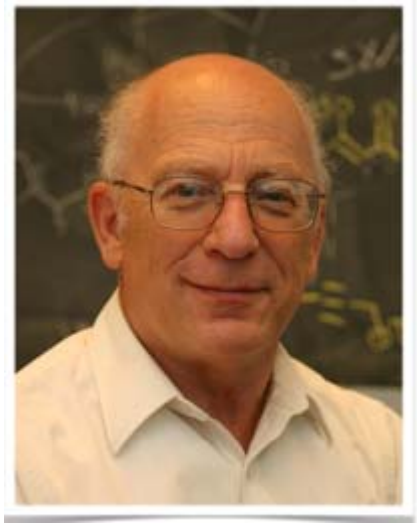
Direct Catalytic Asymmetric Mannich Reactions for the Construction of Quaternary Carbon Stereocenters

Reporter: Lian-Jin Liu
Checker: Yue Ji
Date: 24/05/2016

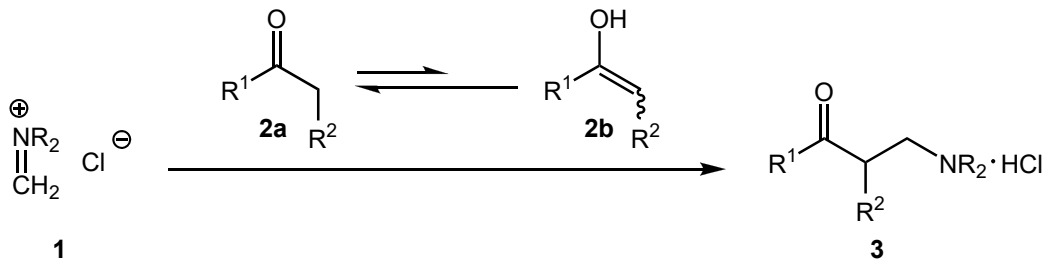


Barry M. Trost
Stanford University

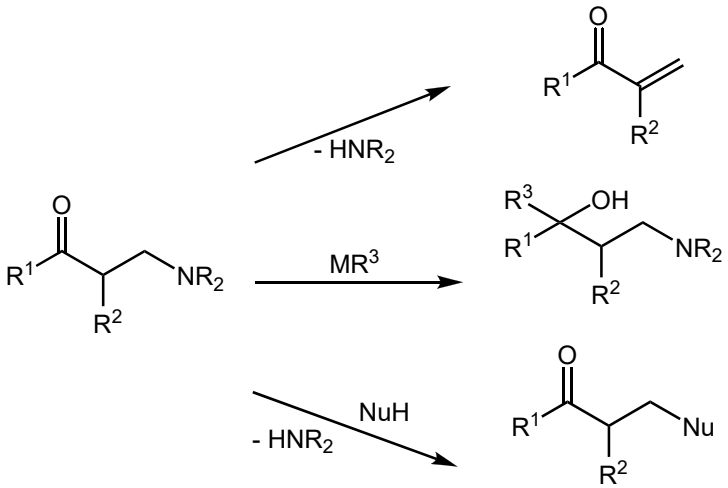
Trost, B. M. *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 3659-3662

Contents

Introduction

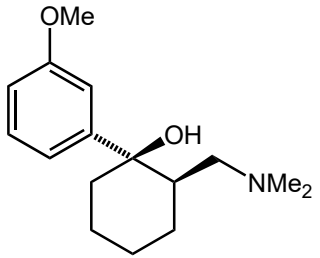


Simplified mechanism of the Mannich reaction

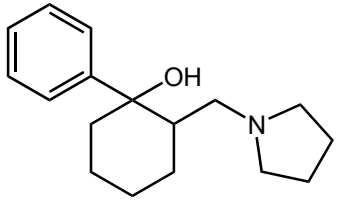


Mannich bases as synthesis building blocks

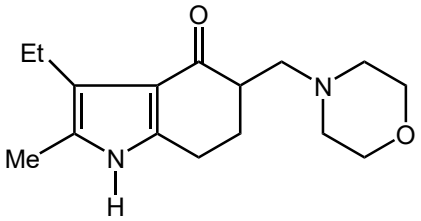
Introduction



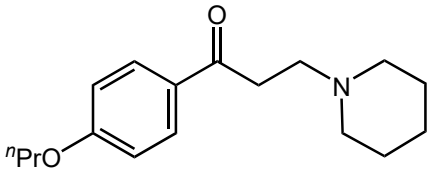
Tramadol
Analgesic



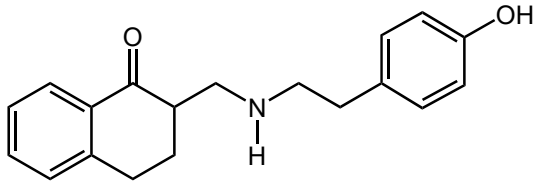
Osnervan
Antiparkinsonic



Moban
Neuroleptic

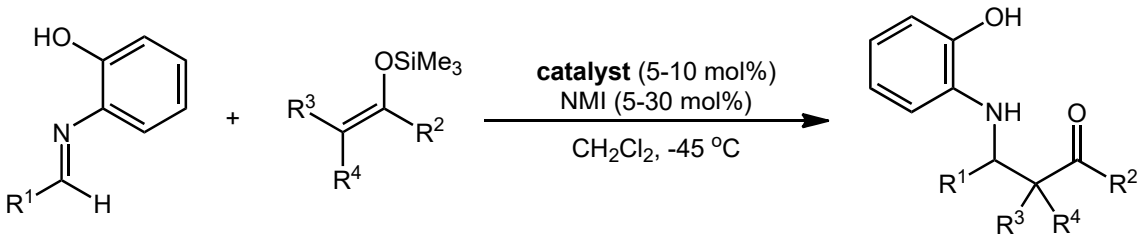


Falicain
Anaesthetic

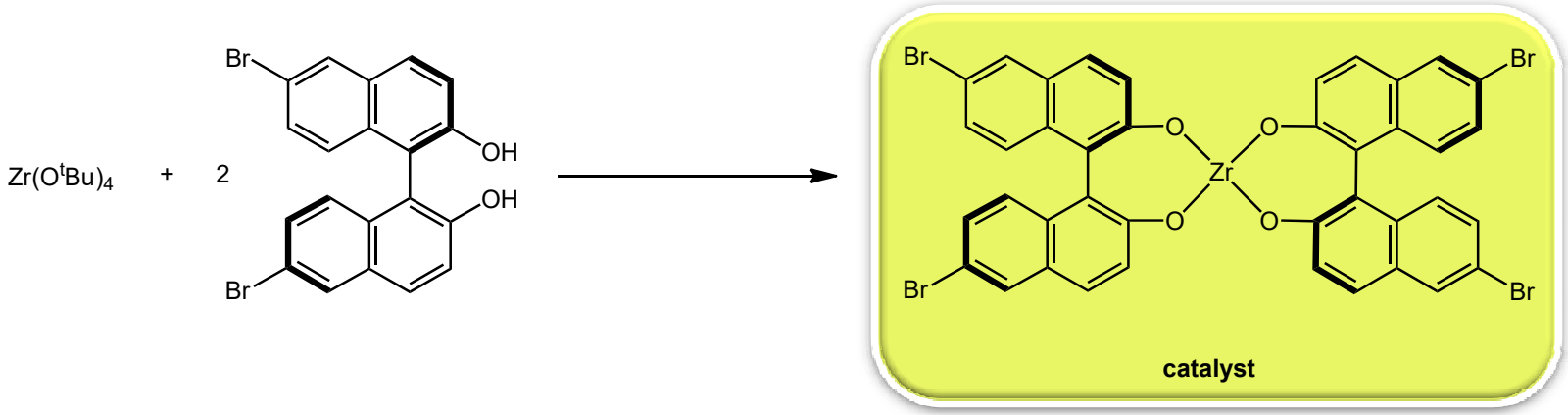


Be-2254
Antihypertensive

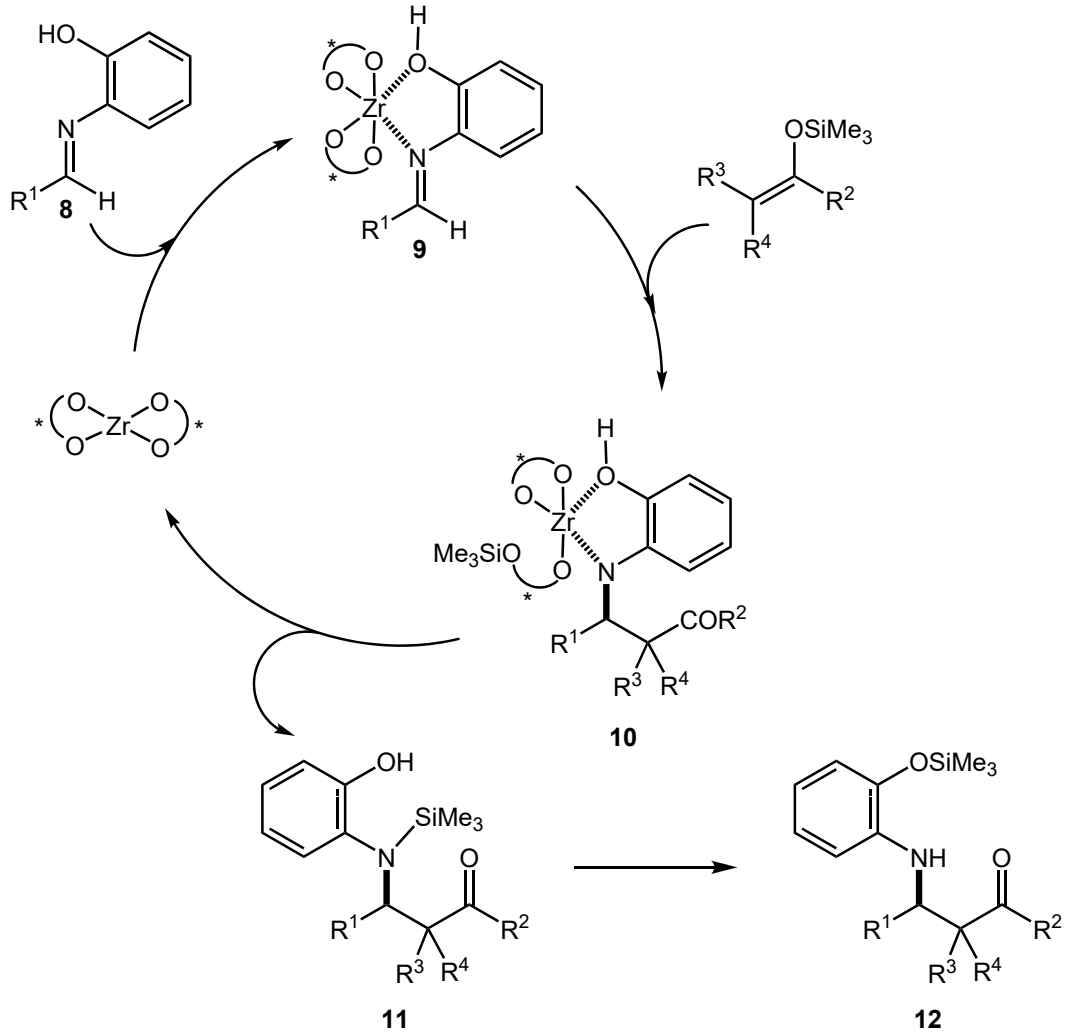
➢ Enantioselective Mannich-Type Reaction Using a Chiral Zirconium Catalyst



chiral zirconium catalyst
8 examples
up to quant. yield, > 98% *ee*

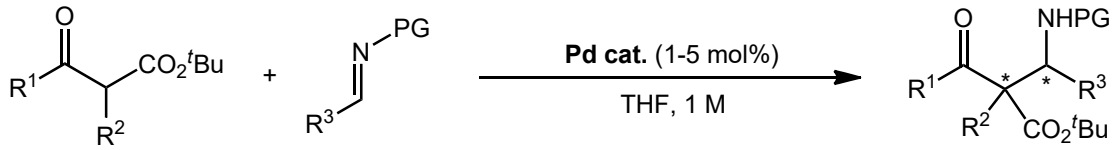


Assumed Catalytic Cycle

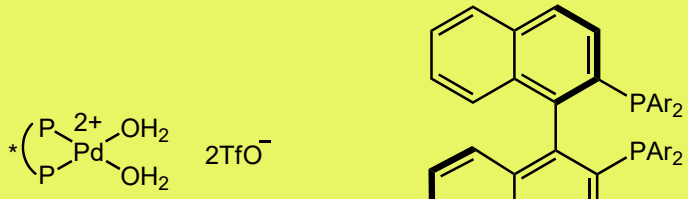


Kobayashi, S. *et al. J. Am. Chem. Soc.* **1997**, *119*, 7153-7154

➢ Enantioselective Mannich-Type Reaction Using a Chiral Palladium Catalyst

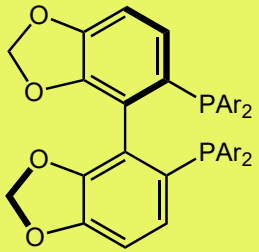


chiral palladium catalyst
10 examples
up to 99% *ee*



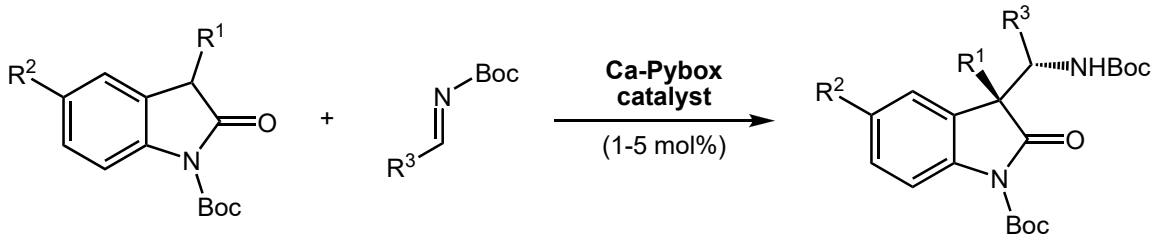
Pd cat

a: Ar = C_6H_5: (*R*)-binap
b: Ar = 4-MeC_6H_4: (*R*)-tol-binap

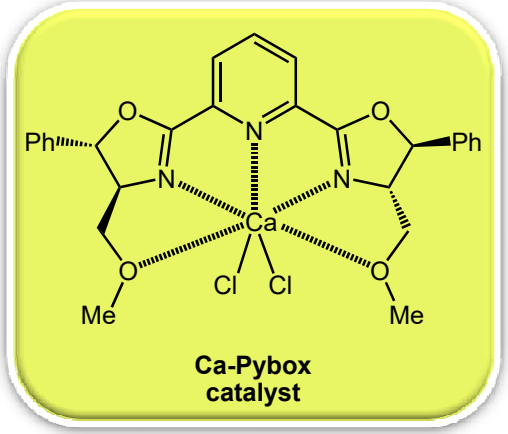


c: Ar = C_6H_5: (*R*)-segphos
d: Ar = 3,5-$Me_2C_6H_3$: (*R*)-dm-segphos

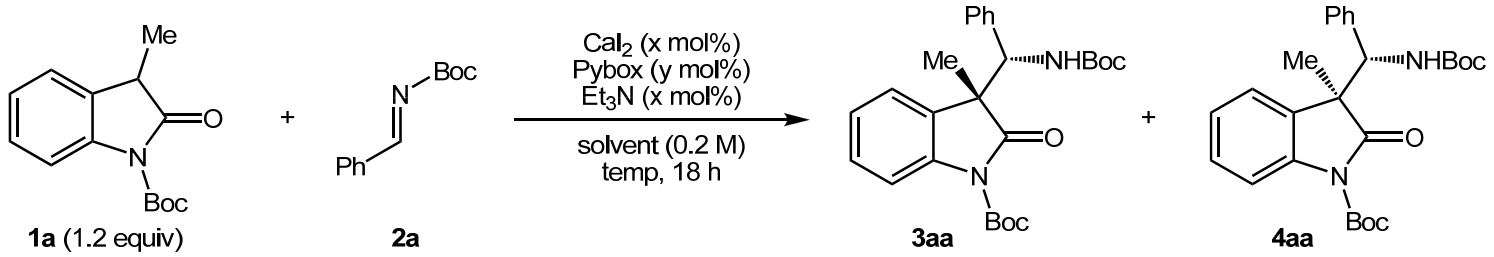
➢ Enantioselective Mannich-Type Reaction Using a Chiral Calcium Catalyst

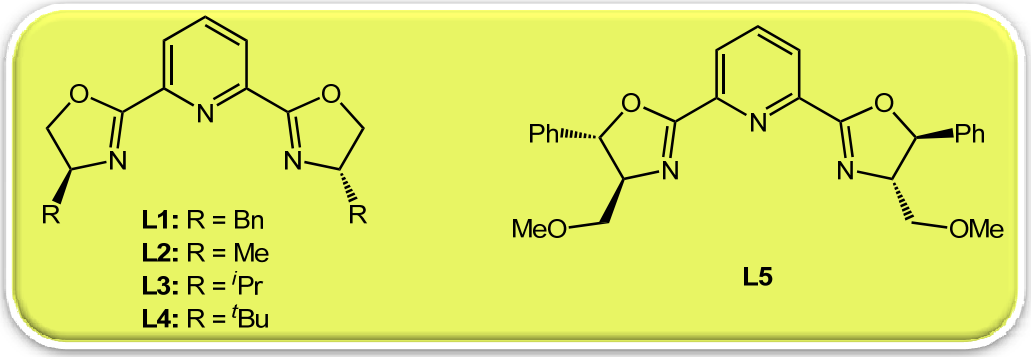


chiral calcium catalyst
26 examples
high to excellent *d.r.* and *ee*



Optimization of the Reaction Conditions

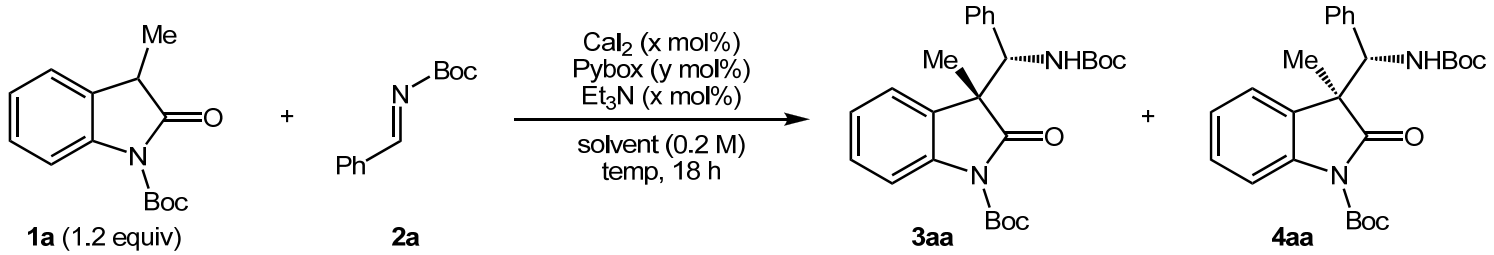




entry	x	y	temp [°C]	Pybox	solvent	yield [%]	**3aa : 4aa**	ee [%]
1	10	10	-40	**L1**	Tol	85	94 : 6	57
2	10	10	-40	**L2**	Tol	85	94 : 6	21
3	10	10	-40	**L3**	Tol	87	94 : 6	66
4	10	10	-40	**L4**	Tol	86	95 : 5	21
5	10	10	-40	**L5**	Tol	78	94 : 6	75

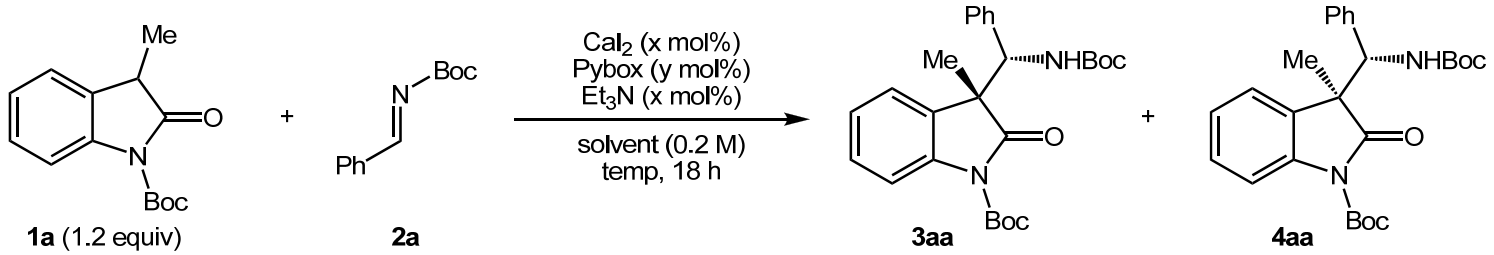
Kobayashi, S. *et al. Org. Lett*. **2015**, *17*, 2006-2009

Optimization of the Reaction Conditions



entry	x	y	temp [°C]	Pybox	solvent	yield [%]	**3aa : 4aa**	ee [%]
6	10	10	-40	**L5**	Et_2O	83	95 : 5	78
7	10	10	-40	**L5**	THF	80	95 : 5	31
8	10	10	-40	**L5**	DCM	83	94 : 6	78
9	10	10	-78	**L5**	DCM	88	94 : 6	93
10	5	5	-78	**L5**	DCM	85	94 : 6	76
11	5	7.5	-78	**L5**	DCM	85	93 : 7	99

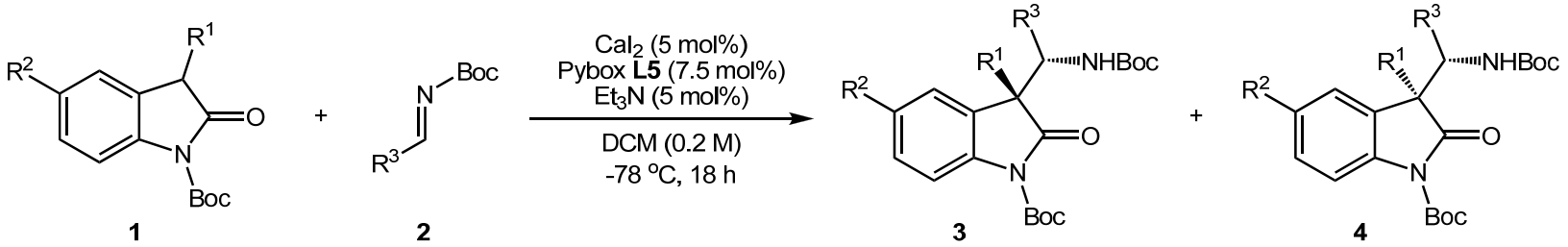
Optimization of the Reaction Conditions



entry	x	y	temp [°C]	Pybox	solvent	yield [%]	**3aa : 4aa**	ee [%]
12[a]	5	7.5	-78	**L5**	DCM	87	95 : 5	98
13	3	4.5	-78	**L5**	DCM	91	95 : 5	97
14	2	3	-78	**L5**	DCM	81	95 : 5	92
15	1	1.5	-78	**L5**	DCM	97	94 : 6	98
16[b]	5	7.5	-78	**L5**	DCM	92	94 : 6	87
17[c]	5	7.5	-78	**L5**	DCM	89	94 : 6	14

[a] **1a** (1.0 equiv), **2a** (1.5 equiv). [b] $CaCl_2$ was used instead of CaI_2. [c] $Ca(O^iPr)_2$ was used instead of CaI_2.

Substrate Scope



entry	R^1	R^2	R^3	yield [%]	**3 : 4**	ee [%]
1	Me (**1a**)	H	Ph (**2a**)	87 (**3aa**)	95 : 5	98
2	Me (**1a**)	H	*o*-MeC_6H_4 (**2b**)	93 (**3ab**)	97 : 3	97
3	Me (**1a**)	H	*m*-MeC_6H_4 (**2c**)	80 (**3ac**)	95 : 5	97
4	Me (**1a**)	H	*p*-MeC_6H_4 (**2d**)	95 (**3ad**)	96 : 4	95
5	Me (**1a**)	H	*m*-$CF_3C_6H_4$ (**2e**)	93 (**3ae**)	96 : 4	97
6	Me (**1a**)	H	*p*-$OMeC_6H_4$ (**2f**)	91 (**3af**)	94 : 6	95
7	Me (**1a**)	H	*p*-ClC_6H_4 (**2g**)	92 (**3ag**)	97 : 3	96
8	Me (**1a**)	H	*2*-furyl (**2h**)	89 (**3ah**)	97 : 3	96
9	Me (**1a**)	H	*2*-thienyl (**2i**)	91 (**3ai**)	98 : 2	98

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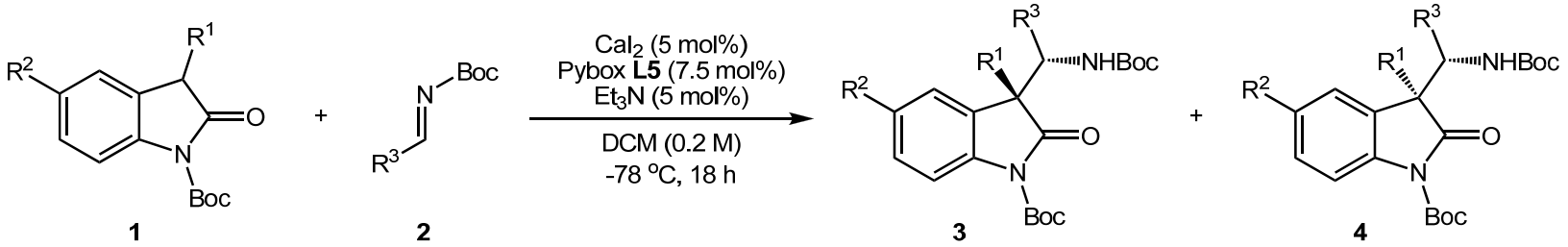
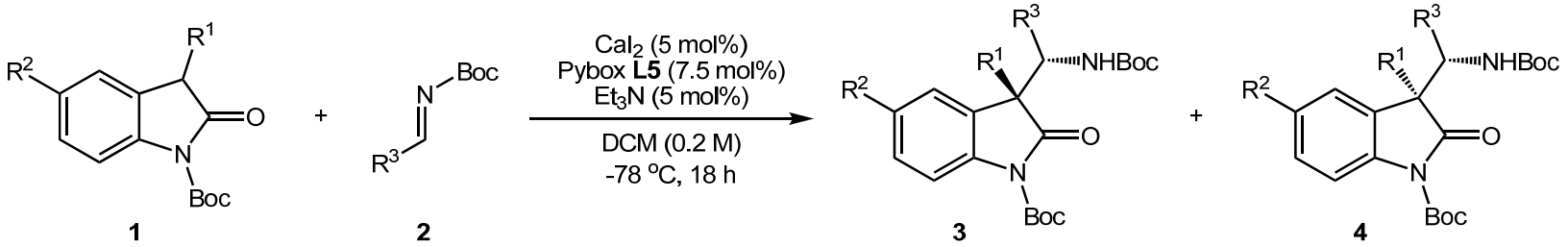
Substrate Scope



entry	R^1	R^2	R^3	yield [%]	**3 : 4**	ee [%]
10	Me (**1a**)	H	2-naphthyl (**2j**)	84 (**3aj**)	97 : 3	97
11	Me (**1a**)	H	Et (**2k**)	96 (**3ak**)	97 : 3	90
12	Me (**1a**)	H	*n*-C_5H_{11} (**2l**)	95 (**3al**)	93 : 7	72
13	Me (**1a**)	H	^{i}Bu (**2m**)	99 (**3am**)	94 : 6	84
14	Bn (**1b**)	H	Ph (**2a**)	81 (**3ba**)	94 : 6	95
15	Bn (**1b**)	H	*2*-thienyl (**2i**)	84 (**3bi**)	96 : 4	98
16	^{n}Pr (**1c**)	H	Ph (**2a**)	83 (**3ca**)	94 : 6	98
17	^{n}Pr (**1c**)	H	Et (**2k**)	43 (**3ck**)	97 : 3	72
18	^{n}Pr (**1c**)	H	^{i}Bu (**2m**)	93 (**3cm**)	97 : 3	74

Substrate Scope



entry	R^1	R^2	R^3	yield [%]	**3 : 4**	ee [%]
19	^{i}Pr (**1d**)	H	Ph (**2a**)	80 (**3da**)	95 : 5	> 99
20	^{i}Pr (**1d**)	H	^{i}Bu (**2m**)	77 (**3dm**)	95 : 5	73
21	**1e**	H	Ph (**2a**)	80 (**3ea**)	95 : 5	93
22	**1e**	H	*p*-MeC_6H_4 (**2d**)	82 (**3ed**)	94 : 6	95
23	**1e**	H	*p*-ClC_6H_4 (**2g**)	88 (**3eg**)	96 : 4	97
24	**1e**	H	*2*-furyl (**2h**)	93 (**3eh**)	96 : 4	91
25	**1f**	Me	Ph (**2a**)	93 (**3fa**)	94 : 6	95
26	**1g**	F	Ph (**2a**)	82 (**3ga**)	94 : 6	93

1e: $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = H. **1f:** $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = Me.
1g: $R^1 = CH_2CH(O(CH_2)_2O)$, R^2 = F

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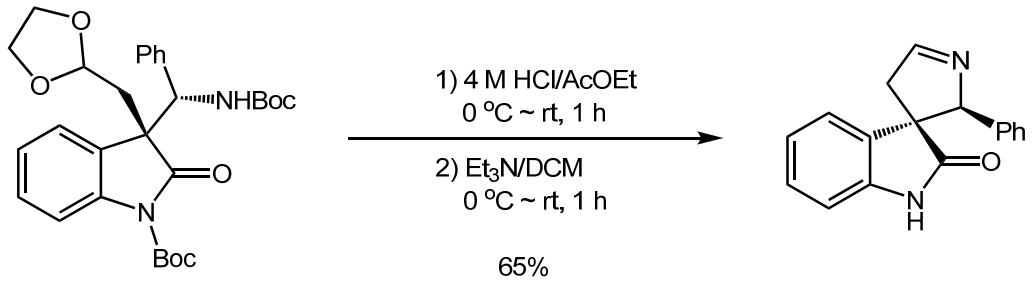
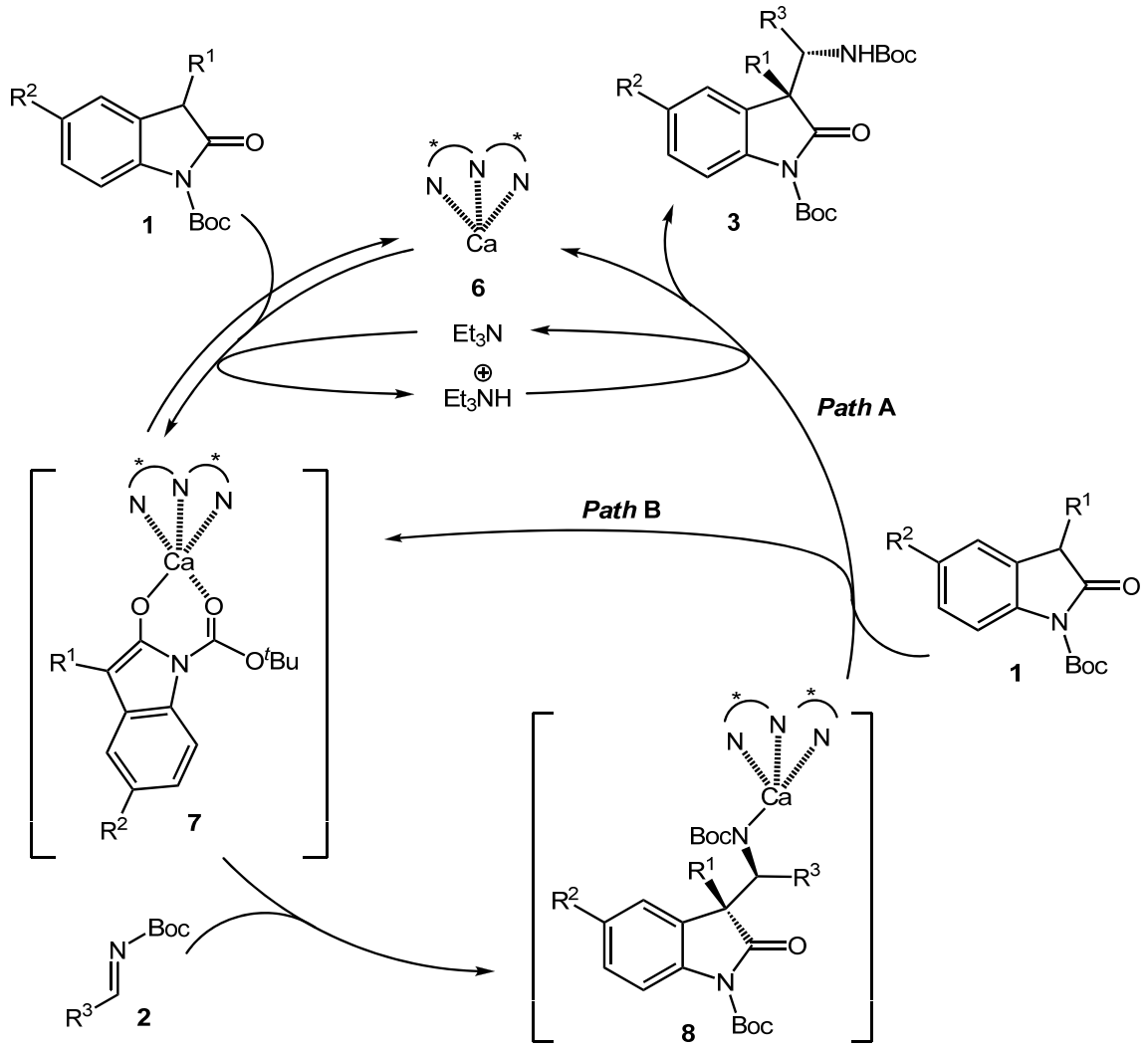
Transformation to Spirooxindole



3ea (93% ee)

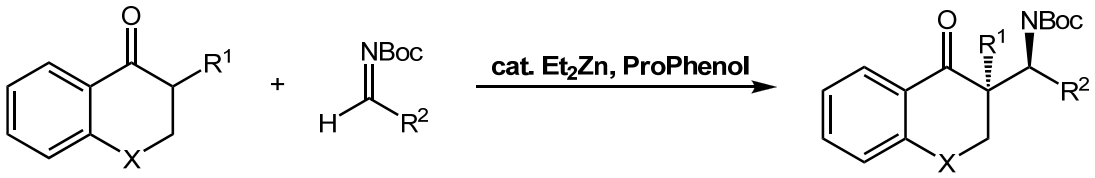
5ea (92% ee)

Assumed Catalytic Cycle

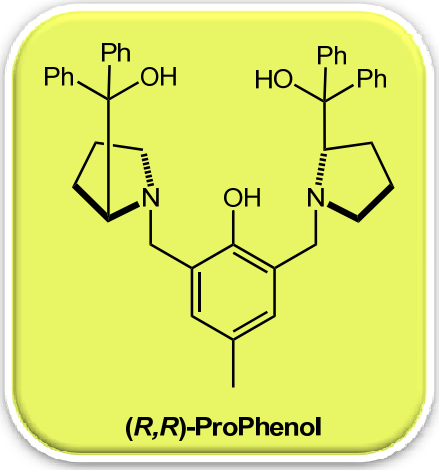


Kobayashi, S. *et al. Org. Lett*. **2015**, *17*, 2006-2009

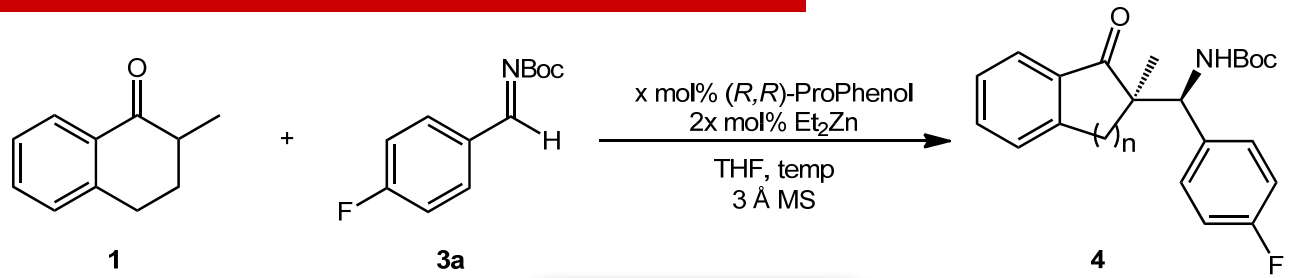
➢ Enantioselective Mannich-Type Reaction Using a Chiral Zinc Catalyst



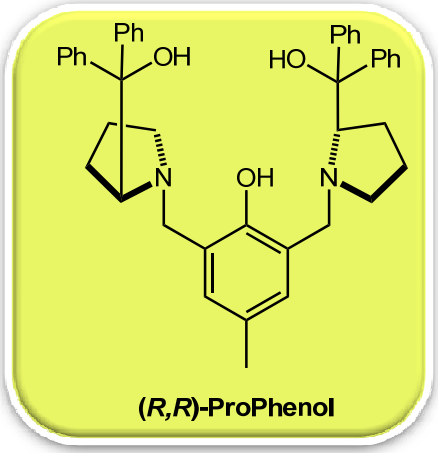
chiral zinc catalyst
26 examples
high *d.r.*, high *ee*



Optimization of the Reaction Conditions[a]



1 + 3a → 4



entry	x	[conc.], temp	yield[b]	d.r.[c]	ee[d]
1	20	(0.4 M), 60 °C	28%	> 20 : 1	97%
2	20	(0.4 M), 80 °C	76%	> 20 : 1	96%
3[e]	20	(1.0 M), 80 °C	93%	> 20 : 1	99%
4[e]	10	(1.0 M), 80 °C	75%	> 20 : 1	95%

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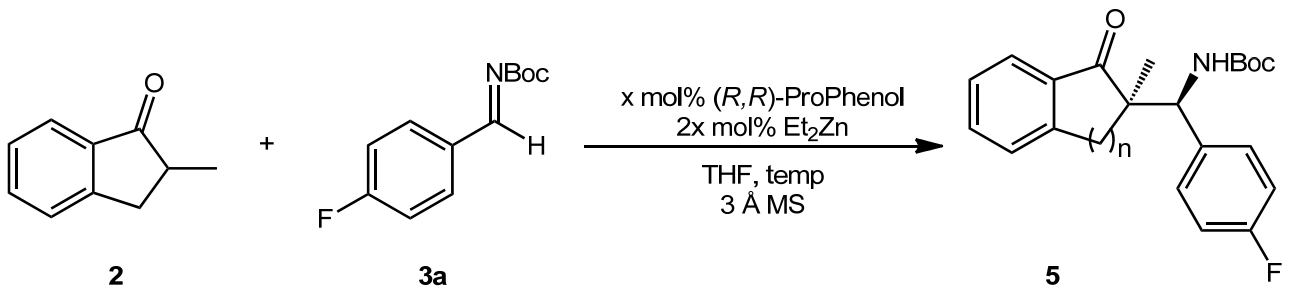
➢ Optimization of the Reaction Conditions[a]

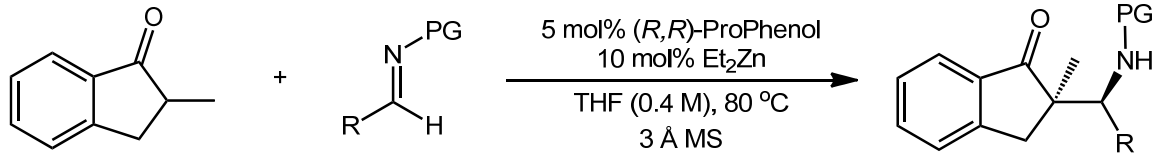


2 **3a** **5**

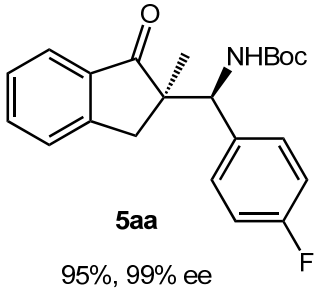
entry	x	[conc.], temp	yield[b]	d.r.[c]	ee[d]
5	20	(0.4 M), 60 °C	99%	> 20 : 1	99%
6	10	(0.4 M), 60 °C	91%	> 20 : 1	99%
7[e]	10	(0.4 M), 80 °C	99%	> 20 : 1	99%
8[e]	5	(0.4 M), 80 °C	95%	> 20 : 1	99%

[a] Reaction conditions: 0.20 mmol **1a** or **2a**, 0.24 mmol **3a**, x mol% (*R,R*)-ProPhenol, 2x mol% Et_2Zn (1 M in hexanes), 3 Å molecular sieves (5 mg), in THF for 40 h at the indicated temperature and concentration. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction time is 16 h.

Scope of the Reaction

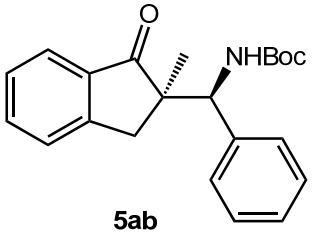


2 **3** **5**



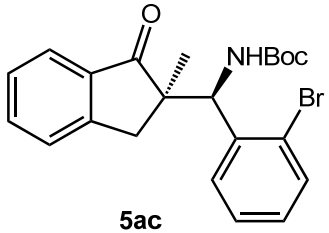
5aa

95%, 99% ee
> 20:1 d.r.



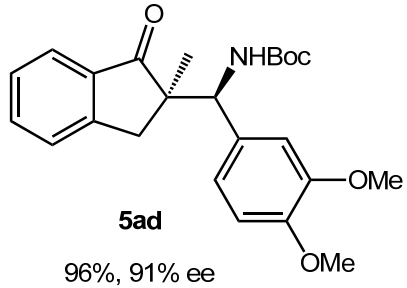
5ab

95%, 99% ee
> 20:1 d.r.



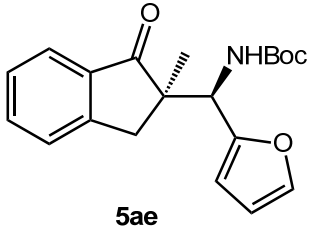
5ac

88%, 99% ee
> 20:1 d.r.



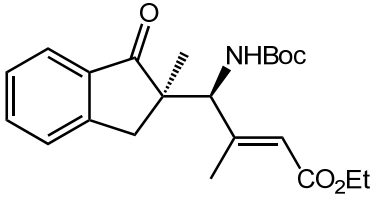
5ad

96%, 91% ee
> 20:1 d.r.



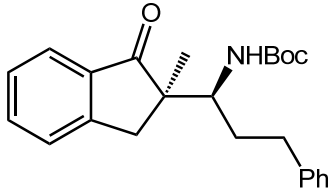
5ae

92%, 97% ee
> 20:1 d.r.



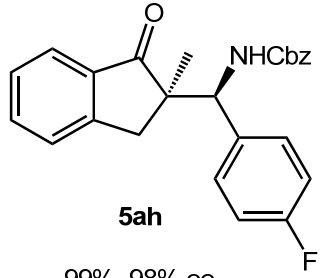
5af

94%, 99% ee
> 20:1 d.r.



5ag

80%, 99% ee
> 20:1 d.r.

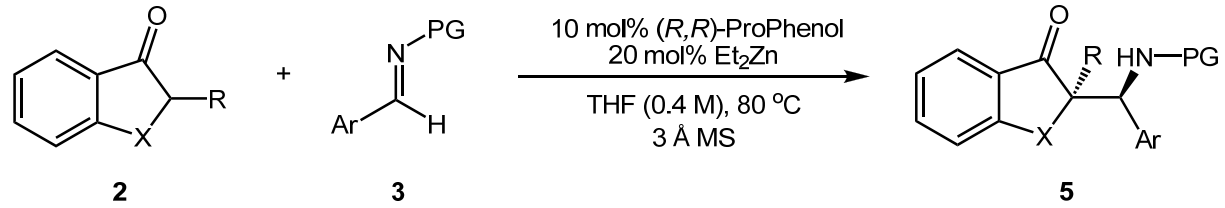


5ah

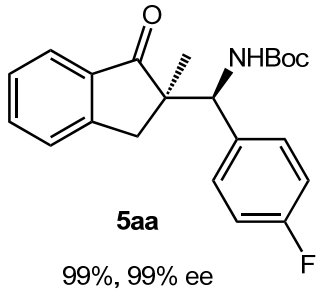
99%, 98% ee
> 20:1 d.r.

Trost, B. M. *et al. J. Am. Chem. Soc.* **2016**, *138*, 3659-3662

Scope of the Reaction

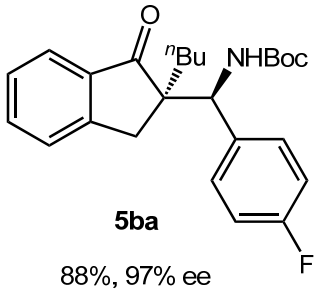


2 **3** **5**



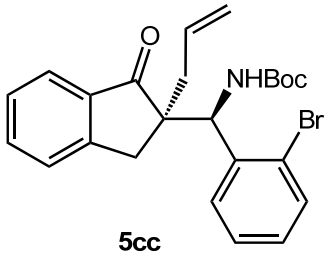
5aa

99%, 99% ee
> 20:1 d.r.



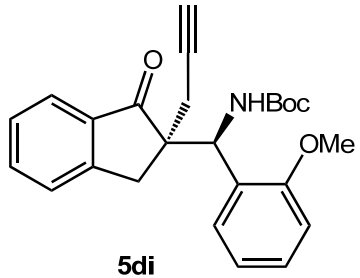
5ba

88%, 97% ee
> 20:1 d.r.



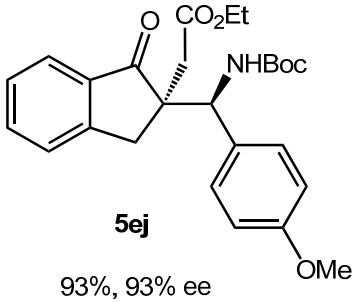
5cc

96%, 99% ee
> 20:1 d.r.



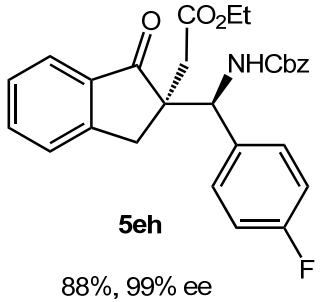
5di

90%, 91% ee
> 20:1 d.r.



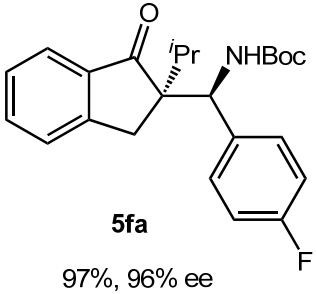
5ej

93%, 93% ee
> 20:1 d.r.



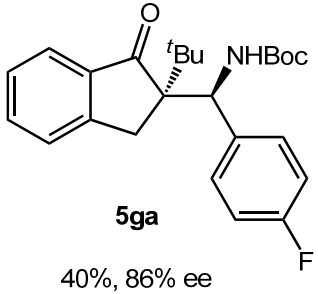
5eh

88%, 99% ee
> 20:1 d.r.



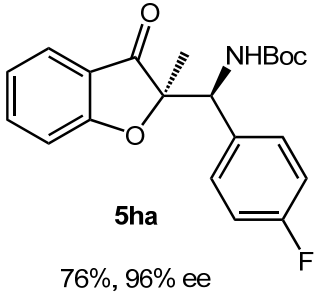
5fa

97%, 96% ee
> 20:1 d.r.



5ga

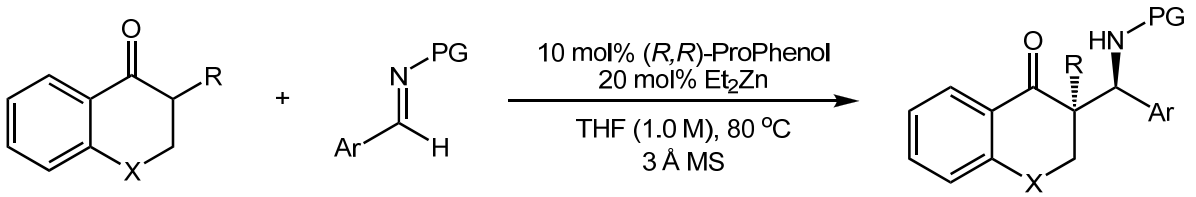
40%, 86% ee
7:1 d.r.



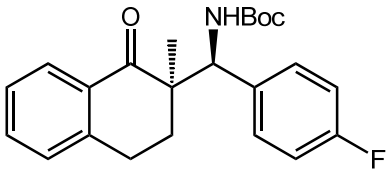
5ha

76%, 96% ee
> 20:1 d.r.

Scope of the Reaction

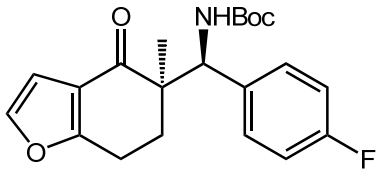


1 **3** **4**



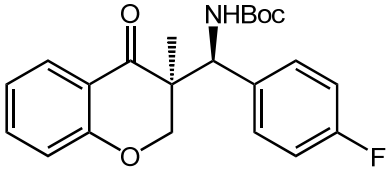
4aa

75%, 95% ee
> 20:1 d.r.



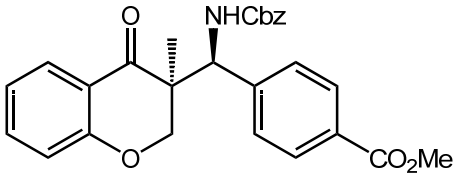
4ba

96%, 99% ee
> 20:1 d.r.



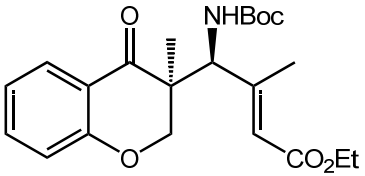
4ca

92%, 98% ee
> 20:1 d.r.



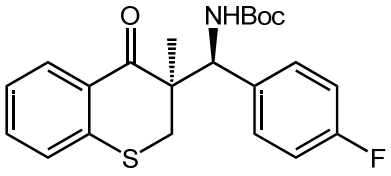
4ck

95%, 91% ee
> 20:1 d.r.



4cf

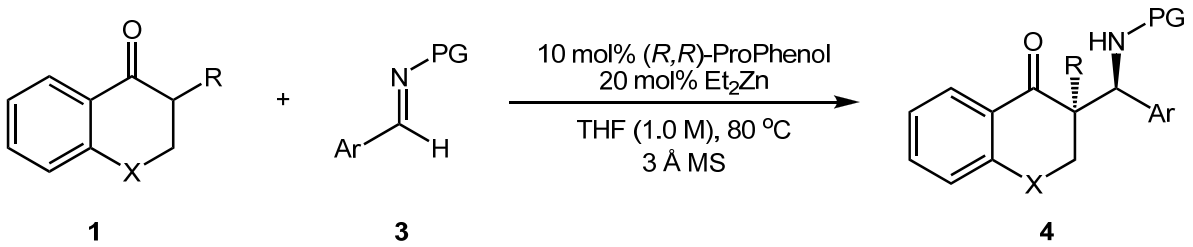
72%, 92% ee
> 20:1 d.r.



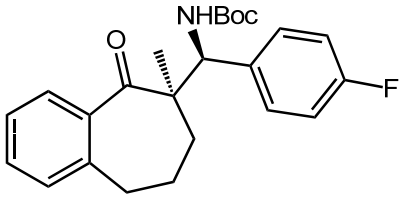
4da

72%, 99% ee
> 2.6:1 d.r.

Scope of the Reaction

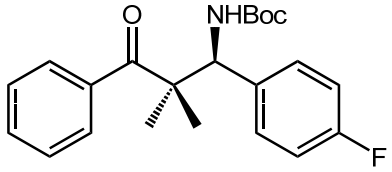


1 **3** **4**



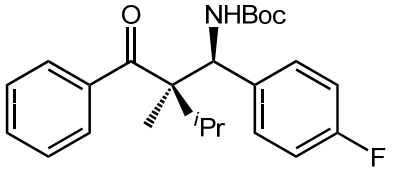
4ea

89%, 99% ee
9:1 d.r.



4fa

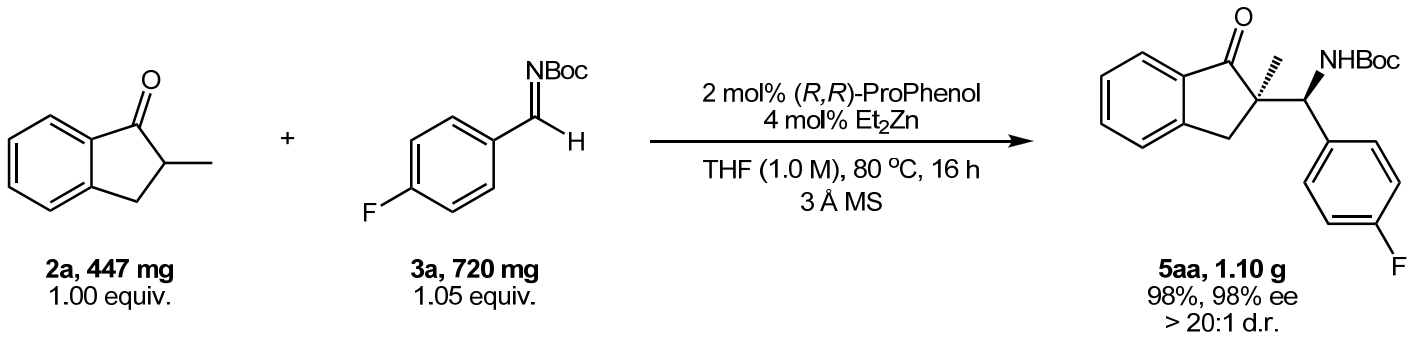
75%, 96% ee
.



4ga

< 5%, n.r.

➢ Gram-Scale Reaction

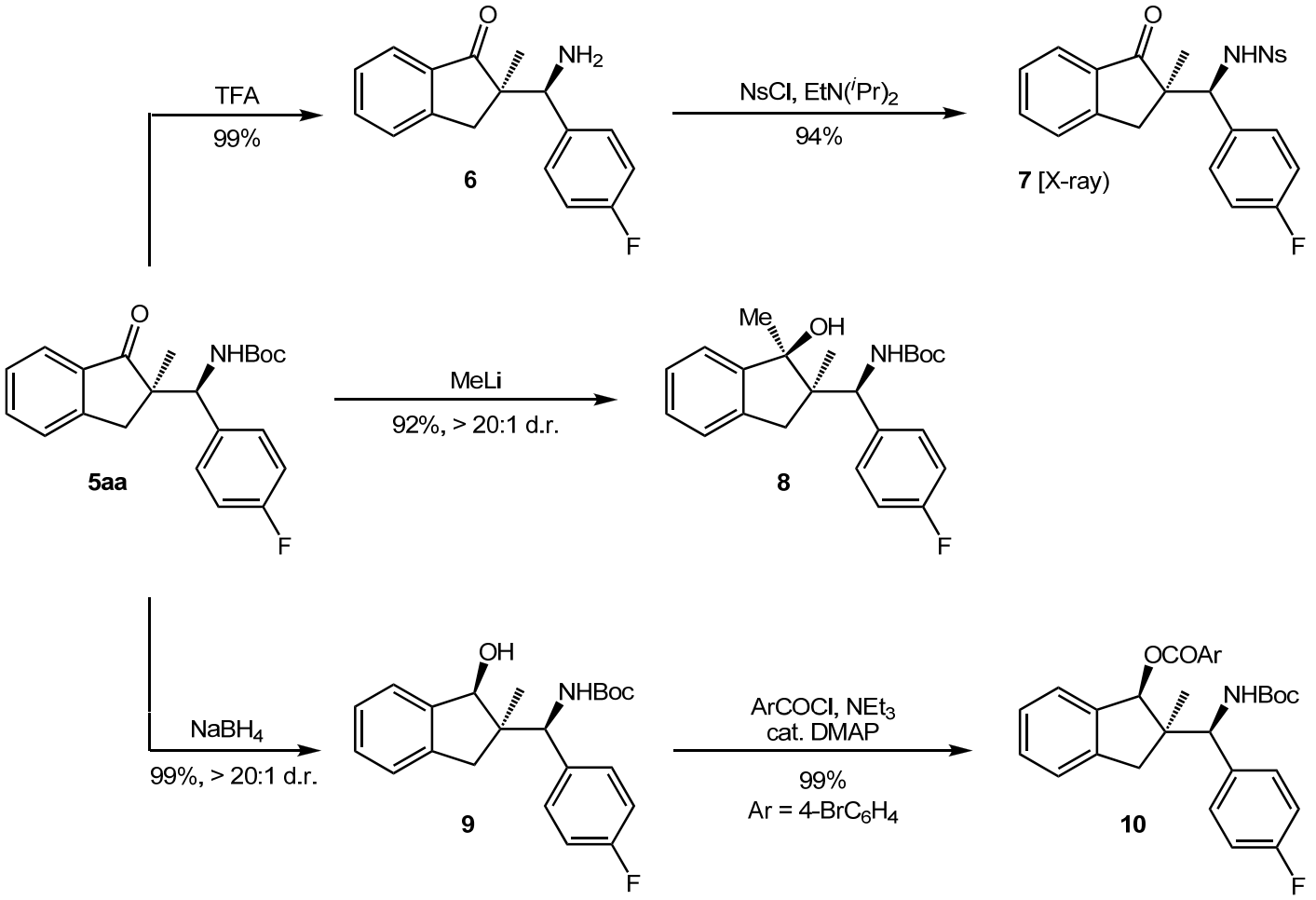


2a, 447 mg
1.00 equiv.

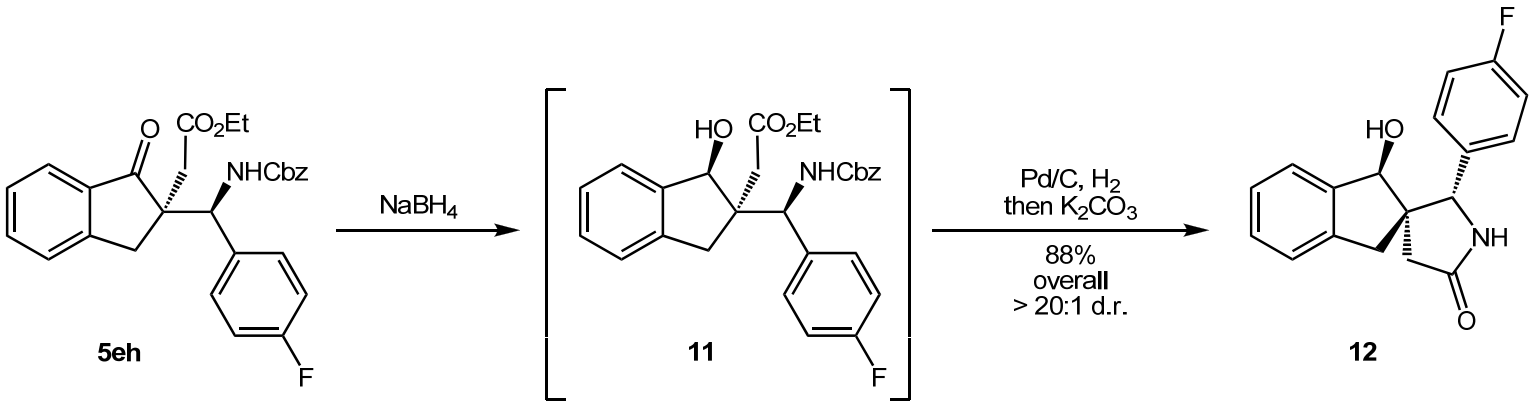
3a, 720 mg
1.05 equiv.

5aa, 1.10 g
98%, 98% ee
> 20:1 d.r.

Synthetic Applications

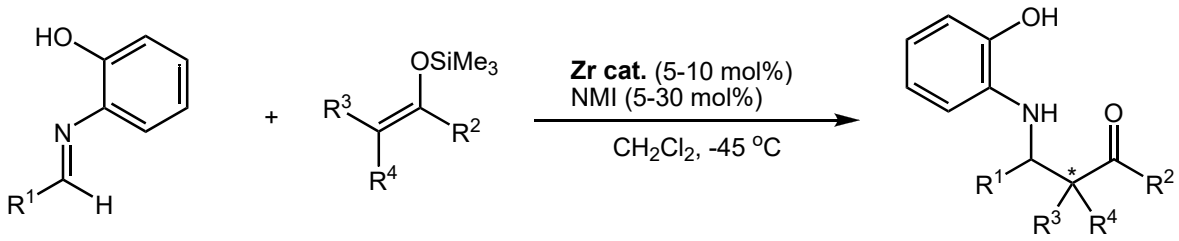


Synthetic Applications



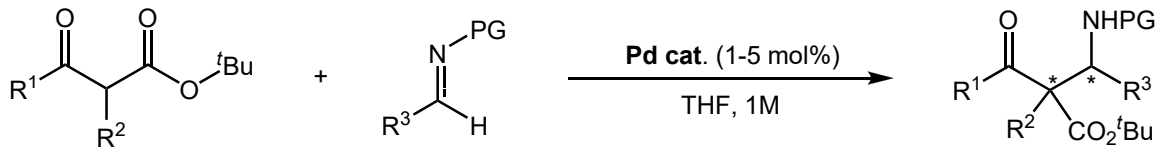
➢ Summary

Kobayashi, S.



chiral zirconium catalyst
8 examples
up to quant. yield, >98% *ee*

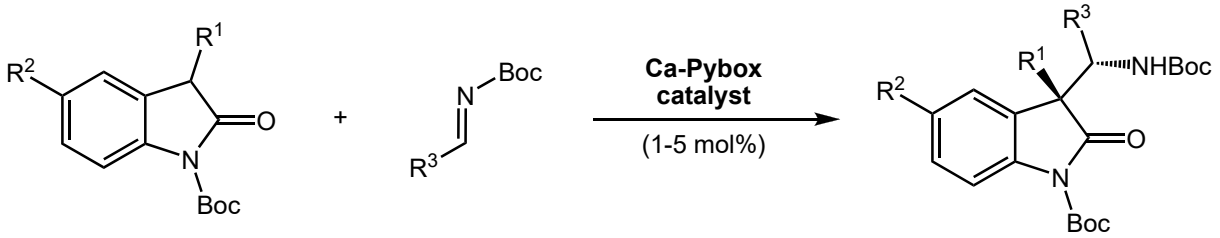
Sodeoka, M.



chiral palladium catalyst
10 examples
up to 99% *ee*

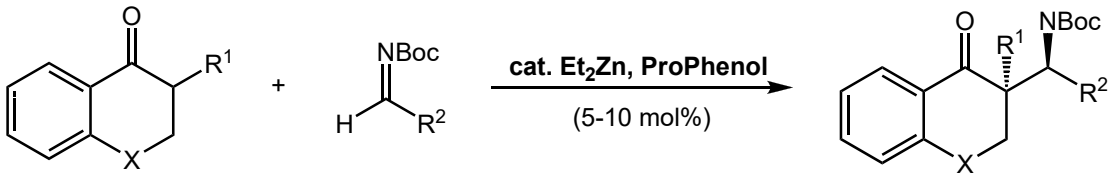
➢ Summary

Kobayashi, S.



chiral calcium catalyst
26 examples
high to excellent *d.r.* and *ee*

Trost, B. M.



chiral zinc catalyst
26 examples
high *d.r.*, high *ee*

One of the modern challenges for the synthetic chemist is the fast, selective, and atom-economic access to molecular complexity starting from simple and widely available starting materials. The Mannich reaction is an important tool for C−C bond formation. Moreover, it is also one of the most robust ways to produce nitrogen-containing compounds which are ubiquitous in nature. All-carbon quaternary stereocenters are also a common feature of natural products, and their construction still represents a synthetic challenge, especially in a catalytic enantioselective fashion. In this context, we report herein the first direct asymmetric Mannich reaction that allows the use of *α*-branched ketone donors. This atom-economic transformation provides an efficient enantio- and diastereoselective access to chiral *β*-amino ketones decorated with a quaternary carbon stereocenter.

In summary, we have developed the first direct asymmetric Mannich reaction using *α*-branched ketones. This strategy allows an enantio- and diastereoselective access to a range of functionalized *β*-amino ketones featuring an all-carbon quaternary stereocenter. The reaction exhibits many interesting features: the preactivation of the reaction partners is not required; the reaction is highly atom-economic and can be run on a gram-scale with a low catalyst loading. Moreover, two convenient and orthogonal protecting groups can be used on the imines with similar efficiency.

Finally, the Mannich adducts can be further elaborated to complex molecules possessing three contiguous stereogenic centers with complete control of diastereoselectivity. The extension of this strategy to the synthesis of quaternary carbon in acyclic systems is a major goal of our future efforts and will be reported in due course.