Literature Report VI

Palladium/L-Proline-Catalyzed Enantioselective *α*-Arylative Desymmetrization of Cyclohexanones

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Checker : Cong Liu
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Jia, Y.-X. *et al*.
J. Am. Chem. Soc. **2016**, *138*, 5198.

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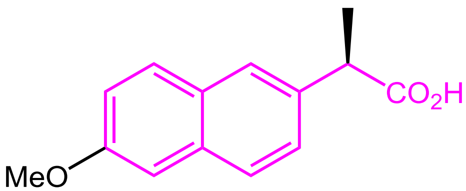
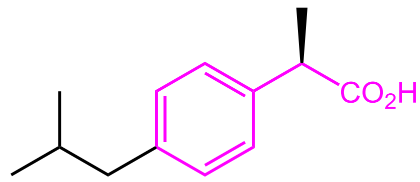
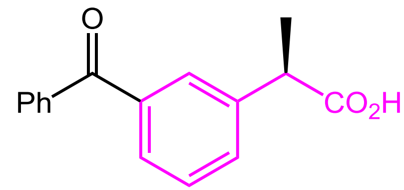
Introduction



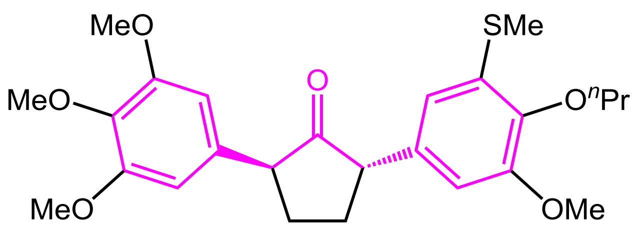
(*R*)-Naproxen



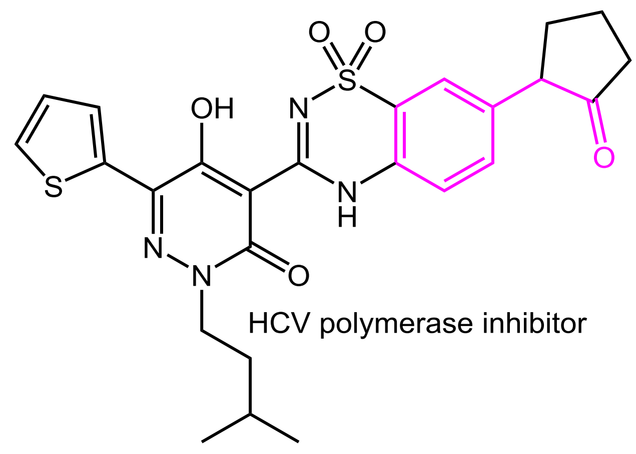
Ibuprofen



Ketoprofen

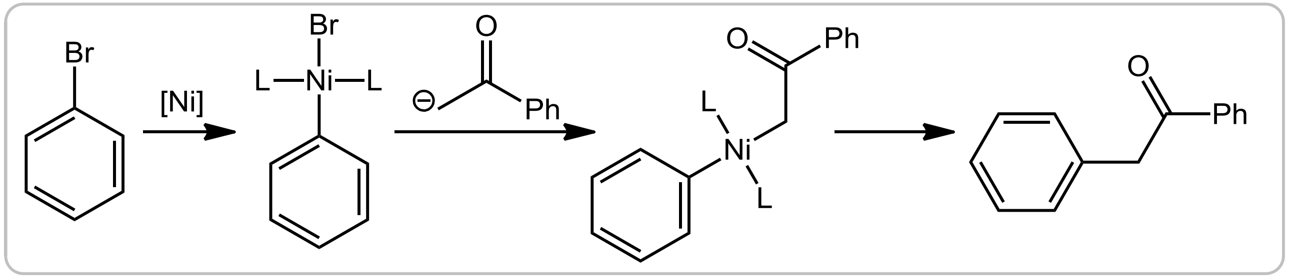


Platelet activating factorantagonist

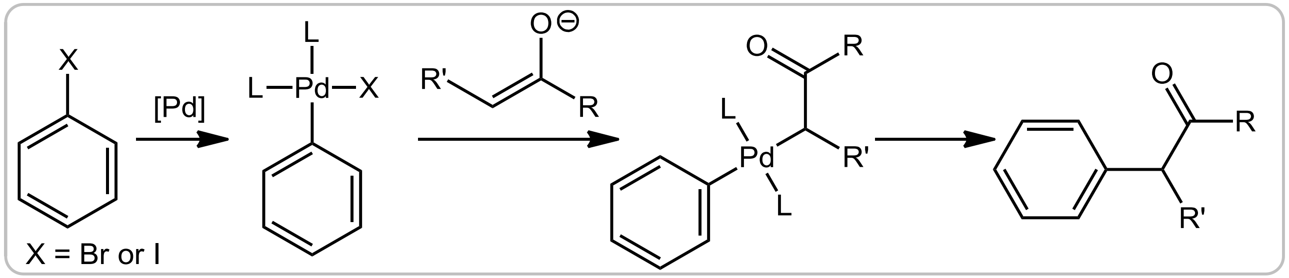


HCV polymerase inhibitor

Introduction

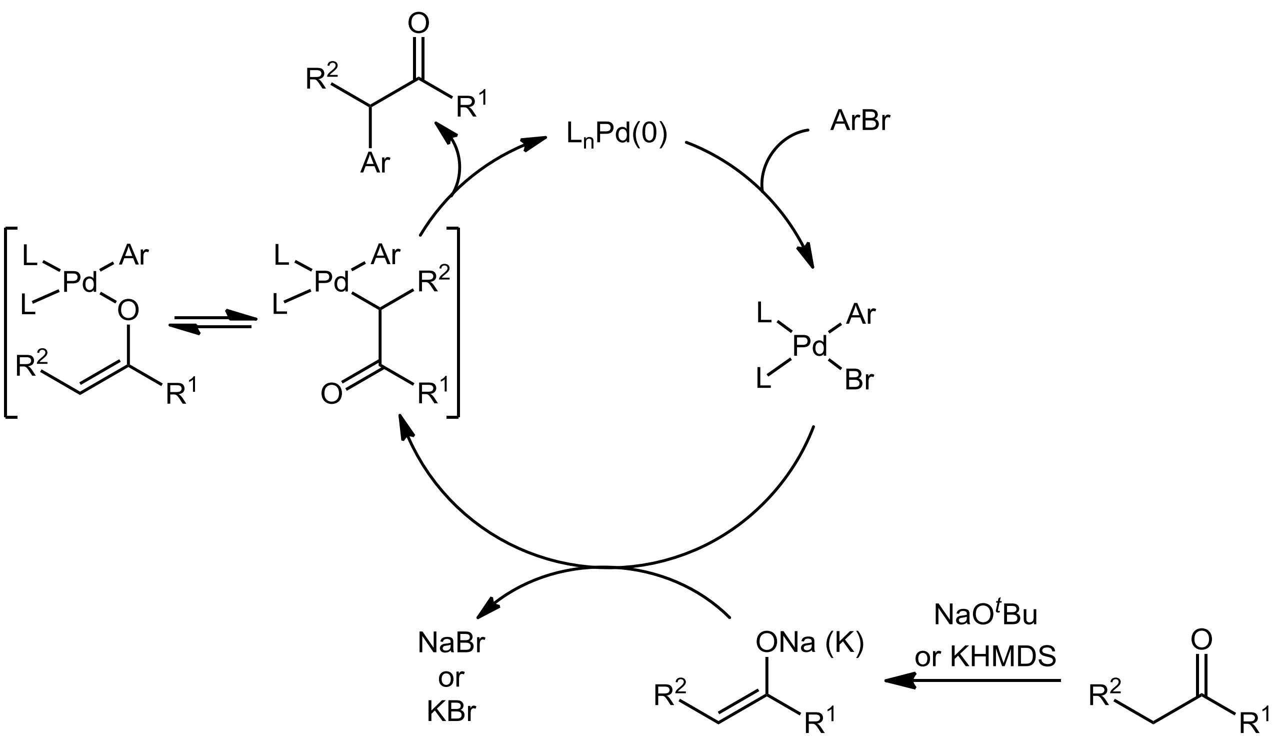


Semmelhack, M. F. *et al*. *Tetrahedron Lett.* **1973**, *14*, 4519.



Buchwald, S. L. *et al*. *J. Am. Chem. Soc.* **1997**, *119,* 11108.
Hartwig, J. F. *et al*. *J. Am. Chem. Soc.* **1997**, *119,* 12382.
Miura, M. *et al*. *Angew. Chem. Int. Ed.* **1997**, *36,* 1740.

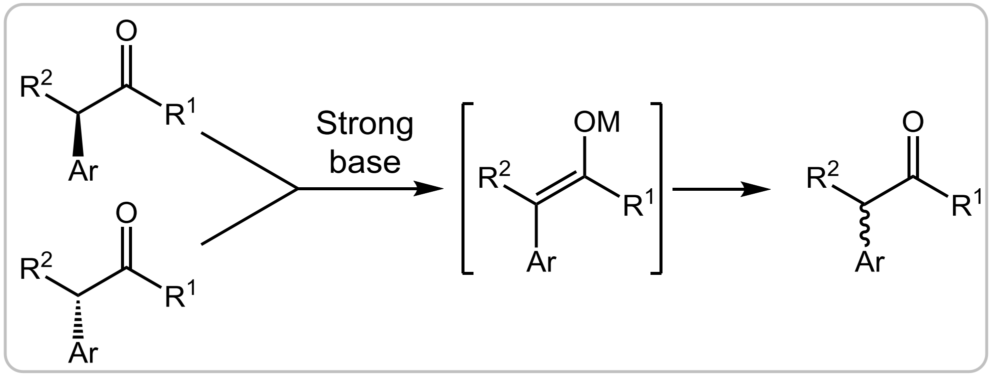
Introduction



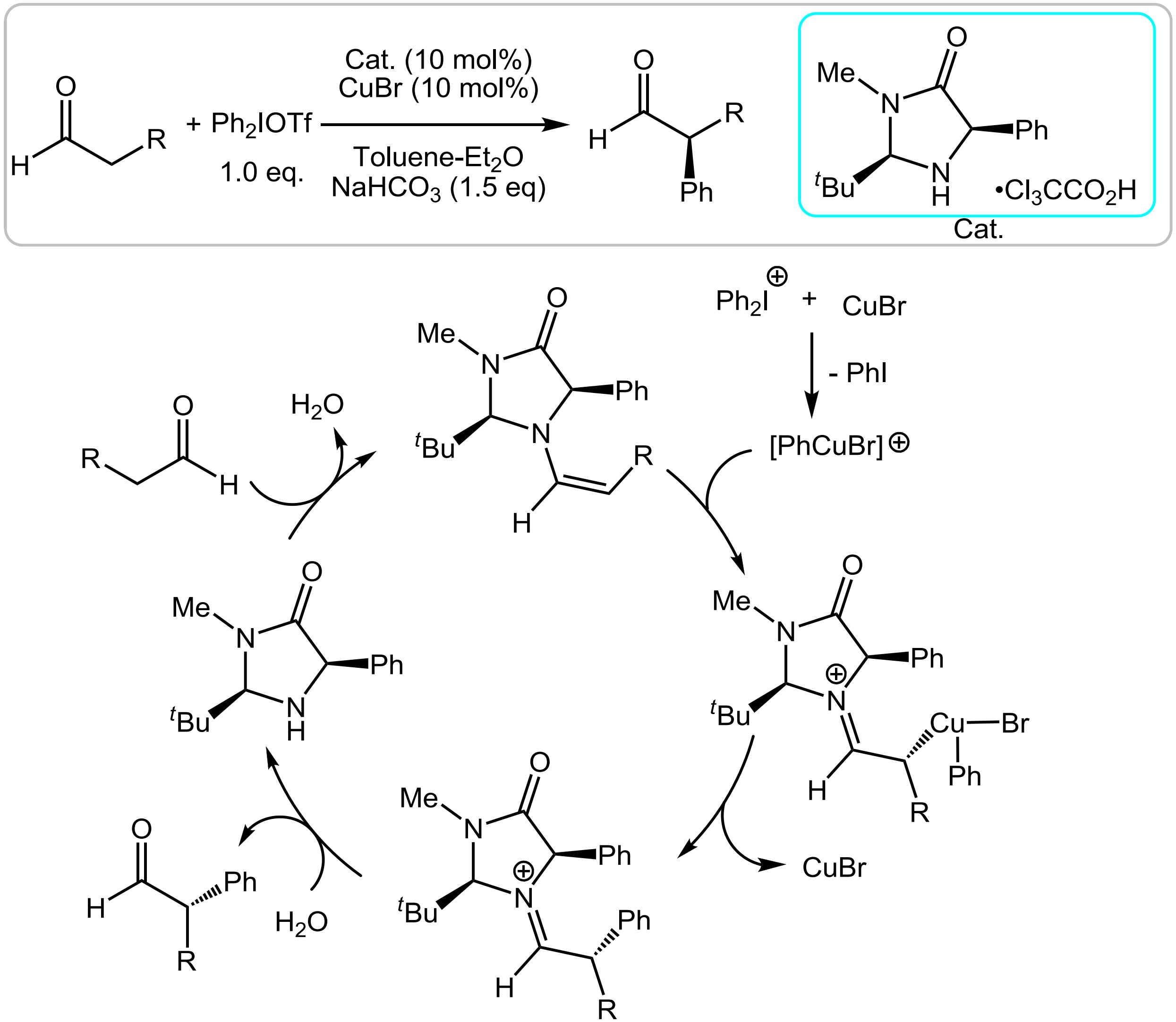
Burtoloso, A. C. B. *Synlett* **2009**, 320.

Introduction

➢ The aforementioned approaches are very limited to the construction of quaternary carbon stereocenters: α-H atom of the tertiary carbon stereocenter is more acidic and prone to racemization under basic conditions.

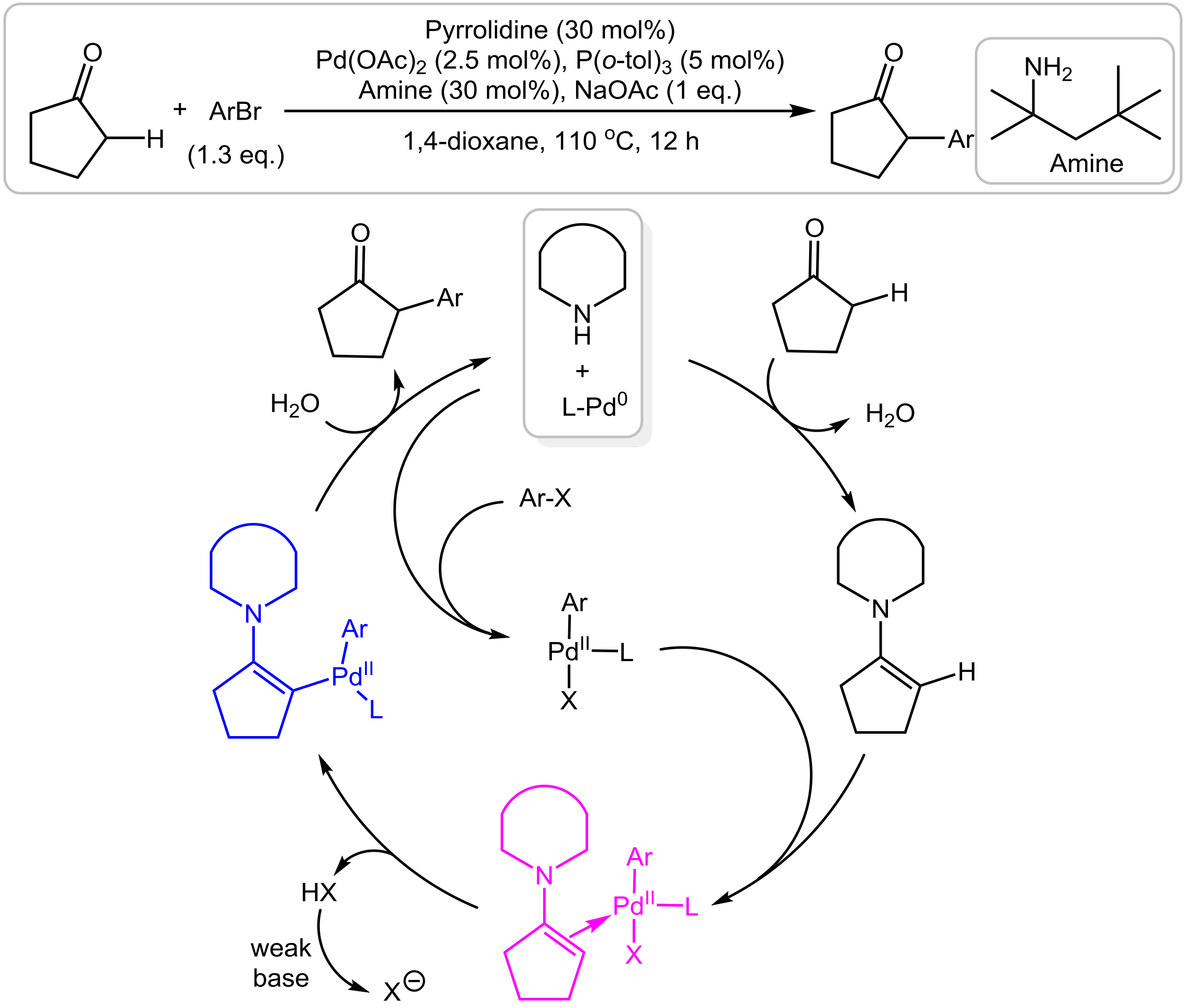


Introduction



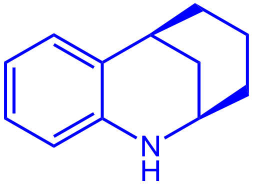
MacMillan, D. W. C. *et al*. *J. Am. Chem. Soc.* **2011**, *133,* 4260.

Introduction

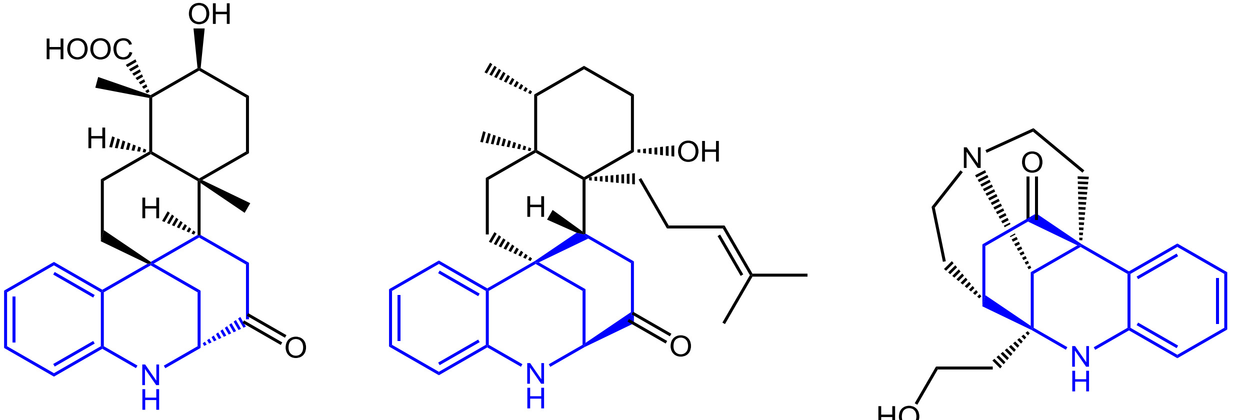


Dong, G. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 2559;
Kurth, M. J. *et al. Angew. Chem. Int. Ed*. **2012**, *51*, 10588.

Introduction

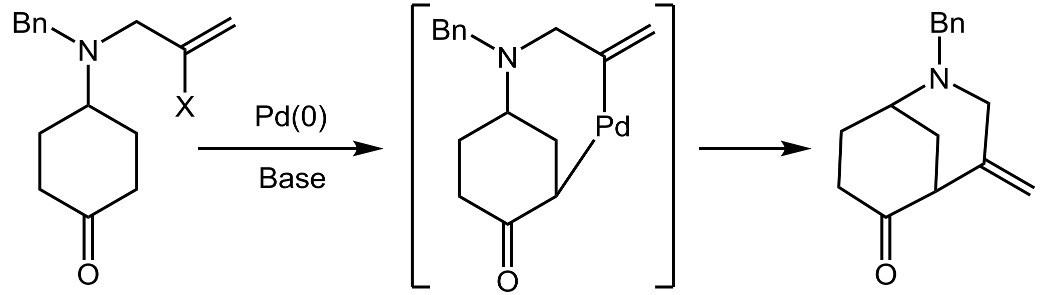


Hexahydro-2,6-methano-
1-benzazocine



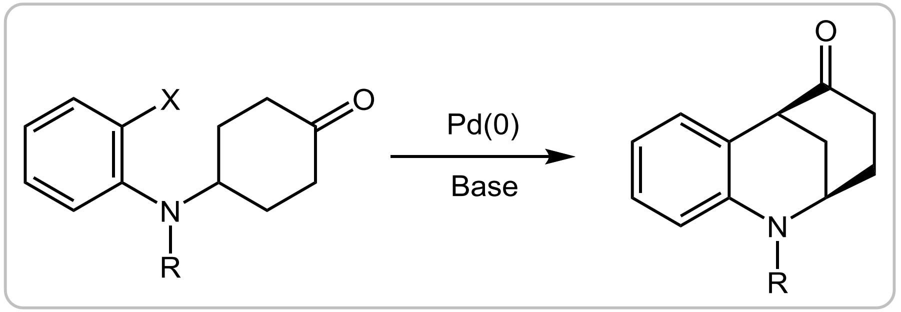
Sespenine Aspernomine Strychnochromine

Racemic α-Arylation of Cyclohexanones



Presumed to procceed by sequential oxidative addition and deprotonation, followed by conversion to a palladacycle, which undergoes a simple reductive elimination.

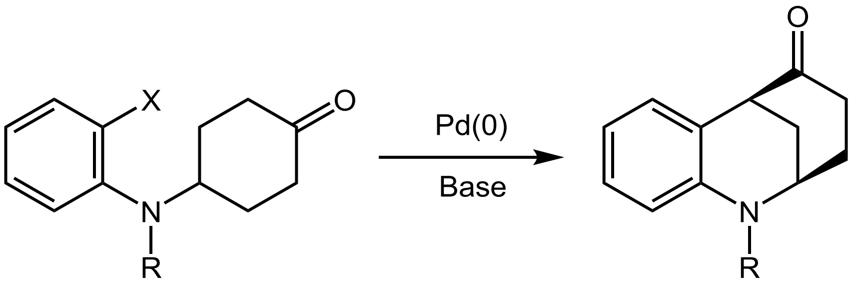
Solé, D.; Bonjoch, J. *et al*. *Org. Lett.* **2000**, *2*, 2225.



Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

Optimization of Reaction Conditions

1a, X = I, R = Bn
1b, X = Br, R = Bn
3, X = I, R = Ac
5, X = I, R = COOMe



2, R = Bn
4, R = Ac
6, R = COOMe

Entry	Substrate	Method[a]	Product	Yield (%) [b]
1	**1a**	A	**2**	84
2	**1a**	B	**2**	68
3	**1a**	C[c]	**2**	76
4	**1b**	A	**2**	67
5	**1b**	B	**2**	60
6	**1b**	C[d]	**2**	78

[a] Method A: $Pd(PPh_3)_4$ (0.2 eq.), KO^tBu (3 eq.), THF, reflux, 3.5 h.
Method B: $PdCl_2(PPh_3)_2$ (0.2 eq.), Cs_2CO_3 (3 eq.), THF, 100-110 ^oC, 24 h.
Method C: $Pd(PPh_3)_4$ (0.2 eq.), K_3PO_4 (3 eq.), THF, 100-110 ^oC, 24 h.
[b] The yield refers to pure isolated products. [c] $Pd(PPh_3)_4$ (0.1 eq.). [d] 48 h.

Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

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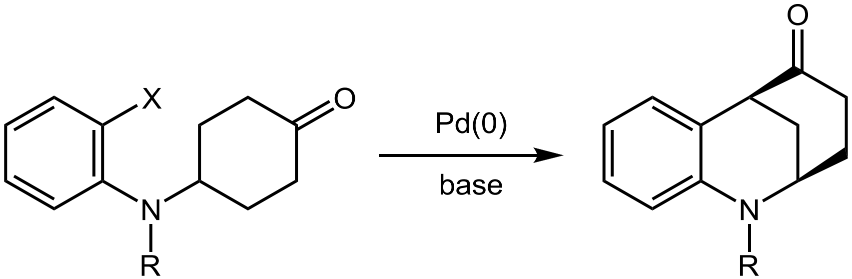

2, R = Bn
4, R = Ac
6, R = COOMe

Entry	Substrate	Method[a]	Product	Yield (%)[b]
7	**3**	A	--	--
8	**3**	B	**4**	33
9	**3**	C	**4**	38
10	**5**	A	**6**	48
11	**5**	B[e]	**6**	92
12	**5**	C	**6**	35

[a] Method A: $Pd(PPh_3)_4$ (0.2 eq.), KO^tBu (3 eq.), THF, reflux, 3.5 h.
Method B: $PdCl_2(PPh_3)_2$ (0.2 eq.), Cs_2CO_3 (3 eq.), THF, 100-110 ^oC, 24 h.
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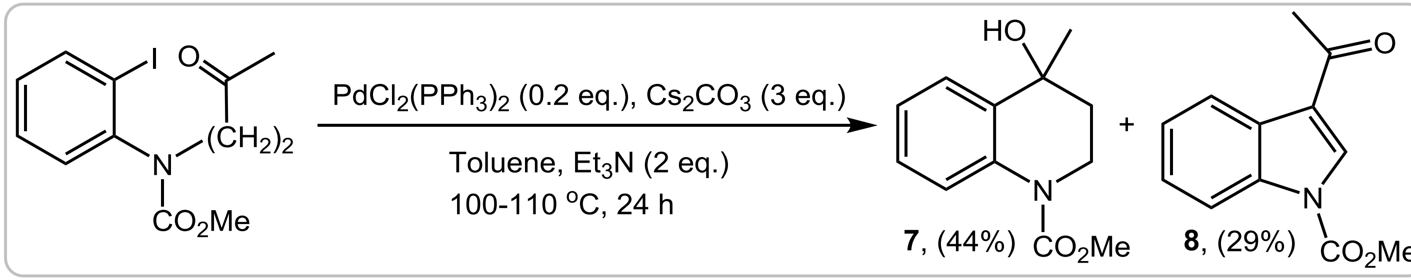
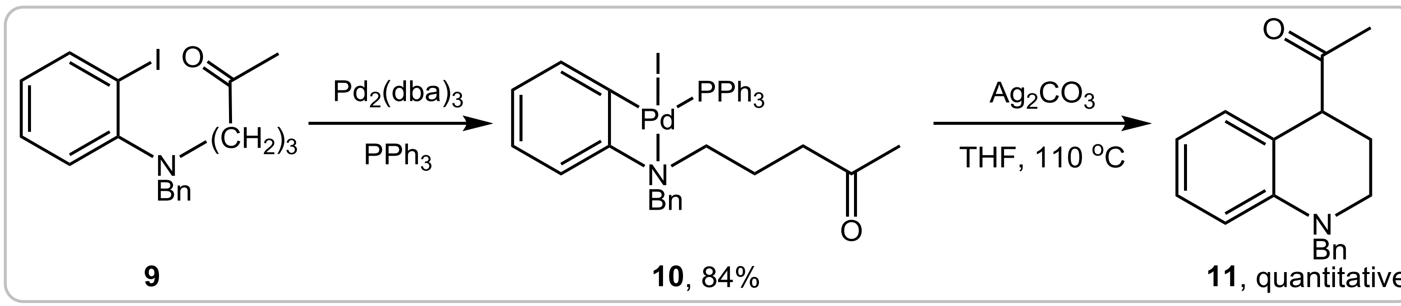
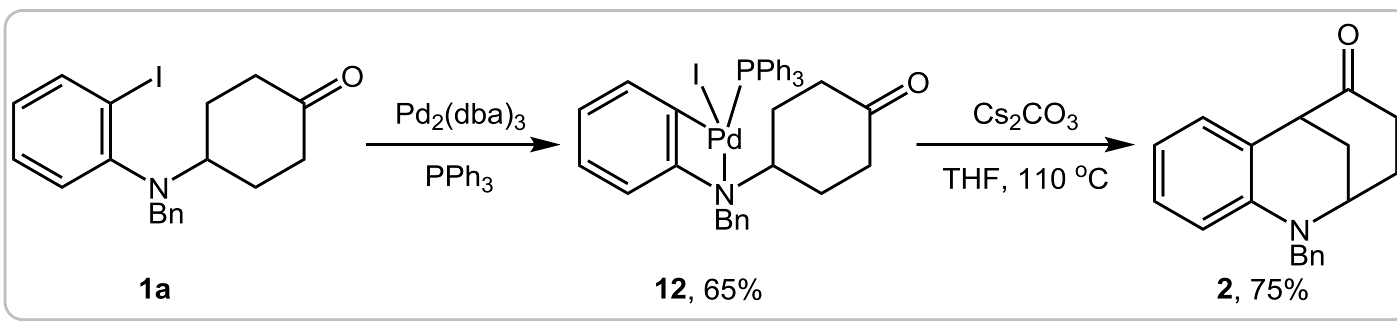
[b] The yield refers to pure isolated products. [c] $Pd(PPh_3)_4$ (0.1 eq.). [d] 48 h.
[e] $PdCl_2(PPh_3)_2$ (0.3 eq.), 48 h.

Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

Substrate Scope

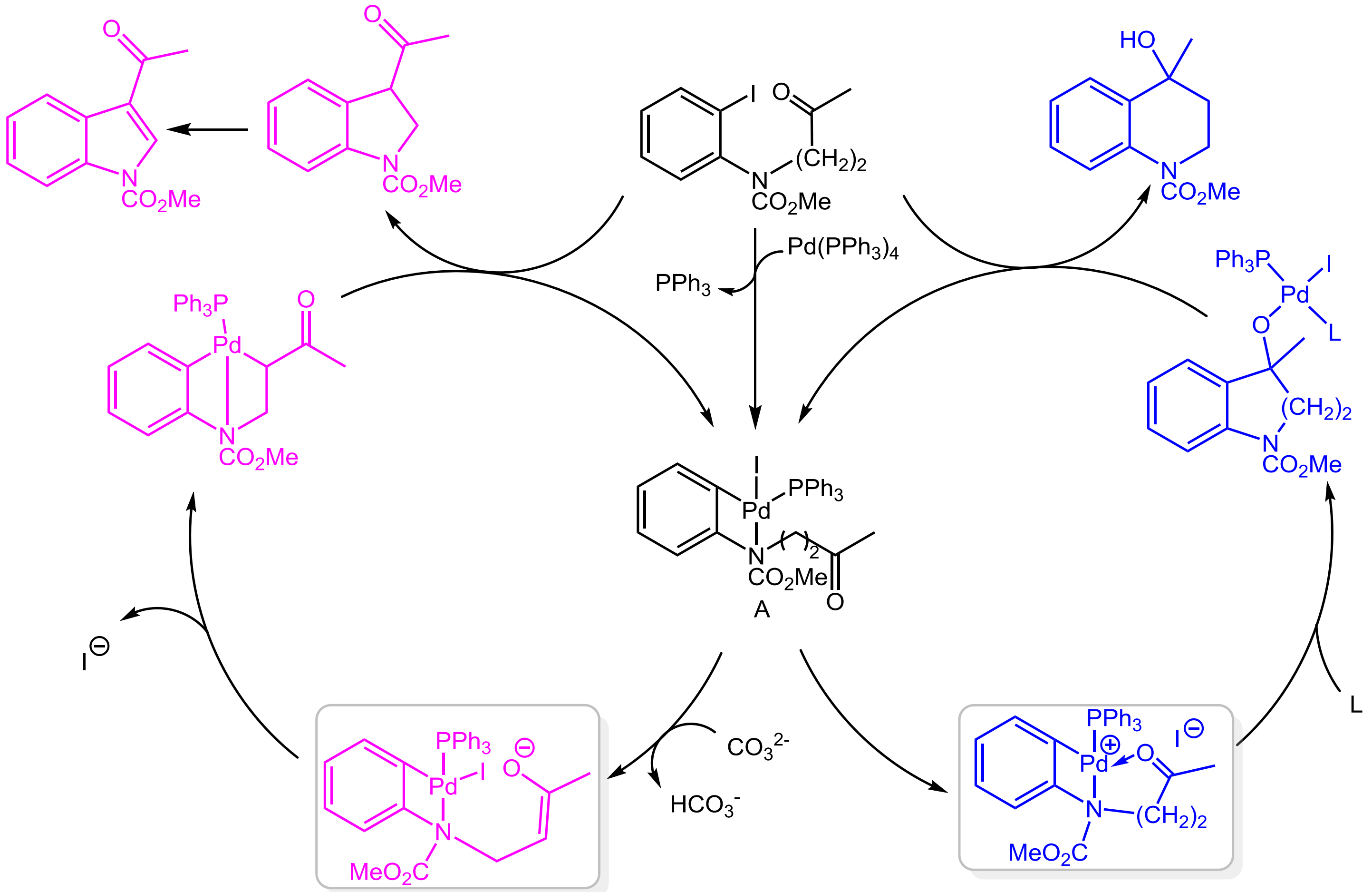






Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

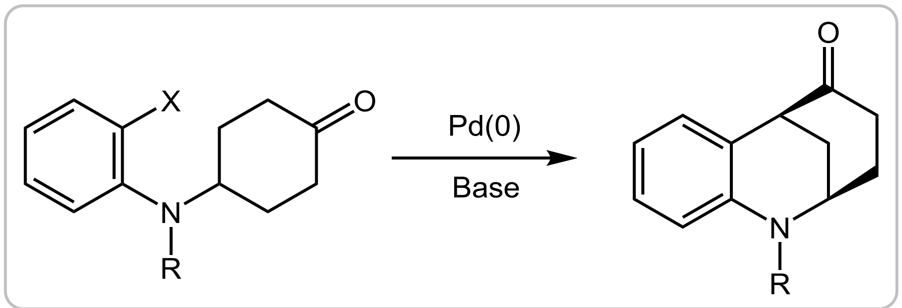
Racemic α-Arylation of Cyclohexanones



Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

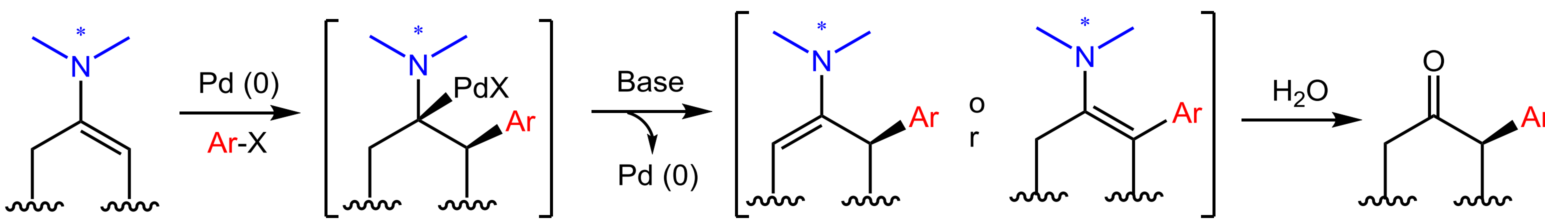
Asymmetric α-Arylation of Cyclohexanones

Racemic α-Arylation of Cyclohexanones

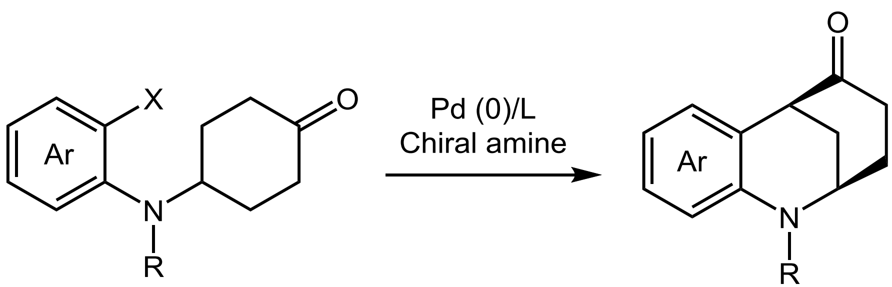


Solé, D. *et al*. *J. Am. Chem. Soc*. **2003**, *125*, 1587.

a) Proposed α-arylation of ketone via palladium/enamine catalysis



b) α-Arylative desymmetrization of cyclohexanone



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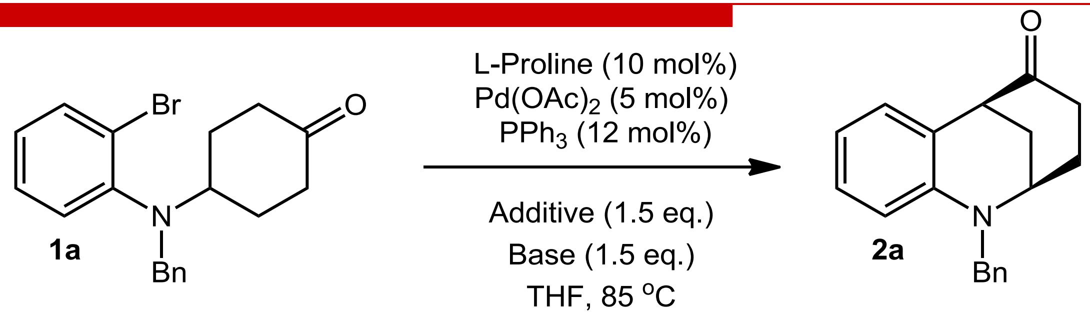
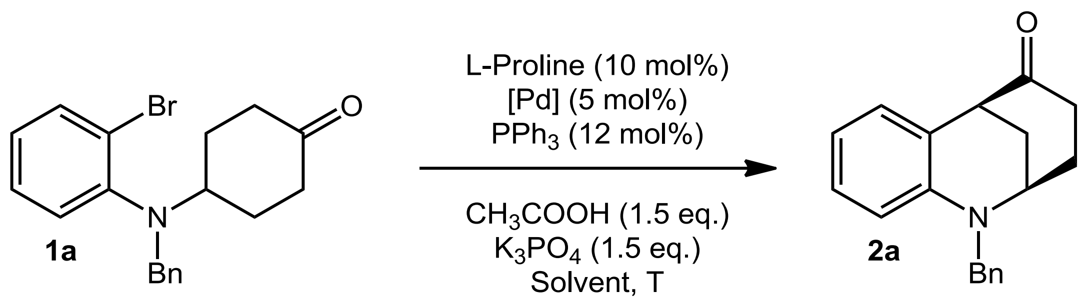
Optimization of Reaction Conditions



Entry	Base	Additive	Yield (%)	Ee (%)
1	Cs_2CO_3	--	60	23
2	NaO*t*Bu	--	71	<10
3	K_3PO_4	--	60	60
4	K_2CO_3	--	NR	--
5	K_3PO_4	4-$NO_2C_6H_4CO_2H$	60	73
6	K_3PO_4	2-$NO_2C_6H_4CO_2H$	20	70
7	K_3PO_4	2-$MeOC_6H_4CO_2H$	40	72
8	K_3PO_4	3-$ClC_6H_4CO_2H$	87	73
9	K_3PO_4	CF_3COOH	79	81
10	K_3PO_4	CH_3COOH	95	76

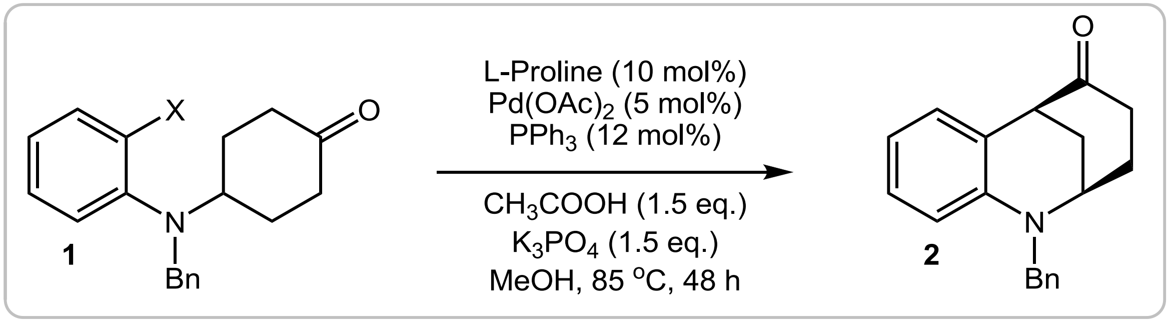
Optimization of Reaction Conditions

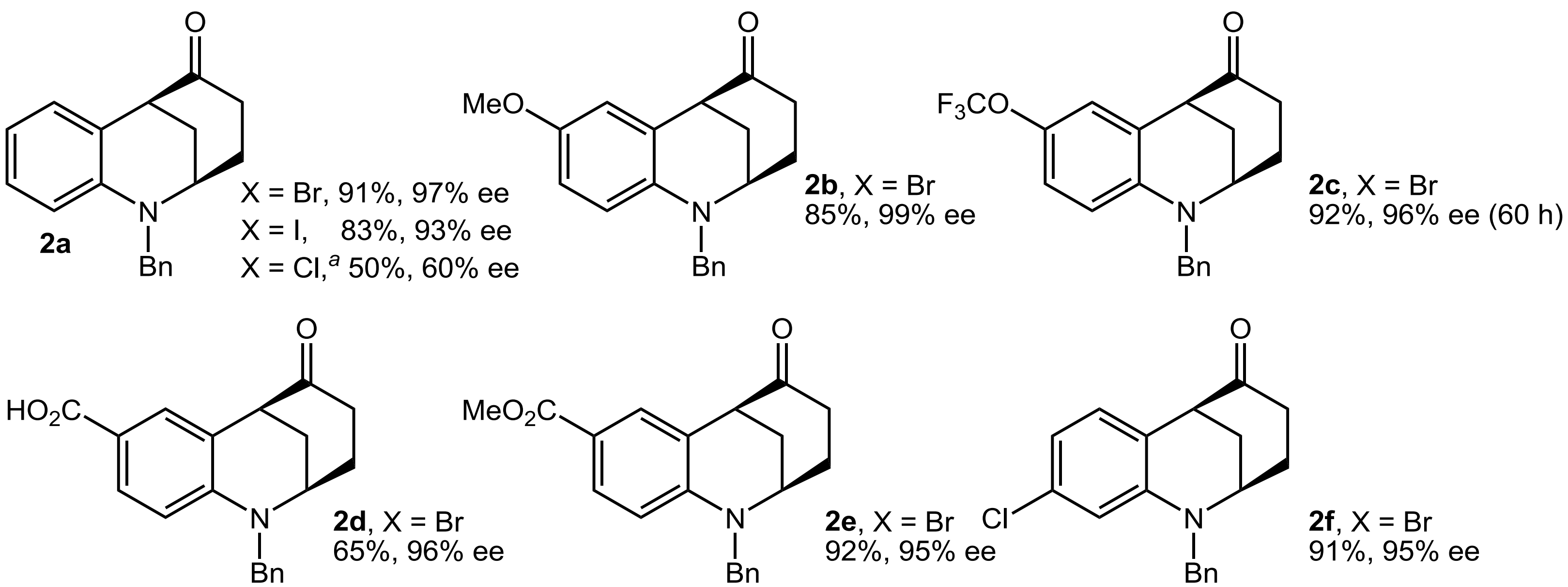


Entry[a]	Solvent	[Pd]	T (°C)	Yield (%) [b]	Ee (%)[c]
11	DMSO	$Pd(OAc)_2$	85	10	ND
12	Toluene	$Pd(OAc)_2$	85	70	20
13	MeOH	$Pd(OAc)_2$	85	91	97
14	MeOH	$Pd(dba)_2$	85	70	63
15	MeOH	$Pd(PPh_3)_4$	85	50	76
16[d]	MeOH	$Pd(OAc)_2$	70	31	ND

[a] Reaction condtions: **1a** (0.2 mmol), [Pd] (5 mol%), PPh_3 (12 mol%), L-proline (10 mol%), Base (0.3 mmpl), Solvent (2.0 mL), 85 °C, 48 h. [b] Isolated yield. [c] Determined by HPLC. [d] 60 h.

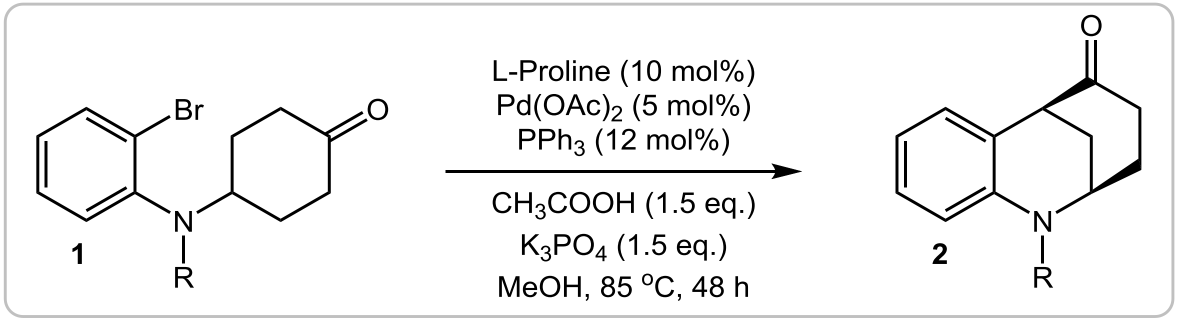
Substrate Scope

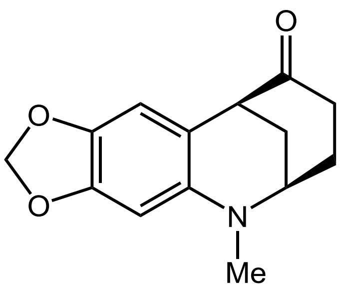




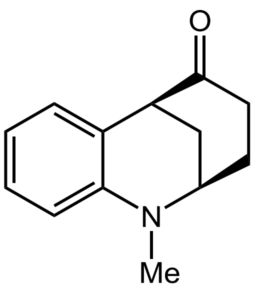
[a] With 12 mol% $Cy_3P \cdot HBF_4$ instead of PPh_3.

Substrate Scope

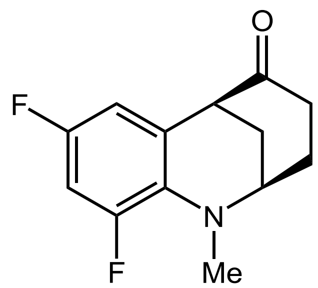




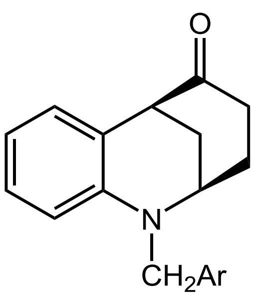
2g
94%, 99% ee



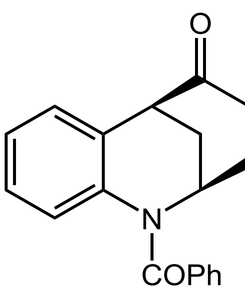
2h
93%, 97% ee



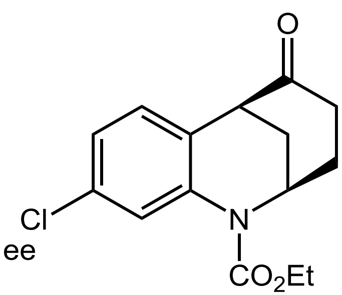
2i
89%, 98% ee



2j
Ar = 4-MeC_6H_4
95%, 96% ee

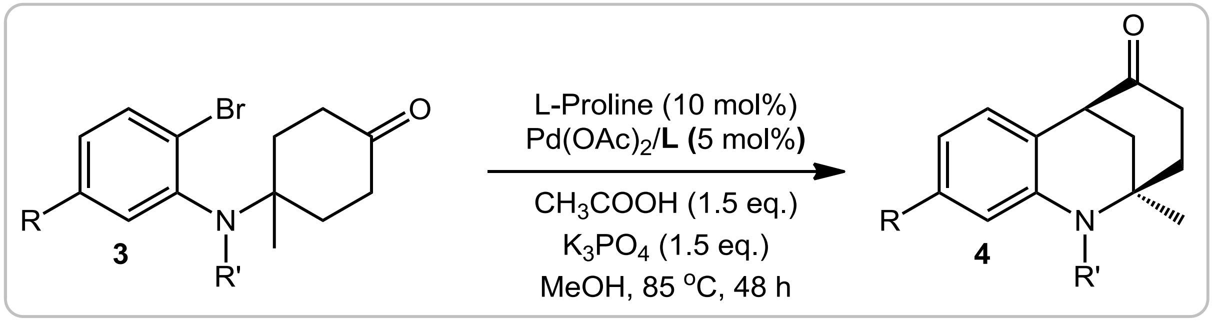


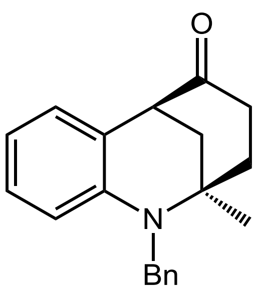
2k
63%, 76% ee



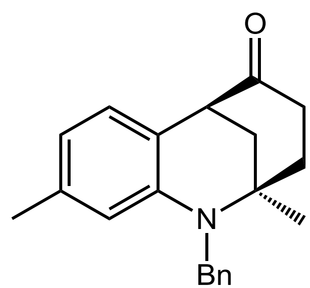
2l
39%, 70% ee

Substrate Scope

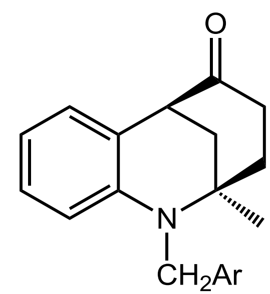




4a
L = PPh_3 (12 mol%)
82%, 59% ee
L = dpph (6 mol%)
80%, 81% ee

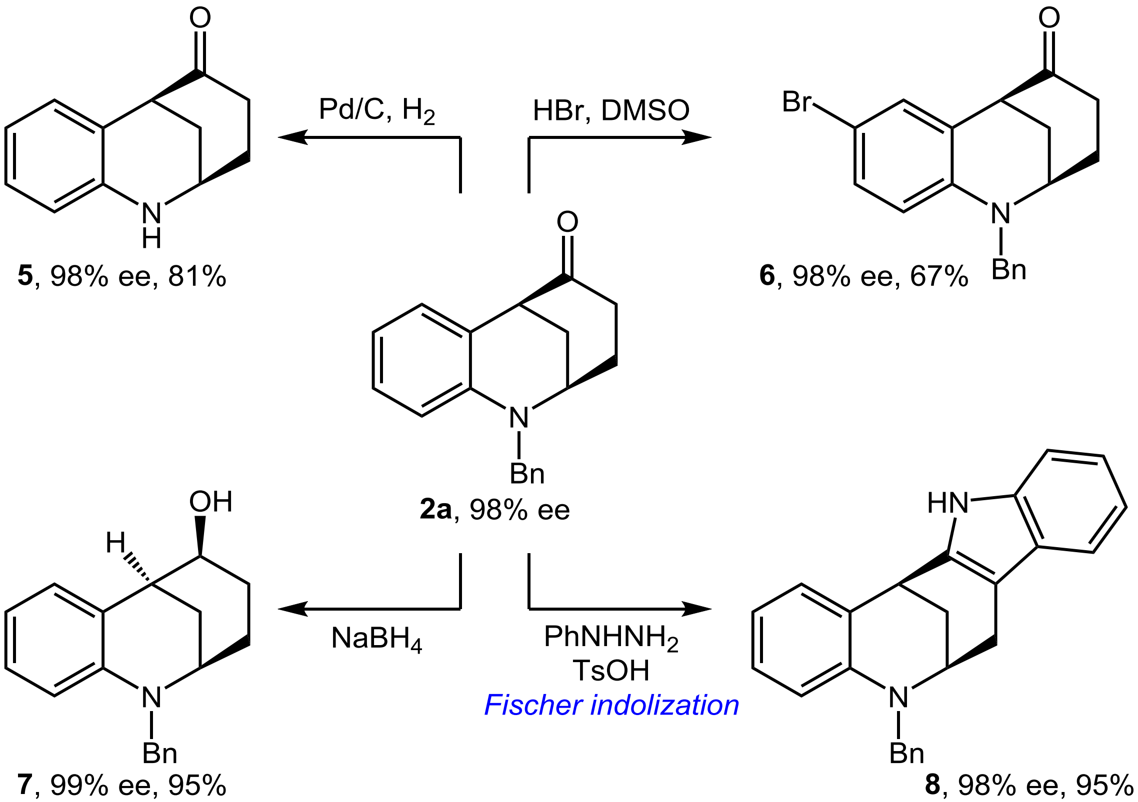


4b
L = dpph (6 mol%)
82%, 87% ee

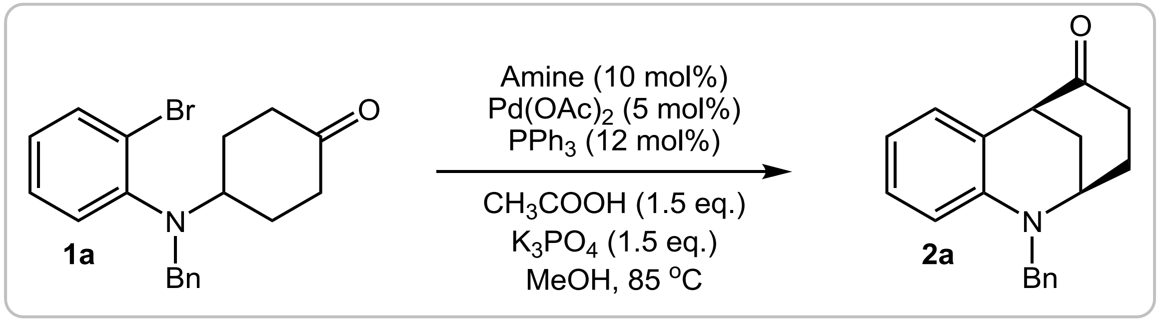


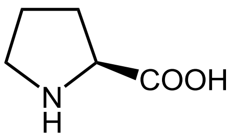
4c, Ar = 4-F-C_6H_4
L = dpph (6 mol%)
88%, 85% ee

Synthetic Transformations

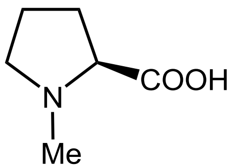


Control Experiments

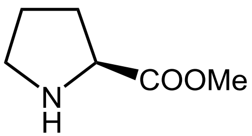




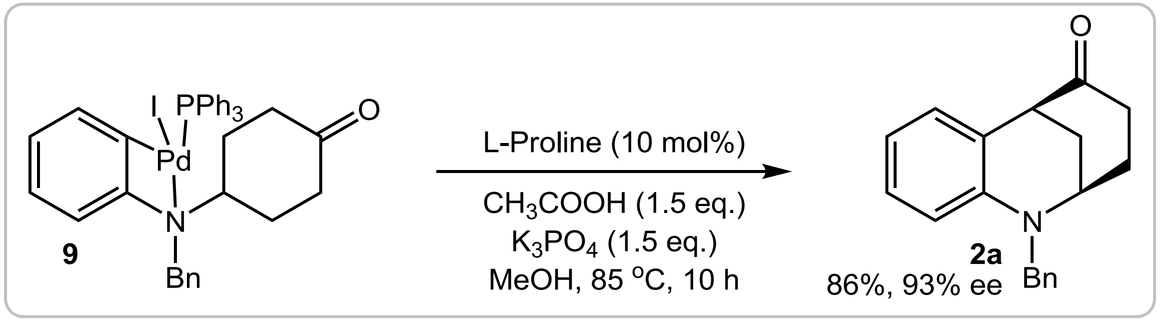
A1: 91%, 97% ee
without **A1**: 92%, rac



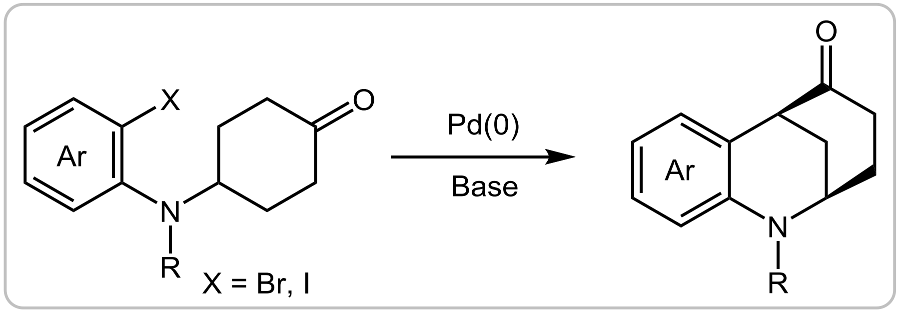
A2: 89%, rac



A3: 86%, 93% ee



Summary



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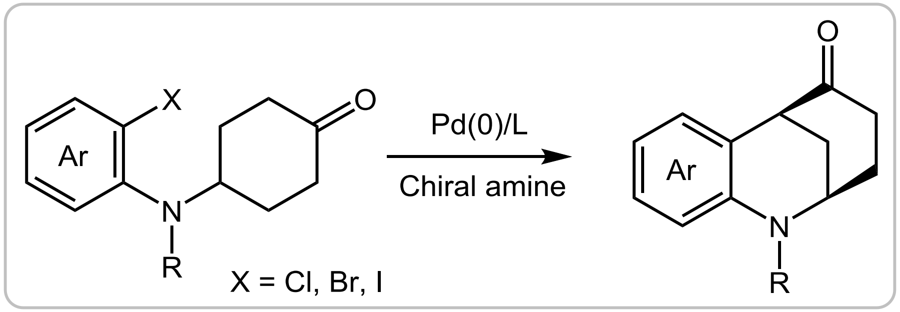

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Transition-metal-catalyzed enantioselective *α*-arylation of carbonyls represents one of the most important approaches to optically active *α*-aryl carbonyl compounds. Since the seminal studies from the groups of Buchwald, Hartwig, and Miura, a range of carbonyl compounds have been investigated in enantioselective cross-coupling with aryl halides, including ketones, aldehydes, esters, and amides. However, the aforementioned approaches are very limited to the construction of quaternary carbon stereocenters because the benzylic *α*-H atom of the tertiary carbon stereocenter is more acidic and prone to racemization under basic conditions.

In addition, the demand of commercially unavailable chiral ligands still remains an issue for these transformations. It is noteworthy that a few other catalytic enantioselective arylation protocols to generate *α*-carbonyl benzylic tertiary stereocenters have been developed, including (1) cross-coupling of *α*-halo carbonyls with arylmetal reagents, (2) electrophilic coupling of diaryliodonium salts with silyl enolates, or aldehydes, and (3) cross-coupling of aryl triflates with silyl ketene acetals or tin enolates. In comparison, the direct coupling of readily available aryl halides with *α*-C−H bonds of carbonyl moieties to form the tertiary carbon stereocenters is highly attractive from the viewpoint of atom economy and step efficiency.

In conclusion, we have developed a new strategy for the enantioselective *α*-arylative desymmetrization of cyclohexanones by using palladium/chiral amine catalysis. A series of optically active morphan derivatives bearing *α*-carbonyl tertiary stereocenters were produced in good yields with excellent enantioselectivities. The present protocol offers new opportunities for the development of enantioselective *α*-arylation of ketones.