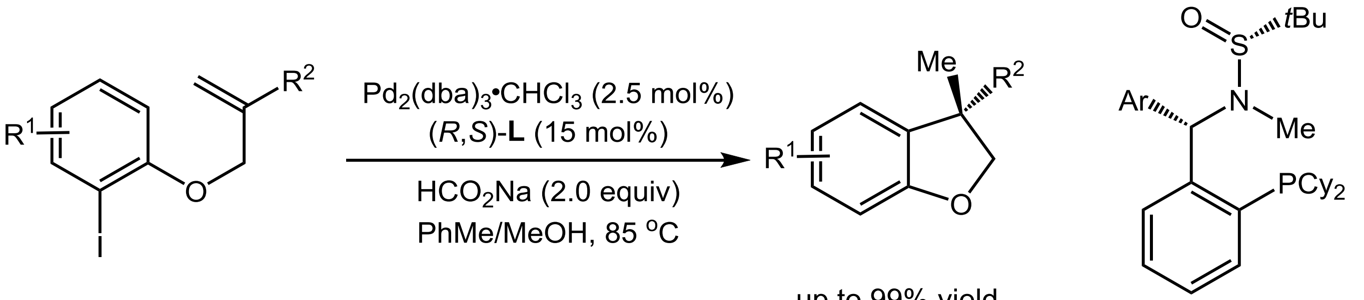
Pd-Catalyzed Reductive Heck Cyclization



up to 88% yield
up to 99% ee

(*S*)-**L**

Tong, X. *et al. Org. Biomol. Chem*. **2017**, *15*, 4803.

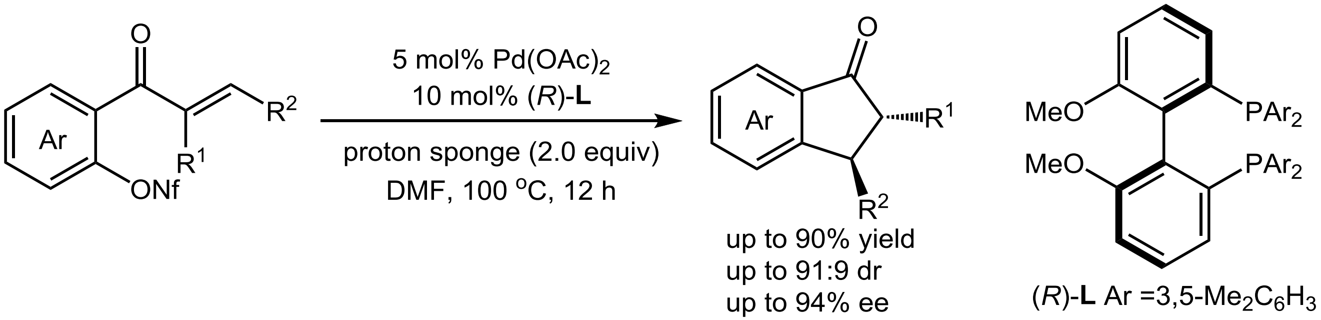


up to 99% yield
up to 95% ee

(*R*,*S*)-**L** Ar = 3,5-$(tBu)_2$-4-$MeOC_6H_2$

Zhang, J. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 10373.

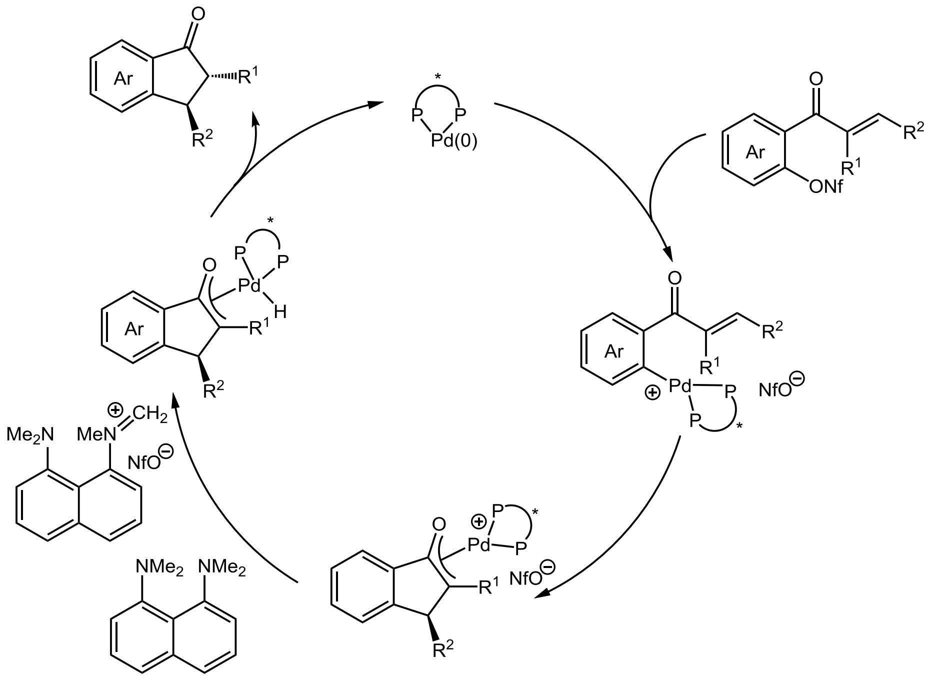
Synthesis of Chiral Indanones



5 mol% $Pd(OAc)_2$
10 mol% (*R*)-**L**
proton sponge (2.0 equiv)
DMF, 100 ^oC, 12 h

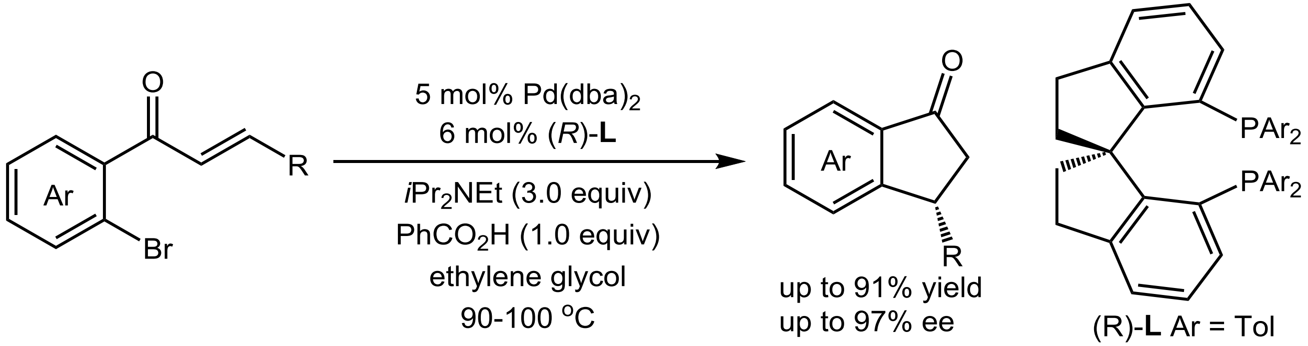
up to 90% yield
up to 91:9 dr
up to 94% ee

(*R*)-**L** Ar =3,5-$Me_2C_6H_3$



Buchwald, S. L. *et al. J. Org. Chem.* **2007**, *72*, 9253.

Synthesis of Chiral Indanones



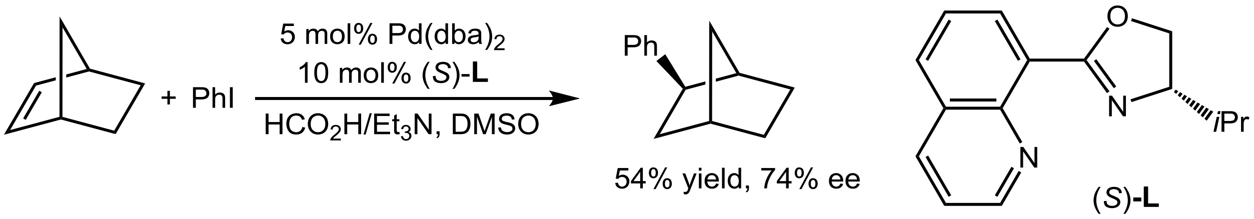
5 mol% Pd(dba)$_2$
6 mol% (*R*)-**L**
*i*Pr$_2$NEt (3.0 equiv)
PhCO$_2$H (1.0 equiv)
ethylene glycol
90-100 ^{o}C

up to 91% yield
up to 97% ee

(R)-**L** Ar = Tol

Zhou, J. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 6531.

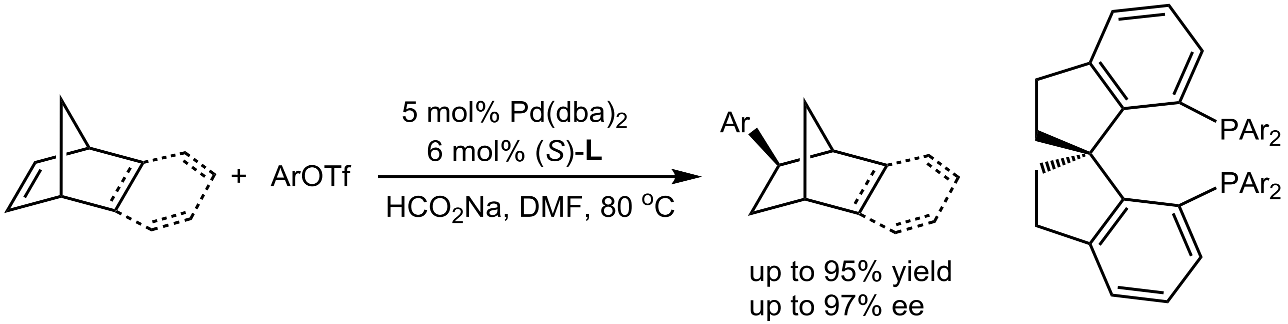
Asymmetric Hydroarylation of Norbornene



54% yield, 74% ee

(*S*)-**L**

Zhou, Q.-L. *et al. Tetrahedron Asymmetry* **2000**, *11*, 1255.

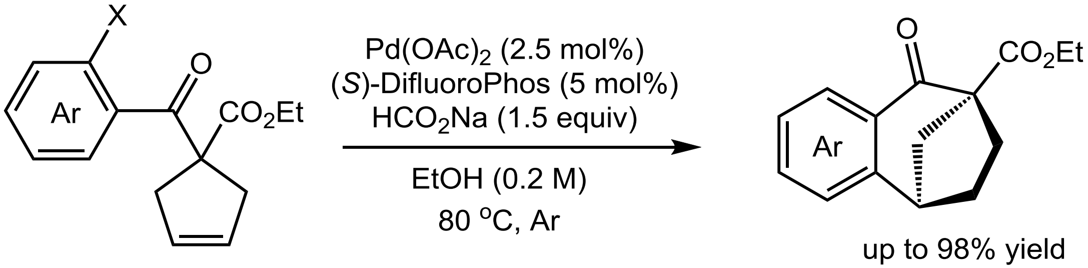


up to 95% yield
up to 97% ee

(*S*)-**L** Ar = *m*-Xyl

Zhou, J. *et al. Chem. Commun.* **2013**, *49*, 11758.

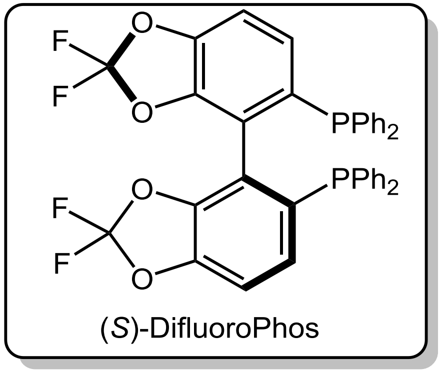
Desymmetrization of Cyclopentenes



Pd(OAc)$_2$ (2.5 mol%)
(*S*)-DifluoroPhos (5 mol%)
HCO$_2$Na (1.5 equiv)

EtOH (0.2 M)
80 ^{o}C, Ar

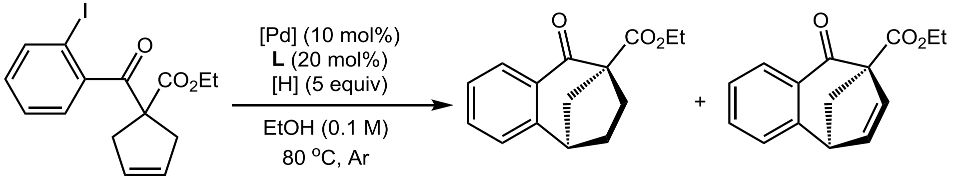
up to 98% yield
up to 98% ee



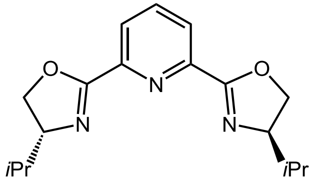
(*S*)-DifluoroPhos

Yao, H. *et al. Angew. Chem. Int. Ed.* **2019**, *58,* 2884.

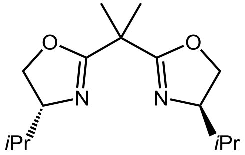
Optimization of Reaction Conditions



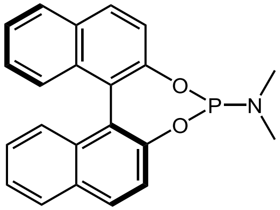
1a **2a** **3a**



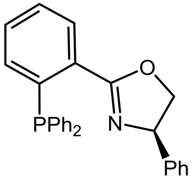
L1



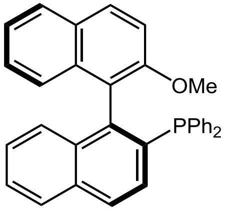
L2



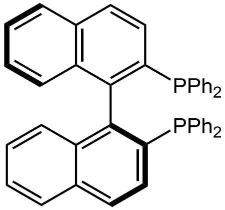
L3



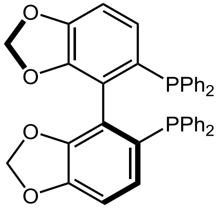
L4



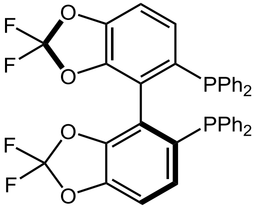
L5



L6



L7



L8

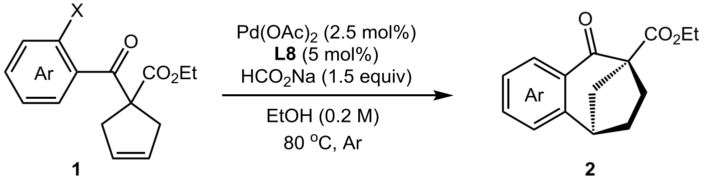
Entry[a]	[Pd]	**L**	Yield (%)[b]	**2a** Ee (%)[c]	**3a** Yield [%]
1	Pd(OAc)$_2$	**L1**	11	2	36
2	Pd(OAc)$_2$	**L2**	18	-6	15
3	Pd(OAc)$_2$	**L3**	9	9	58
4	Pd(OAc)$_2$	**L4**	14	4	52

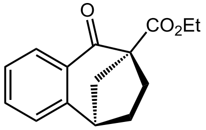
Optimization of Reaction Conditions[a]

Entry[a]	[Pd]	**L**	Yield (%)[b]	**2a** Ee (%)[c]	**3a** Yield [%]
5	$Pd(OAc)_2$	**L5**	<2	-	88
6	$Pd(OAc)_2$	**L6**	99	78	<2
7	$Pd(OAc)_2$	**L7**	98	92	<2
8	$Pd(OAc)_2$	**L8**	98	95	<2
9	$[Pd(allyl)Cl]_2$	**L8**	15	58	52
10	$Pd_2dba_3{\cdot}CHCl_3$	**L8**	43	89	53
11[b]	$Pd(OAc)_2$	**L8**	98	96	<2
12[b,c]	$Pd(OAc)_2$	**L8**	98	96	<2
13[b,c,d]	$Pd(OAc)_2$	**L8**	98	96	<2
14[b,d,e]	$Pd(OAc)_2$	**L8**	<2	97	<2

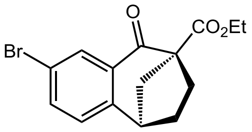
[a] Reaction conditions: **1a** (0.1 mmol), [Pd] (10 mol%), ligand (20 mol%), HCO_2Na (0.5 mmol) in 1 mL EtOH, at 80 ^oC, 12 h, under argon, isolated yields. The ee values were determined by chiral-phase HPLC. [b] 2.5 mol% $Pd(OAc)_2$ and 5 mol% **L8** were used. [c] 1.5 equiv HCO_2Na was added. [d] in 0.5 mL EtOH. [e] without HCO_2Na.

Substrate Scope of the Haloaryl Moiety

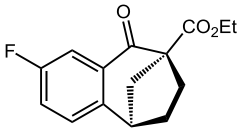




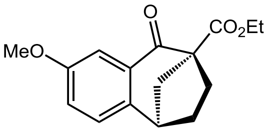
2a
98% yield, 97% ee (X = I)
97% yield, 97% ee (X = Br)



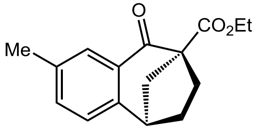
2b
83% yield, 87% ee (X = I)



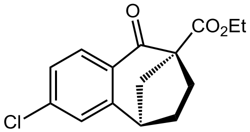
2b
98% yield, 96% ee (X = Br)[a]



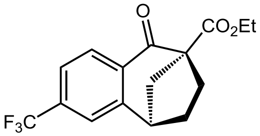
2b
83% yield, 87% ee (X = I)



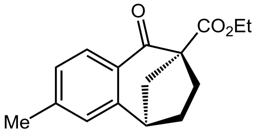
2e
88% yield, 97% ee (X = I)



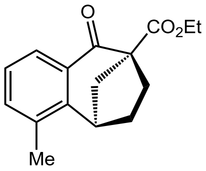
2f
81% yield, 96% ee (X = I)



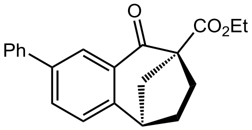
2g
72% yield, 90% ee (X = Br)[a]



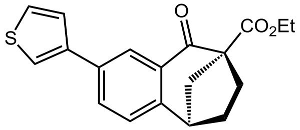
2h
95% yield, 98% ee (X = I)



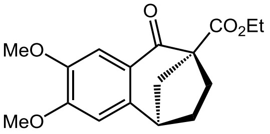
2i
31% yield, 90% ee (X = I)



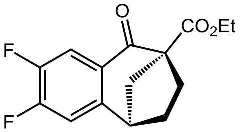
2j
81% yield, 90% ee (X = Br)



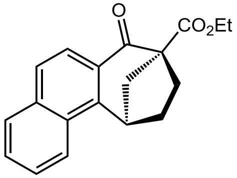
2k
92% yield, 97% ee (X = Br)



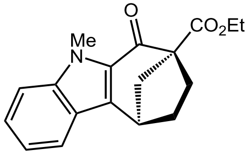
2l
95% yield, 96% ee (X = Br)



2m
86% yield, 95% ee (X = Br)[a]



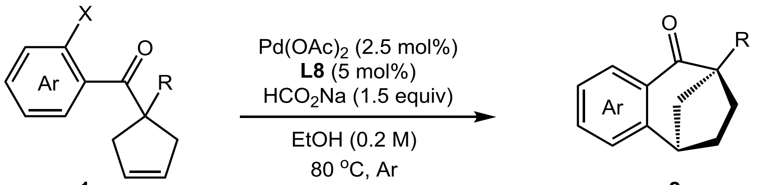
2n
76% yield, 98% ee (X = Br)



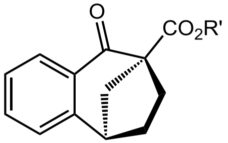
2o
91% yield, 98% ee (X = I)

[a] 5 mol% $Pd(OAc)_2$ and 10 mol% **L8** were used.

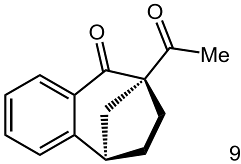
Substrate Scope of the Cyclopentenes



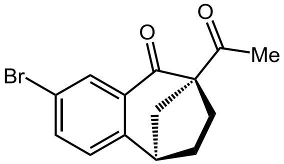
Pd(OAc)$_2$ (2.5 mol%)
L8 (5 mol%)
HCO$_2$Na (1.5 equiv)
EtOH (0.2 M)
80 °C, Ar



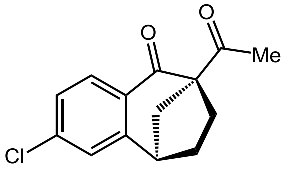
2p R = Me, 97% yield, 97% ee (X = I)
2q R = *i*Pr, 95% yield, 96% ee (X = I)
2r R = *t*Bu, 91% yield, 95% ee (X = I)
2s R = Bn, 90% yield, 97% ee (X = I)



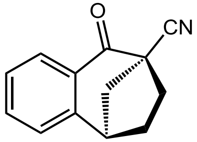
2t
94% yield, 97% ee (X = I)



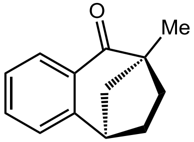
2u
60% yield, 98% ee (X = I)



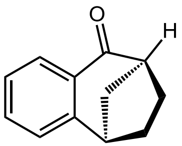
2v
82% yield, 88% ee (X = Br)



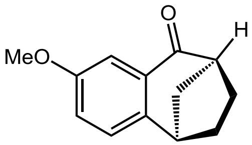
2w
75% yield, 93% ee (X = I)



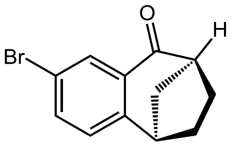
2x
51% yield, 90% ee (X = Br)



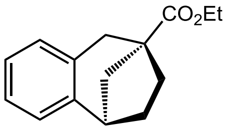
2y
87% yield, 98% ee (X = I)



2z
80% yield, 98% ee (X = I)



2aa
60% yield, 97% ee (X = I)

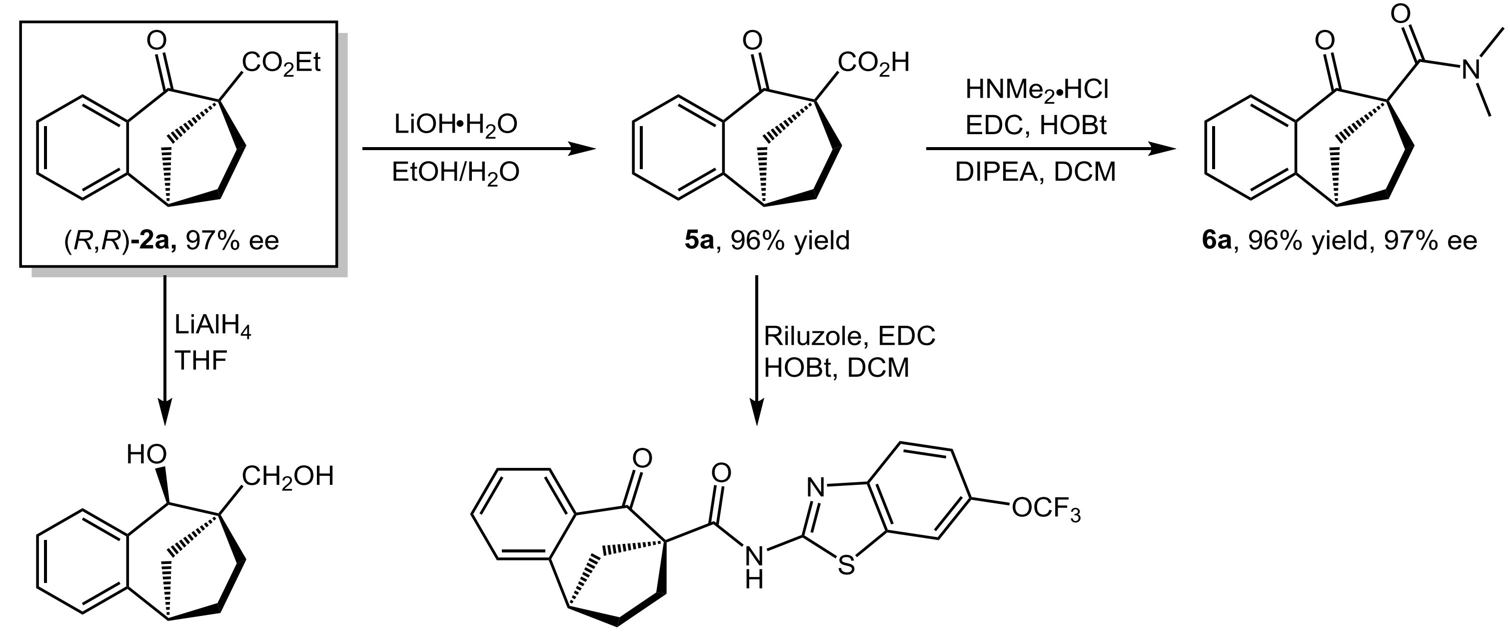


2ab
87% yield, 95% ee (X = I)[a]

---

[a] HCO$_2$NH$_4$ (0.2 mol) was used.

Further Transformation of (*R*,*R*)-2a



(*R*,*R*)**-2a,** 97% ee

5a, 96% yield

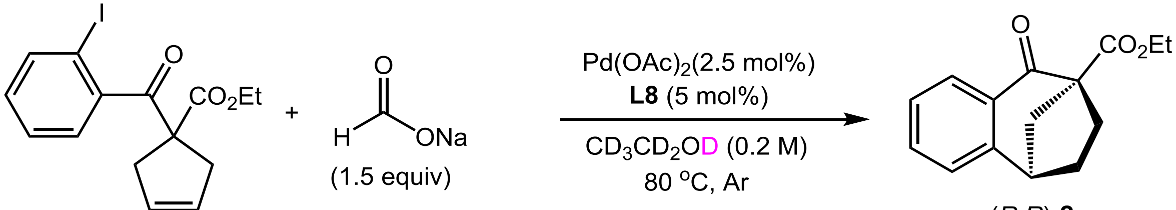
6a, 96% yield, 97% ee

4a, 91% yield, > 20:1 dr, 99% ee

7a, 94% yield, 98% ee

Deuterium Labeling Experiments

Deuterium-labeling experiment in [D_6]ethanol



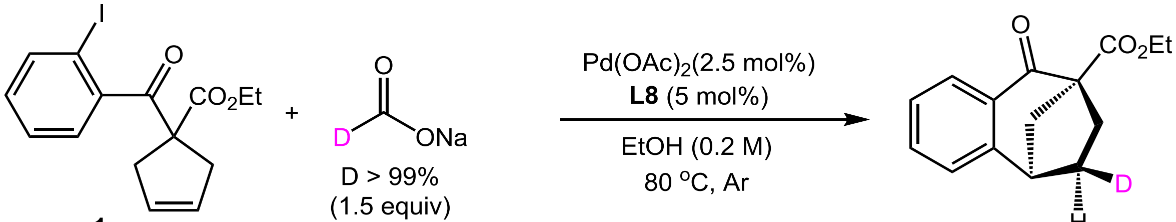
(1.5 equiv)

Pd(OAc)$_2$(2.5 mol%)
L8 (5 mol%)
CD_3CD_2OD (0.2 M)
80 °C, Ar

1a

(*R*,*R*)-**2a**
96% yield, 97% ee

Deuterium-labeling experiments with deuterated sodium formate

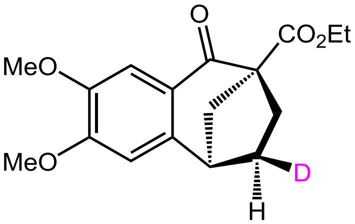


D > 99%
(1.5 equiv)

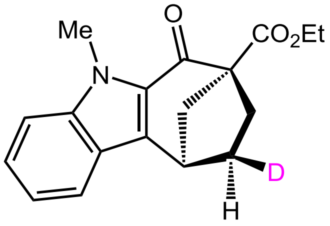
Pd(OAc)$_2$(2.5 mol%)
L8 (5 mol%)
EtOH (0.2 M)
80 °C, Ar

1a

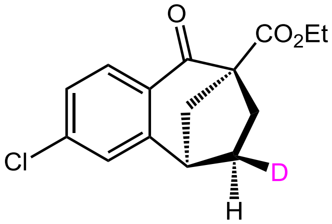
[D]**2a** (> 99%)
90% yield, > 20:1 dr, 98% ee



[D]**2i** (> 99%)
85% yield, > 20:1 dr, 98% ee

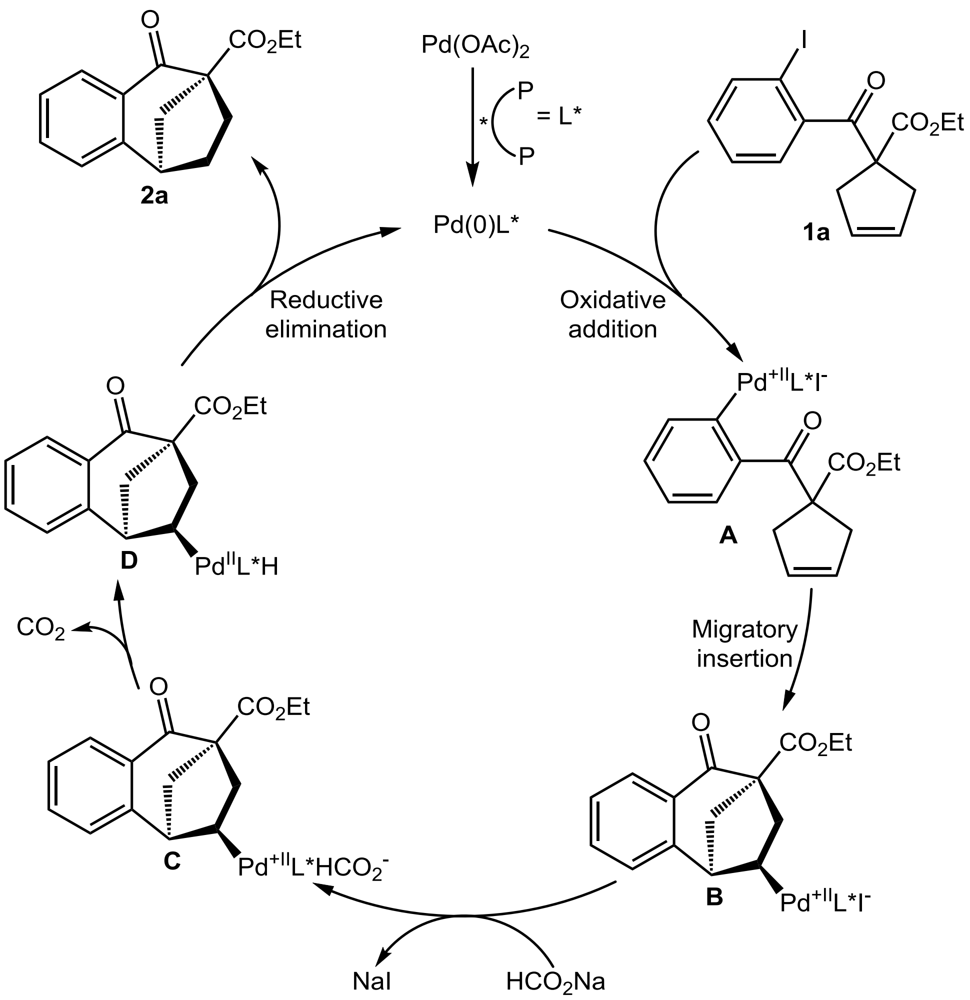


[D]**2o** (> 99%)
76% yield, > 20:1 dr, 98% ee

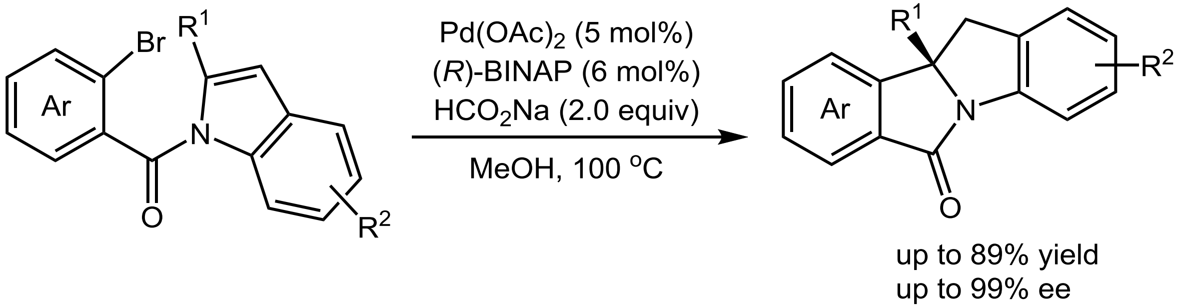


[D]**2v** (> 99%)
80% yield, > 20:1 dr, 96% ee

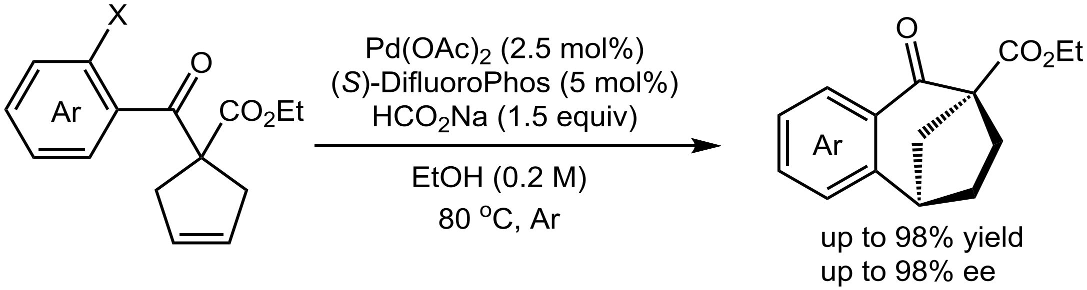
Proposed mechanism



Summary



Jia, Y.-X. *et al. J. Am. Chem. Soc*. **2015**, *137*, 4936.



Yao, H. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 2884.

The First Paragraph

In 1983, Cacchi and co-workers described a Pd-catalyzed cross-coupling reaction between aryl halides and either enones or enals to form conjugate adducts in the presence of hydride species, and it is now known as the reductive Heck reaction. After that, such a reaction has proven to be an efficient and tempting method to construct saturated C-C bonds because of the avoidance of air- and moisture-sensitive organometallic reagents, and it has been widely applied in the synthesis of natural products and pharmaceuticals. However, because of the high propensity of the β-hydride elimination pathway (Heck reaction), the asymmetric version of the reductive Heck reaction is still in its infancy. Prior works on the asymmetric intramolecular reductive Heck reactions of either 1,1-disubstituted olefins or 2-substituted indoles have been realized.

The First Paragraph

In these elegant works, the in situ generated alkylpalladium intermediates were efficiently trapped by the hydride donors to deliver the asymmetric reductive Heck products because they lacked the β-hydrogen. Additionally, the groups of Buchwald, Zhou and Minnaard independently disclosed another type of asymmetric intramolecular reductive Heck reaction with (pseudo)halide-substituted chalcones, in which the stabilized trans-configured H-bound Pd-enolate intermediates did not undergo β-hydride elimination to form the Heck products. Moreover, specific bicyclic alkenes, such as norbornene and its derivatives have also been employed in the asymmetric reductive Heck reactions. In these reactions, the rigidity of the carbocyclic frameworks prevented the alkylpalladium intermediates from undergoing rotation and β-hydride elimination.

The First Paragraph

Very recently, the racemic reductive Heck reactions of unactivated aliphatic alkenes possessing eliminable β-hydrogen atoms have been realized by the groups of Loh and Engle. However, to the best of our knowledge, protocols that enable asymmetric reductive Heck reactions of unactivated aliphatic alkenes have not been described until now.

The Last Paragraph

In conclusion, we have described a Pd-catalyzed asymmetric intramolecular reductive Heck desymmetrization reaction of cyclopentenes, having eliminable β-hydrogen atoms, to achieve chiral bicyclo[3.2.1]octanes bearing quaternary and tertiary carbon stereocenters in good yields and with excellent enantioselectivities. Additionally, the reaction can incorporate deuterium into the bicyclo[3.2.1]octanes with complete deuteration, and excellent diastereo- and enantioselectivities.

Acknowledgement

Thanks
for your attention