Literature Report

Controlling Regioselectivity in the Enantioselective *N*-Alkylation of Indole Analogues Catalyzed by Dinuclear Zinc-ProPhenol

Reporter: Zhong Yan
Checker: Ji Zhou
Date: 2017-09-11

Trost, **B**. **M**.; Gnanamani, E.; Hung, C.-I. *Angew*. *Chem*. *Int*. *Ed*. **2017**, *56*, 10451.

CV of Barry M. Trost

Prof. Barry M. Trost

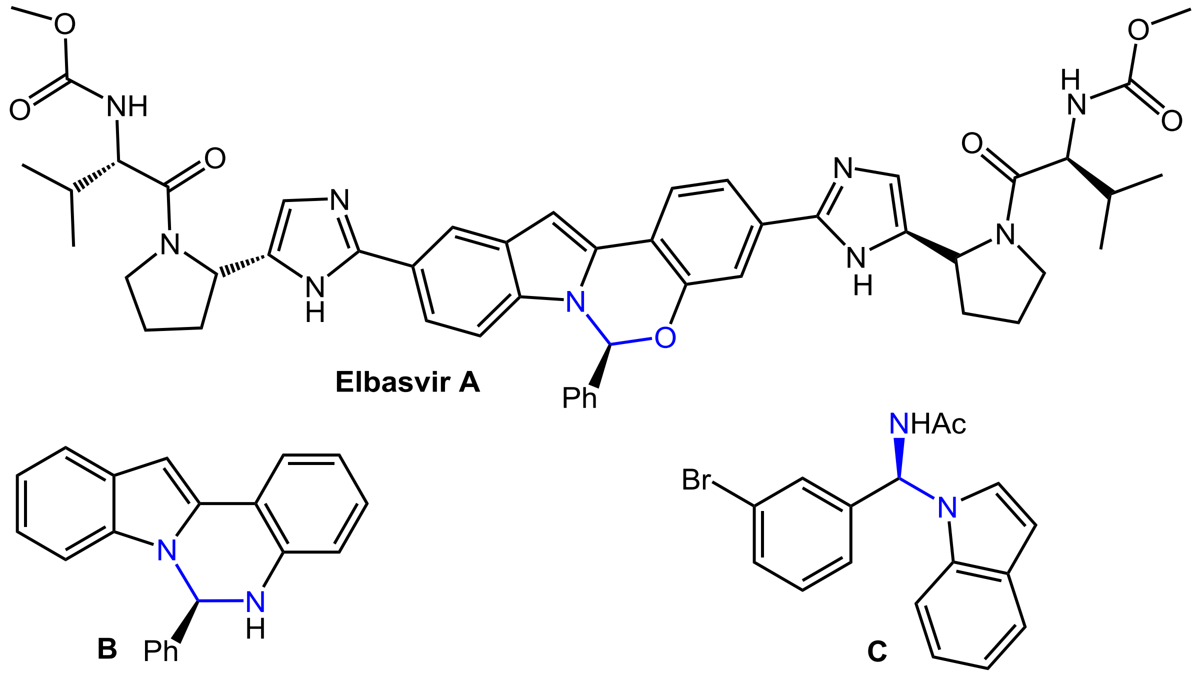
- **1962** B.Sc., University of Pennsylvania
- **1962-1965** Ph.D., Massachusetts Institute of Technology
- **1969-1987** Prof., University of Wisconsin
- **1987-2017** Prof., Stanford University

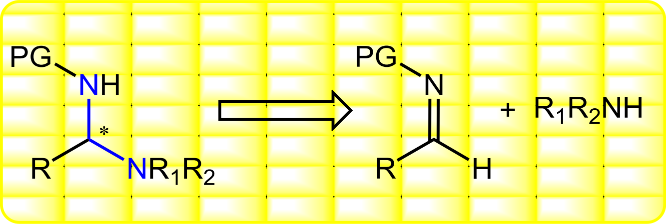
Research:

- 开发使用过渡金属催化的有机合成反应，并以重要天然活性物的全合成作为研究重点

Contents

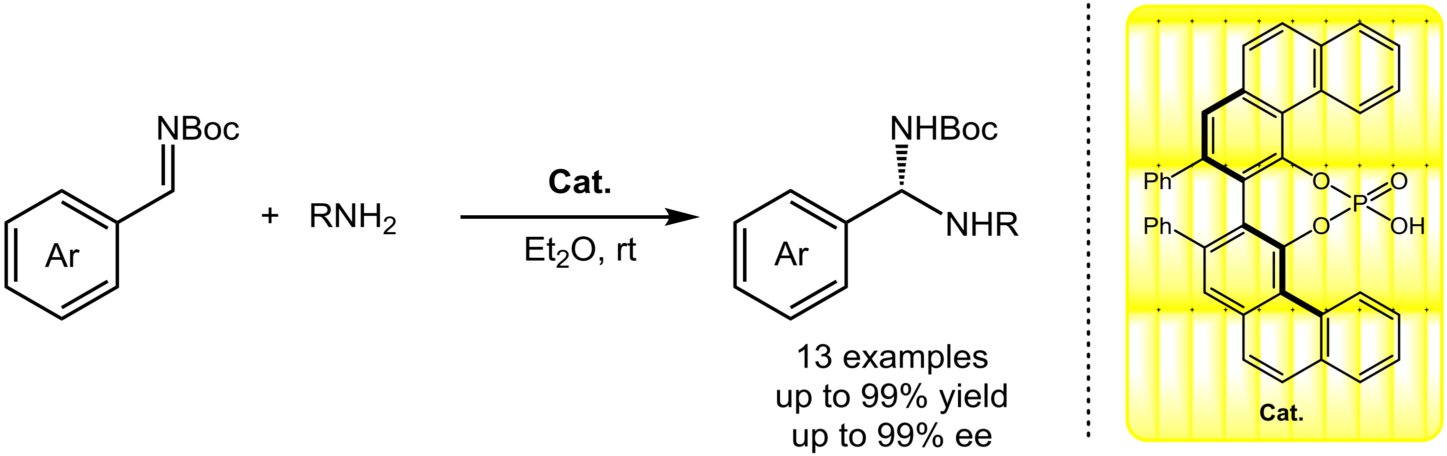
Introduction





Challenges:
- Unstability of the products
- Control of the stereoselectivity

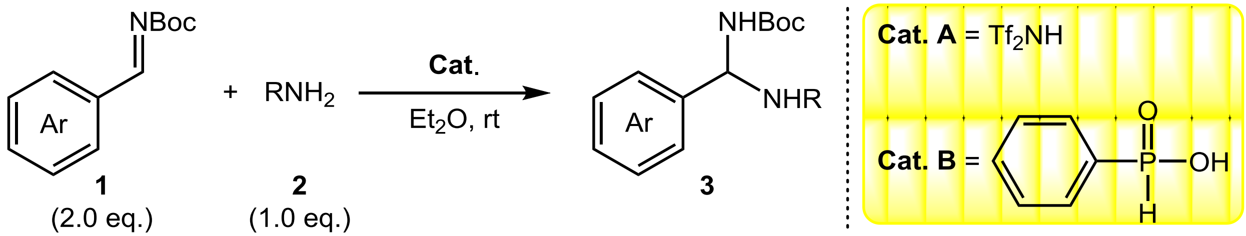
Brønsted Acid-Catalyzed Addition of Amides to Imines



13 examples
up to 99% yield
up to 99% ee

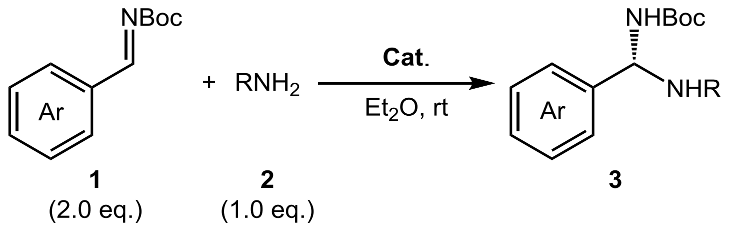
Rowland, G. B.; Zhang, H.; Wang, Y.; **Antilla**, **J**. **C**. *J. Am. Chem*. *Soc*. **2005**, *127*, 15696.

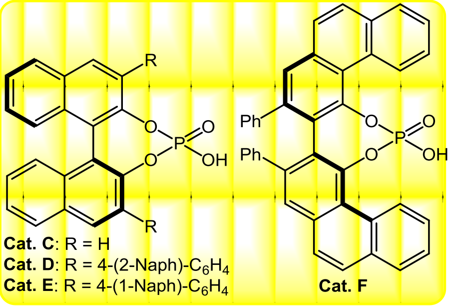
Brønsted Acid-Catalyzed Imines Amidation



Entry	Ar	R	**Cat.**	Time	Yield (%)
1	C_6H_5	$MeSO_2$	0.5 mol% **A**	20 min	99
2	C_6H_5	Ts	5 mol% **B**	20 h	91
3	C_6H_5	CO_2Et	0.5 mol% **A**	20 min	97
4	C_6H_5	CO_2Bn	5 mol% **B**	13 h	81
5	C_6H_5	$C(O)CH{=}CH_2$	0.5 mol% **A**	20 min	97
6	C_6H_5	C(O)H	0.5 mol% **A**	20 min	87
7	C_6H_5	C(O)Me	10 mol% **B**	19 h	91
8	C_6H_5	C(O)Ph	0.5 mol% **A**	20 min	91
9	$2\text{-}MeC_6H_4$	$C(O)CH{=}CH_2$	10 mol% **B**	24 h	98
10	$4\text{-}BrC_6H_4$	$C(O)CH{=}CH_2$	10 mol% **B**	2.5 h	94
11	$4\text{-}MeOC_6H_4$	$C(O)CH{=}CH_2$	5 mol% **B**	14 h	91
12	2-thienyl	$C(O)CH{=}CH_2$	10 mol% **B**	10 h	91
13	2-furyl	$C(O)CH{=}CH_2$	10 mol% **B**	11 h	99

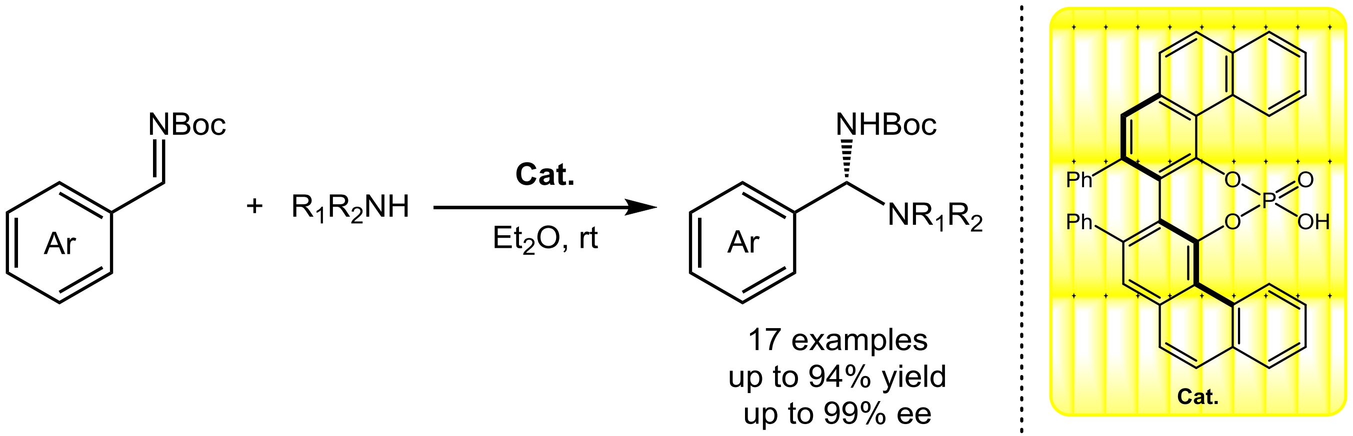
Catalytic Asymmetric Imines Amidation





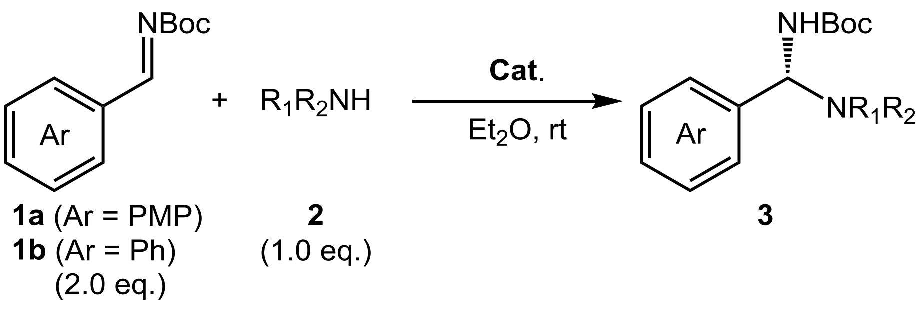
Entry	Ar	R	**Cat.**	Time	Yield (%)	ee (%)
1	C_6H_5	Ts	5 mol% **C**	16 h	95	<5
2	C_6H_5	Ts	4 mol% **D**	20 h	96	60
3	C_6H_5	Ts	5 mol% **E**	24 h	99	71
4	C_6H_5	Ts	5 mol% **F**	1 h	95	94
5	C_6H_5	Ms	5 mol% **F**	1 h	86	93
6	C_6H_5	4-MeO$C_6H_4SO_2$	5 mol% **F**	1 h	89	91
7	C_6H_5	2-Me$C_6H_4SO_2$	20 mol% **F**	50 h	80	73
8	C_6H_5	4-Cl$C_6H_4SO_2$	20 mol% **F**	15 h	98	95
9	4-ClC_6H_4	Ts	10 mol% **F**	17 h	88	94
10	4-BrC_6H_4	Ts	10 mol% **F**	13 h	96	92
11	4-$CF_3C_6H_4$	Ts	10 mol% **F**	20 h	99	99
12	4-MeOC_6H_4	Ts	10 mol% **F**	17 h	92	90
13	2-thienyl	Ts	10 mol% **F**	17 h	94	87

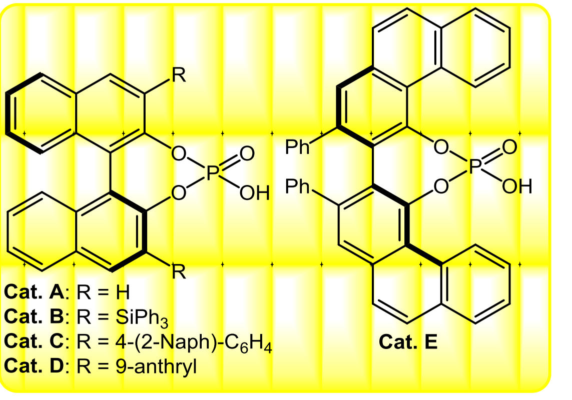
Brønsted Acid-Catalyzed Addition of Amides to Imines



Liang, Y.; Rowland, E. B Rowland, G. B.; Perman, J. A.; **Antilla**, **J. C**. *Chem*. *Commun*. **2007**, 4477.

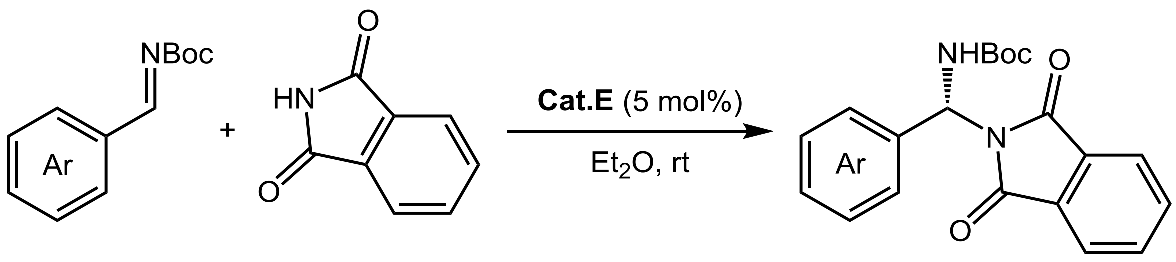
Condition Optimization



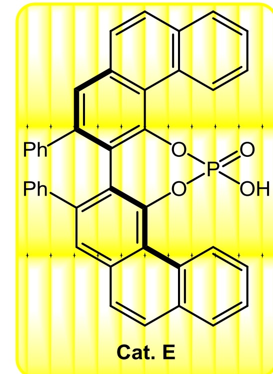


Entry	Ar	R_1R_2NH	**Cat.**	Yield (%)	ee (%)
1	**1a**	phthalimide	5 mol% **A**	31	0
2	**1a**	phthalimide	5 mol% **B**	80	56
3	**1a**	phthalimide	5 mol% **C**	76	34
4	**1a**	phthalimide	5 mol% **D**	82	47
5	**1a**	phthalimide	5 mol% **E**	92	96
6	**1a**	$PhC(O)NH_2$	5 mol% **E**	90	34
7	**1b**	$MeC(O)NH_2$	5 mol% **E**	89	18
8	**1b**	acrylamide	5 mol% **E**	96	21

The Substrate Scope

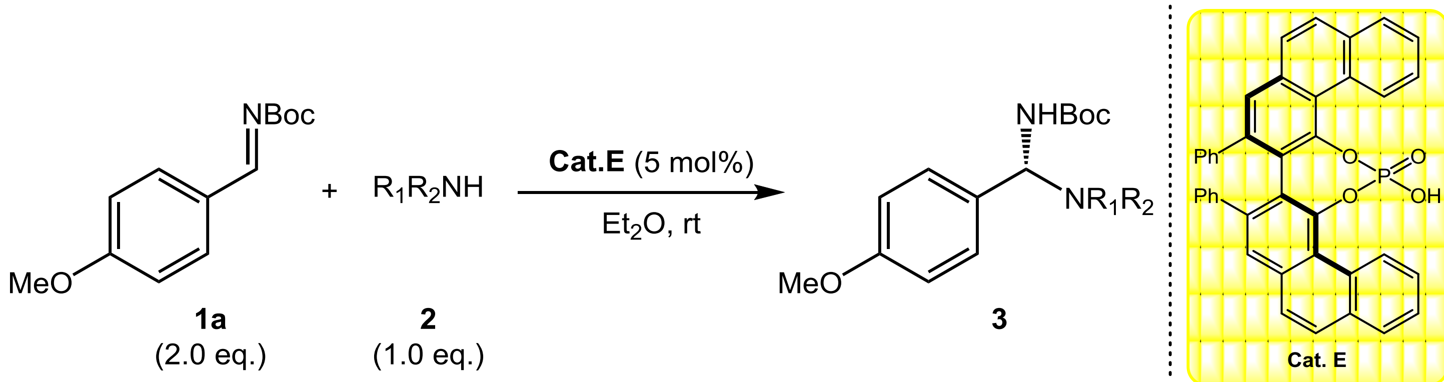


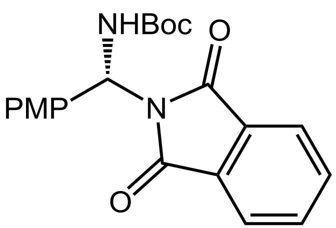
1 (2.0 eq.) **2a** (1.0 eq.) **3**



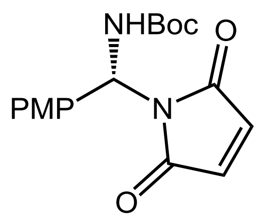
Entry	Ar	Product	Yield (%)	ee (%)
1	4-MeOC_6H_4	**3a**	92	96
2	C_6H_5	**3b**	88	93
3	2-MeC_6H_4	**3c**	94	99
4	3-MeC_6H_4	**3d**	86	90
5	4-MeC_6H_4	**3e**	90	94
6	2-MeOC_6H_4	**3f**	91	93
7	4-ClC_6H_4	**3g**	93	93
8	4-BrC_6H_4	**3h**	87	90
9	4-FC_6H_4	**3i**	90	93
10	1-Naphthyl	**3j**	86	91

The Substrate Scope

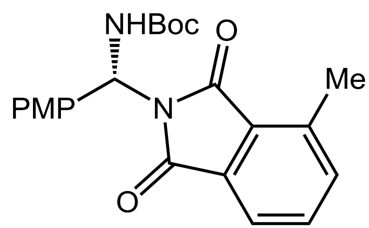




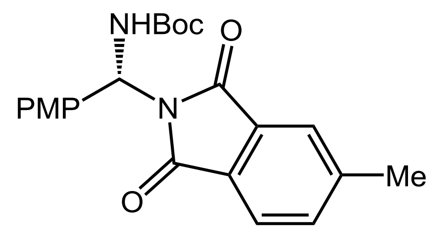
3a
92% yield, 96% ee



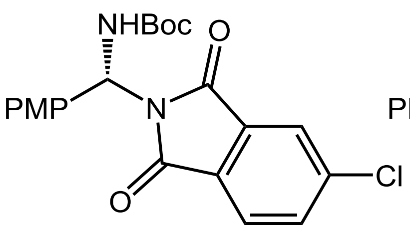
3k
82% yield, 92% ee



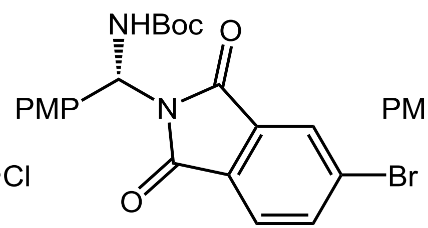
3l
82% yield, 92% ee



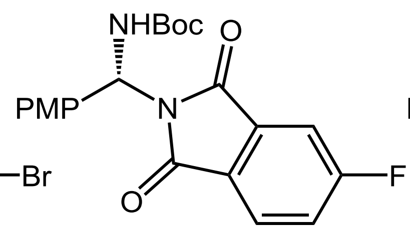
3m
90% yield, 92% ee



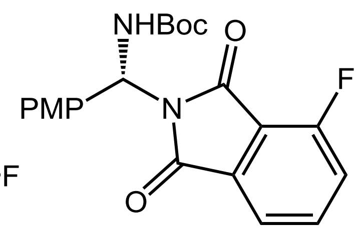
3n
92% yield, 93% ee



3o
84% yield, 90% ee

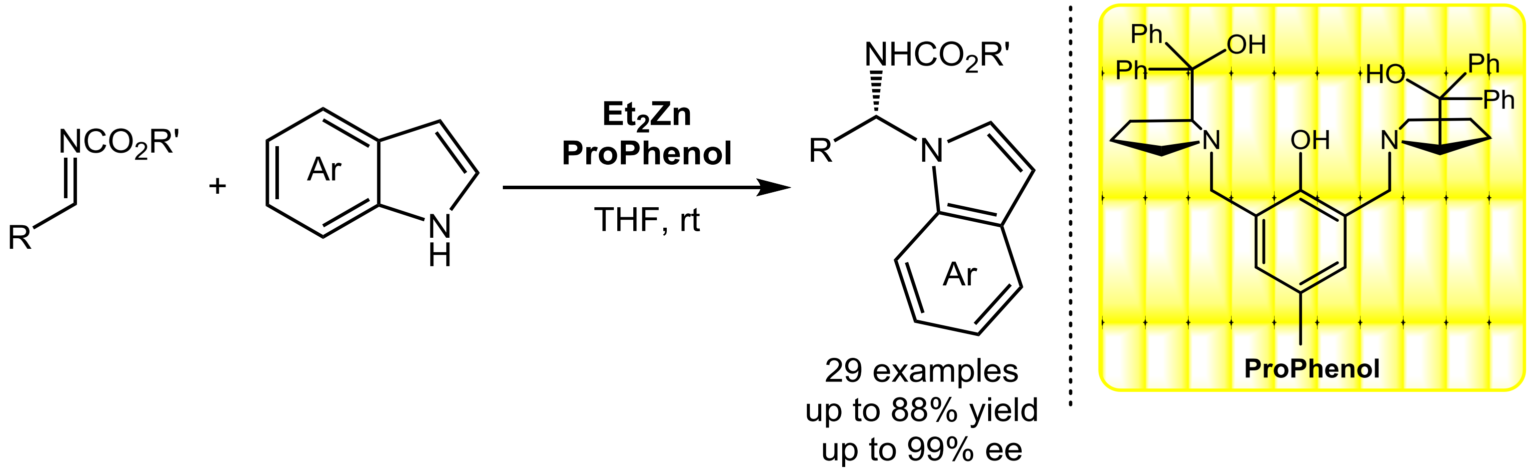


3p
87% yield, 91% ee



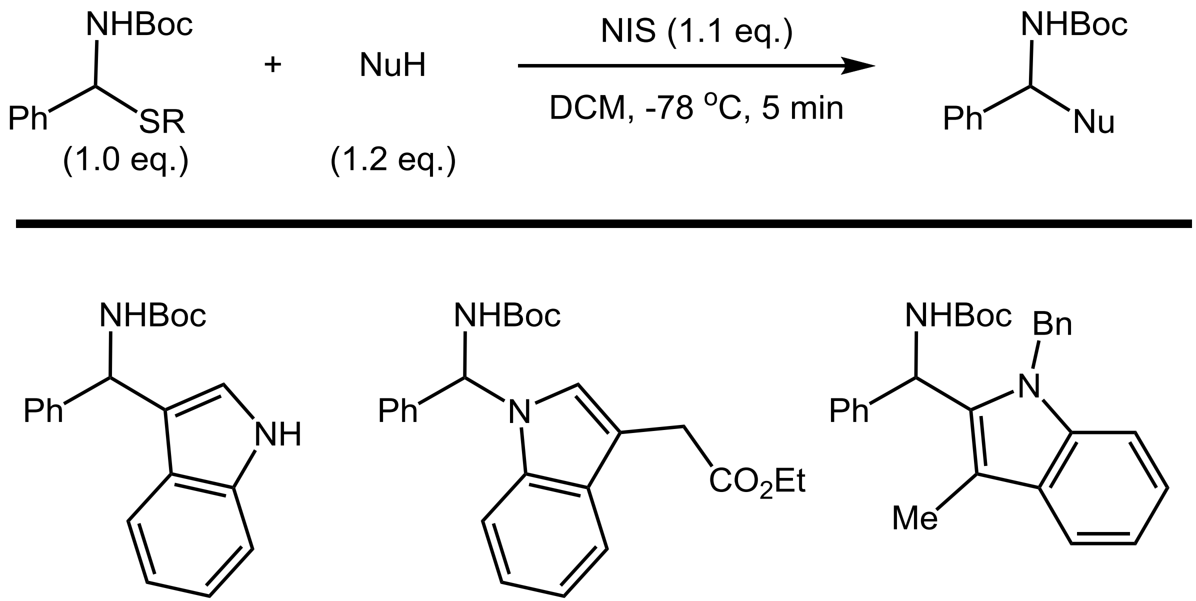
3q
84% yield, 89% ee

Zinc-ProPhenol-Catalyzed Addition of Indoles to Imines



Trost, **B**. **M**.; Gnanamani, E.; Hung, C.-I. *Angew*. *Chem*. *Int*. *Ed*. **2017**, *56*, 10451.

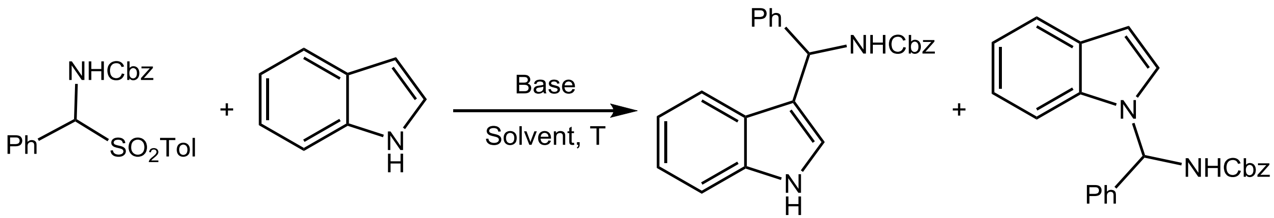
Friedel-Crafts Reation with α-Carbamoysulfides



>99% yield | 92% yield | 74% yield

George, N.; Bakkaye, M.; Alix, A.; Zhu, J.; **Masson**, **G**. *Chem*. *Eur*. *J*. **2014**, *20*, 3621.

Friedel-Crafts Reation with α-Amido Sulfones

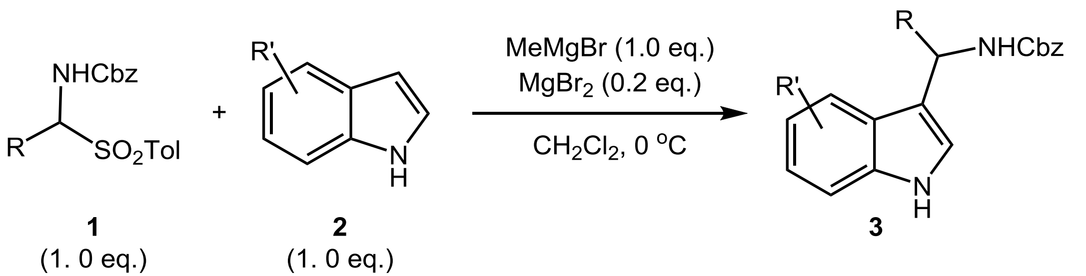


1a (1.0 eq.) **2a** (1.0 eq.) **3a** **4a**

Entry	Base (eq.)	Solvent	T (ºC)	t (h)	**3a** Yield (%)	**4a** Yield (%)
1	CsF (3)	CH_2Cl_2	rt	48	43	--
2	Li_2CO_3 (3)	CH_2Cl_2	rt	72	70	--
3	Na_2CO_3 (3)	CH_2Cl_2	rt	96	60	--
4	K_2CO_3 (3)	CH_2Cl_2	rt	72	70	--
5	Cs_2CO_3 (3)	CH_2Cl_2	rt	3	--	88
6	Cs_2CO_3 (2)	CH_2Cl_2	rt	3	--	87
7	Cs_2CO_3 (1)	CH_2Cl_2	rt	27	12	--
8	Cs_2CO_3 (3)	$CHCl_3$	rt	20	--	87
9	Cs_2CO_3 (3)	$(ClCH_2)_2$	rt	22	--	75
10	Et_2Zn (2)	CH_2Cl_2	0	48	49	--
11	MeMgBr (1)	CH_2Cl_2	0	1.5	74	--
12	MeMgBr (1) + $MgBr_2$ (0.2)	CH_2Cl_2	0	1.5	91	--

Blay, G.; Girón, R. M.; Nontesinos-Magraner, M.; **Pedro**, **J**. **R**. *Eur. J. Org. Chem*. **2013**, 3885.

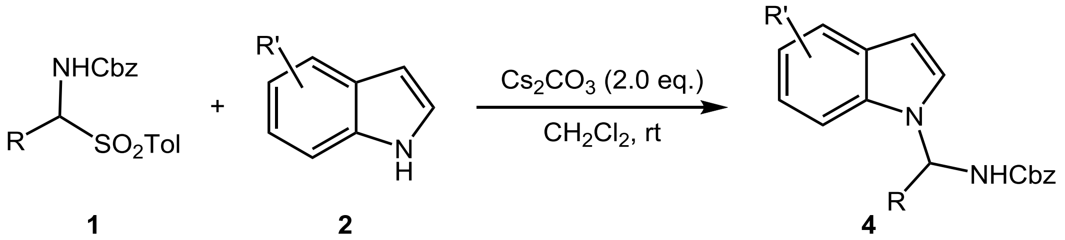
The Substrate Scope



Entry	R	R'	t (h)	**3** Yield (%)
1	C_6H_5	H	3	91
2	4-MeC_6H_4	H	3.5	72
3	4-MeOC_6H_4	H	1	99
4	4-ClC_6H_4	H	3	81
5	3-MeC_6H_4	H	3	99
6	3-furanyl	H	1	95
7[a]	*n*Bu	H	1	75
8[a]	*i*Pr	H	2	85
9[a]	Cy	H	1.5	88
10	Ph	1-Me	1.5	98
11	Ph	2-Me	4	n.d.
12	Ph	4-Me	1	91

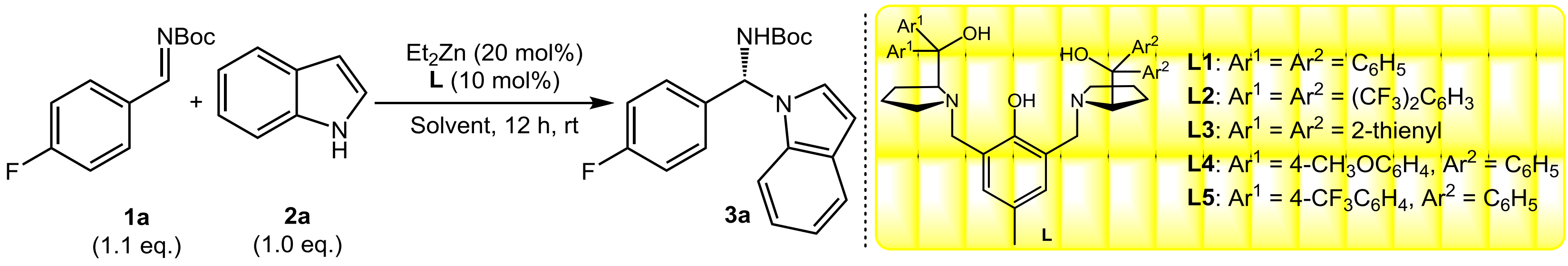
[a] 3.0 eq. of **2** was added.

The Substrate Scope



Entry	R	R’	t (h)	**4** Yield (%)
1	C_6H_5	H	3	87
2	4-MeC_6H_4	H	3.5	89
3	4-MeOC_6H_4	H	12	91
4	4-ClC_6H_4	H	3	84
5	3-MeC_6H_4	H	12	96
6	3-furanyl	H	1	90
7	*n*Bu	H	3	89
8	*i*Pr	H	6	99
9	Cy	H	3	88
10	Ph	2-Me	5	n.d.
11	Ph	3-Me	5	80
12	Ph	4-Me	5	92

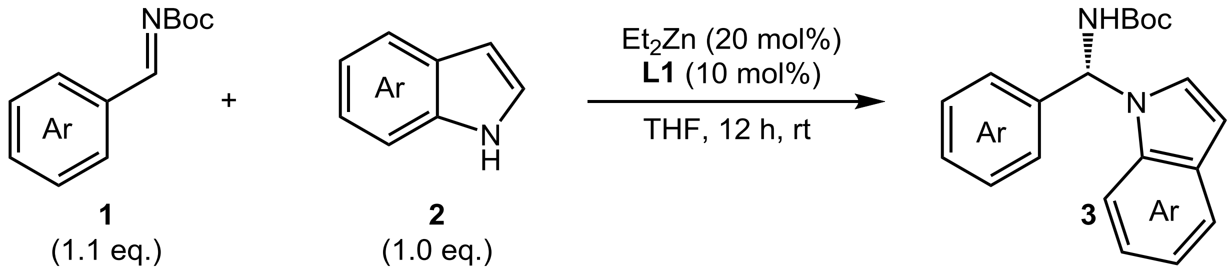
Zinc-ProPhenol-Catalyzed Addition of Indoles to Imines



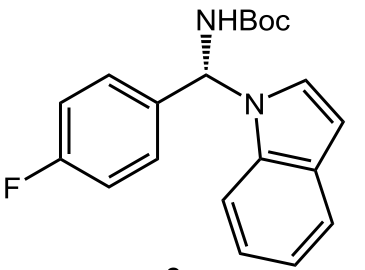
Entry	Solvent/Ligand	*N*-alk. Yield (%)	*N*-alk. er	C3-alk. Yield (%)	C3-alk. er
1	Toluene/**L1**	15	81:19	60	58:42
2	DCM/**L1**	trace	77:23	70	42:58
3	THF/**L1**	61	98:02	11	77:23
4	Benzene/**L1**	14	65:35	65	74:26
5	CH_3CN/**L1**	12	90:10	70	90:10
6	DME/**L1**	7	96:04	42	62:38
7	THF/**L2**	35	82:18	34	56:44
8	THF/**L3**	trace	70:30	14	68:32
9	THF/**L4**	17	98:02	54	85:15
10	THF/**L5**	35	98:02	14	64:36

Trost, **B**. **M**.; Gnanamani, E.; Hung, C.-I. *Angew*. *Chem*. *Int*. *Ed*. **2017**, *56*, 10451.

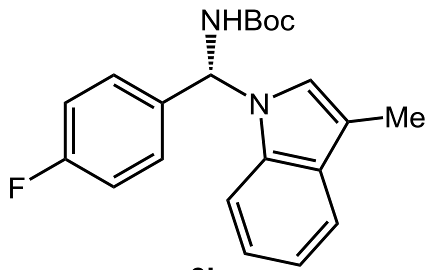
The Substrate Scope



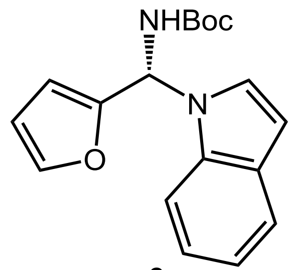
1 (1.1 eq.) **2** (1.0 eq.) **3**



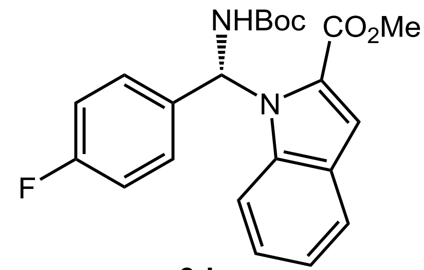
3a
61% yield, 96% ee



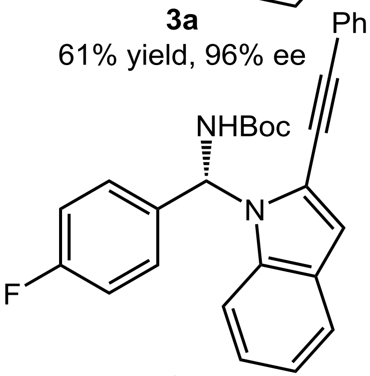
3b
77% yield, 89% ee



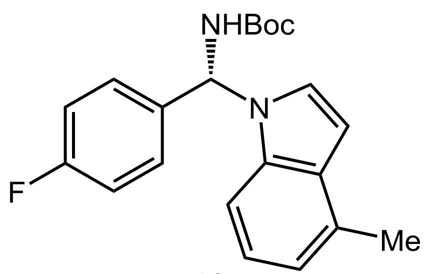
3c
66% yield, 85% ee



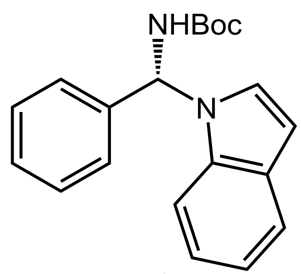
3d
28% yield, 92% ee



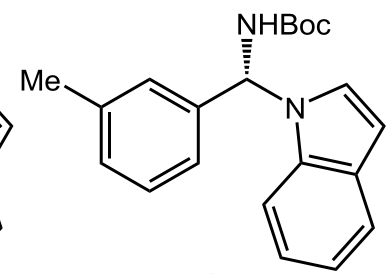
3e
23% yield, 90% ee



3f
56% yield, 90% ee

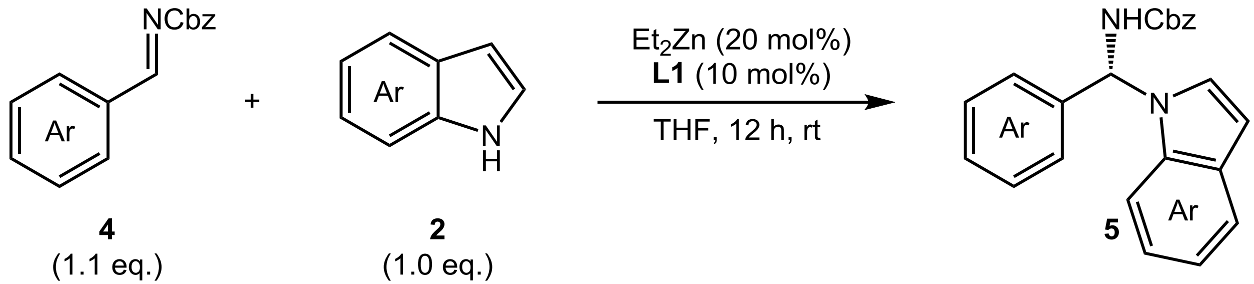


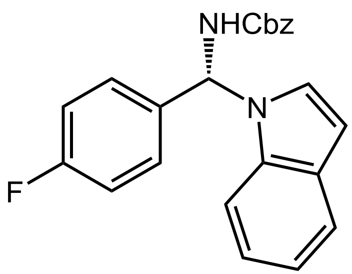
3g
61% yield, 94% ee



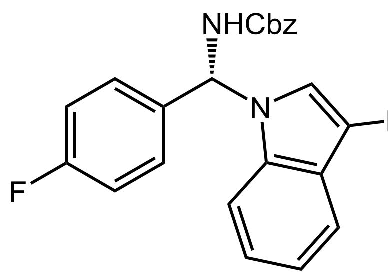
3h
64% yield, 94% ee

The Substrate Scope

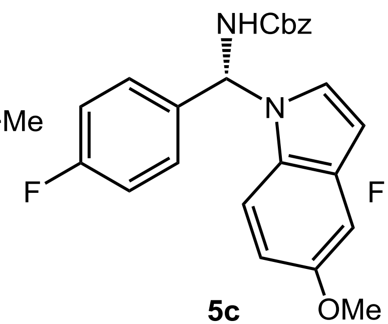




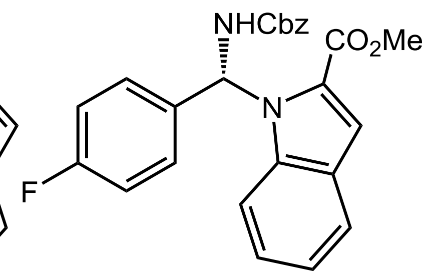
5a
67% yield, 96% ee



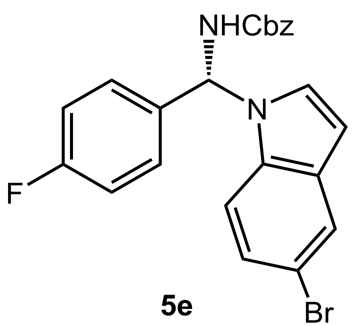
5b
86% yield, 81% ee



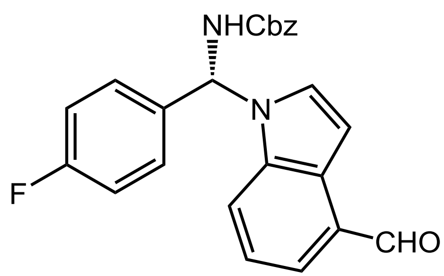
5c
62% yield, 92% ee



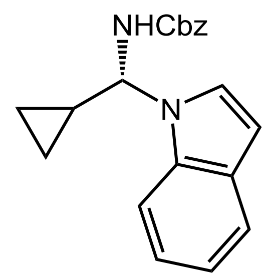
5d
71% yield, 95% ee



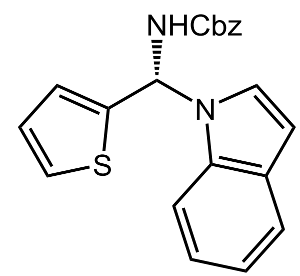
5e
61% yield, 40% ee
4 ^{o}C, 63% yield, 80% ee



5f
56% yield, 80% ee

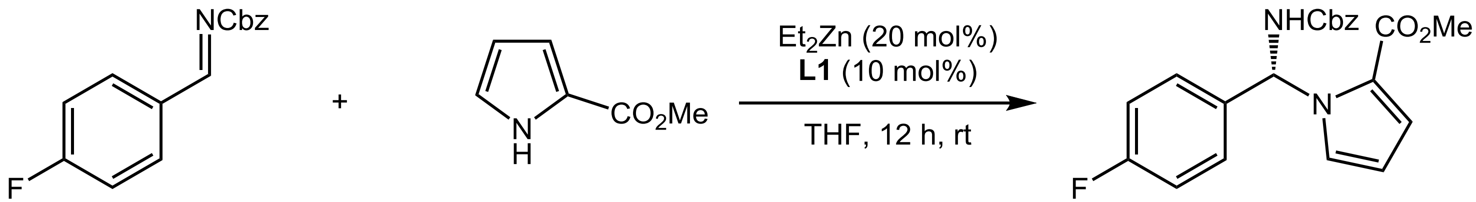


5g
59% yield, 90% ee



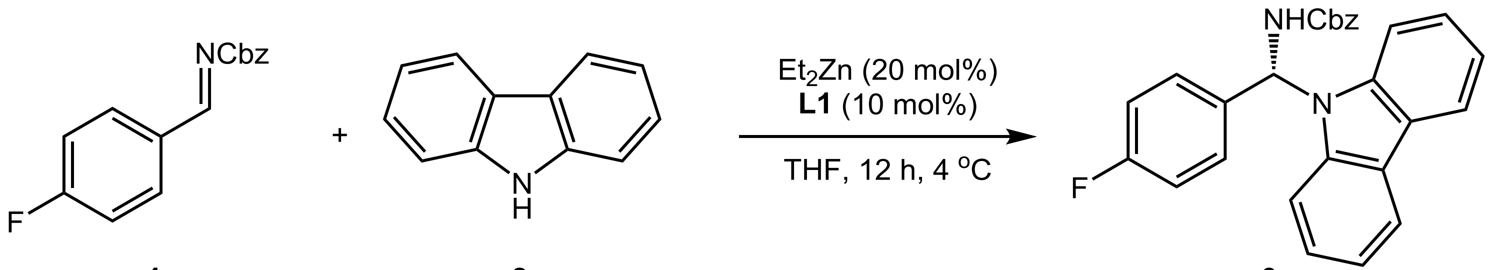
5h
62% yield, 99% ee

The Substrate Scope



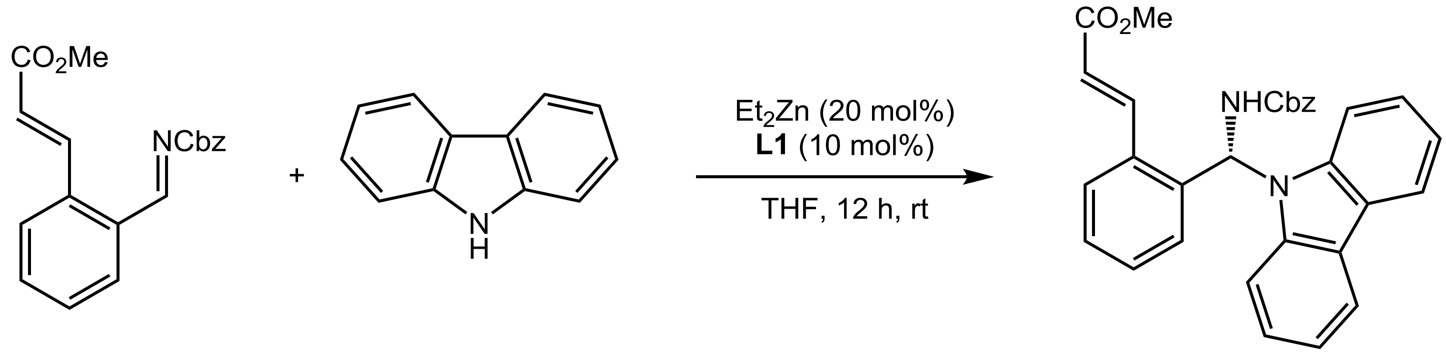
4a **6** **7**

52% yield, 99% ee



4a **8** **9**

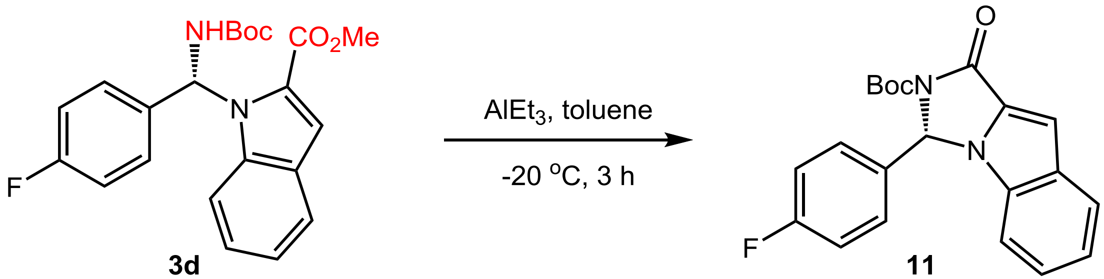
86% yield, 99% ee



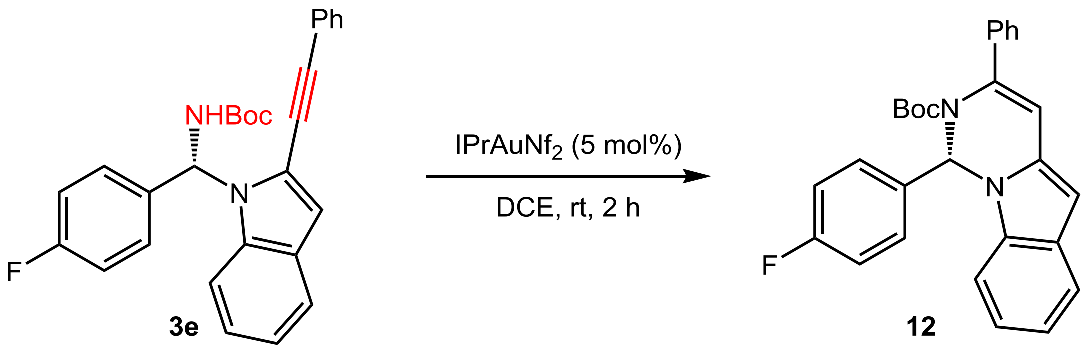
4i **8** **10**

82% yield, 92% ee

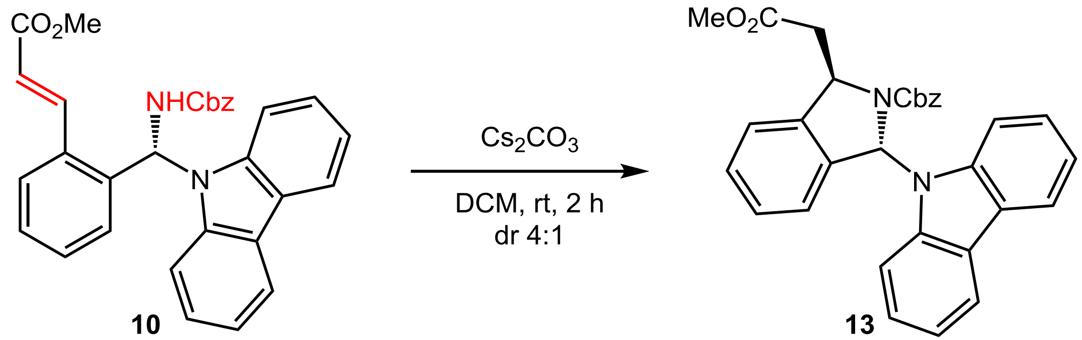
Synthetic Applications



3d 90% ee → **11** 80% yield, 90% ee

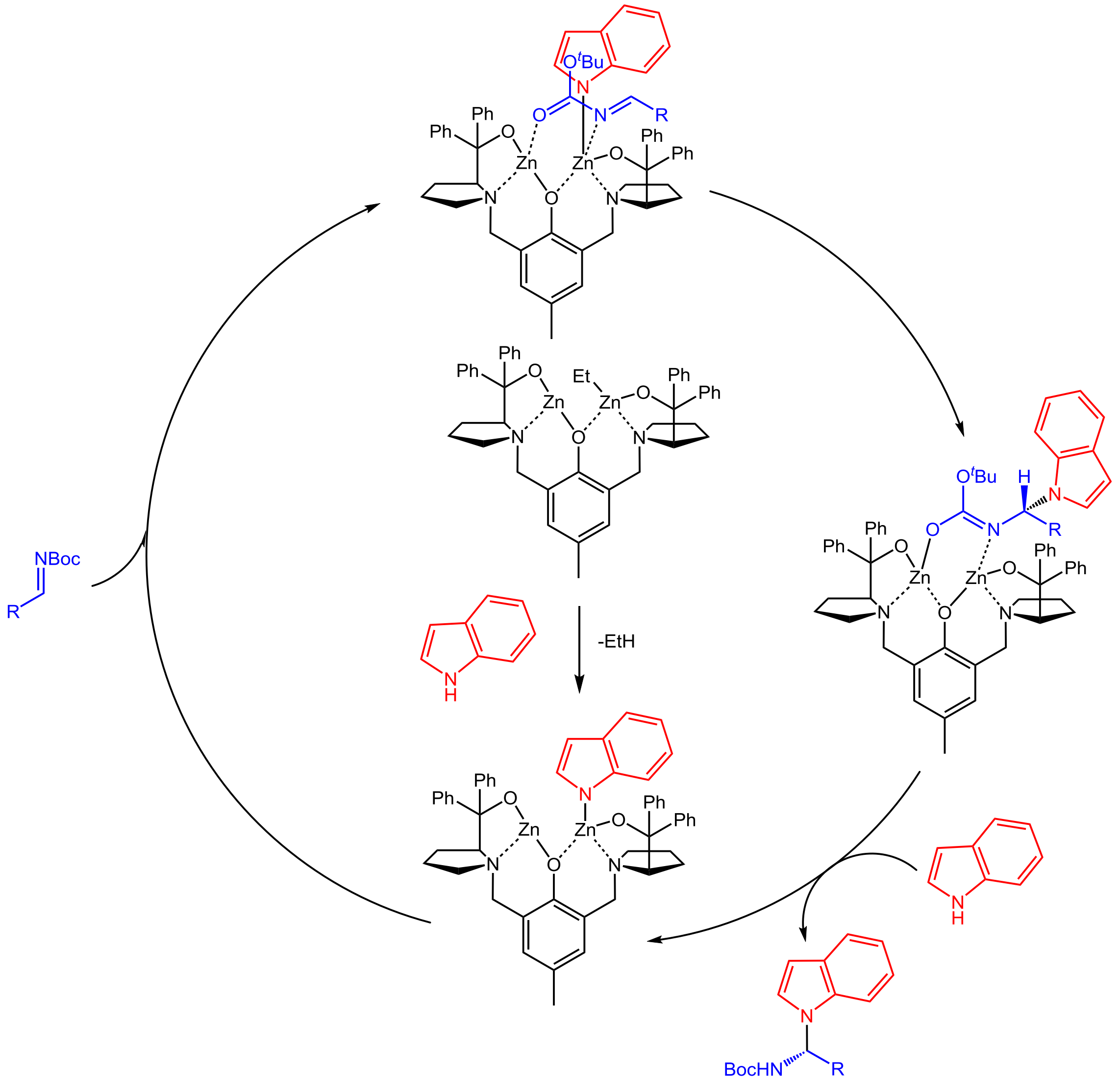


3e 89% ee → **12** 76% yield, 89% ee



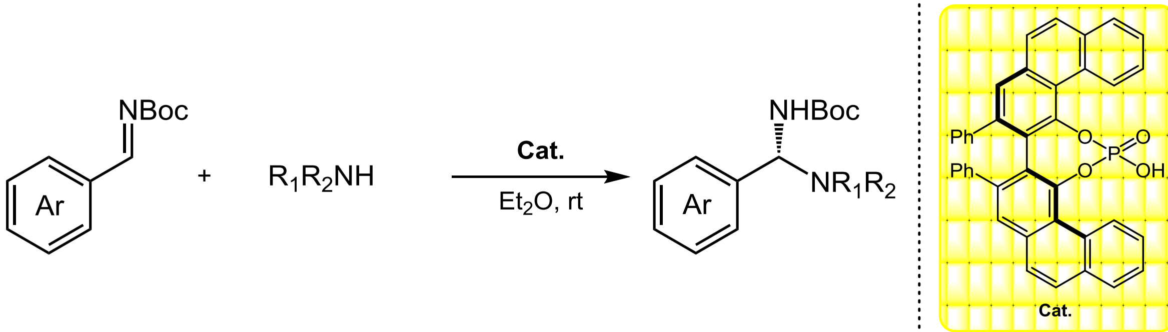
10 92% ee → **13** 52% yield, 92% ee

Mechanistic Hypothesis



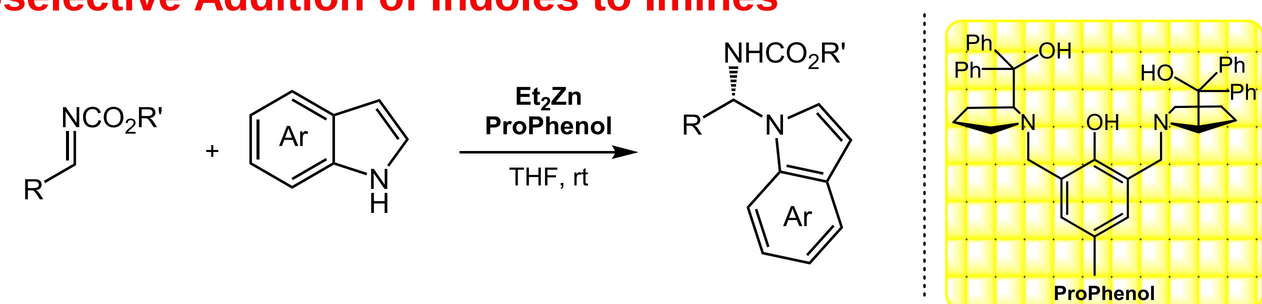
Summary

Enantioselective Addition of Amides to Imines



Rowland, G. B.; Zhang, H.; Wang, Y.; **Antilla**, **J**. **C**. *J. Am. Chem*. *Soc*. **2005**, *127*, 15696.
Liang, Y.; Rowland, E. B Rowland, G. B.; Perman, J. A.; **Antilla**, **J**. **C**. *Chem*. *Commun*. **2007**, 4477.

Enantioselective Addition of Indoles to Imines



Trost, **B**. **M**.; Gnanamani, E.; Hung, C.-I. *Angew*. *Chem*. *Int*. *Ed*. **2017**, *56*, 10451.

The First Paragraph

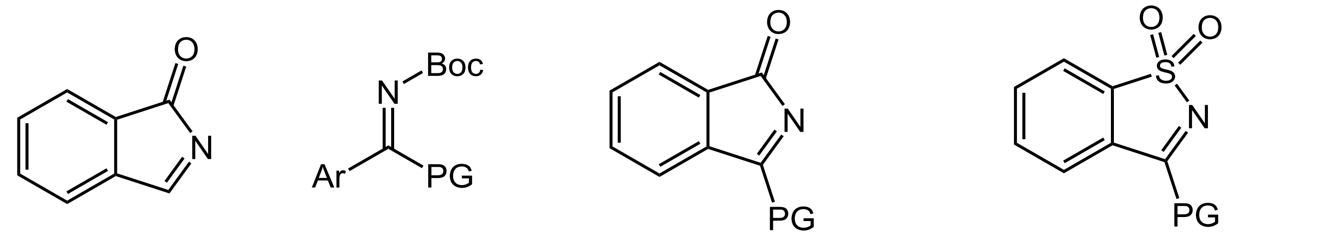
Acetals, hemiaminals and aminals share a structure possessing a carbon bearing two heteroatoms prone to undergo ionization. While they are broadly present both in synthetic and natural product chemistry, they are commonly constrained in ring systems to enhance their intrinsic stability. An exciting recent illustration of this phenomenon is the development of a potentially sensitive hemiaminal, elbasvir, which is a highly potent and selective NS5A inhibitor of the hepatitis C virus. The potential sensitivity of this structural unit is mitigated by its incorporation in a ring. Indeed, its stability is such that the synthetic intermediate can be synthesized asymmetrically using a novel C-N coupling.

The First Paragraph

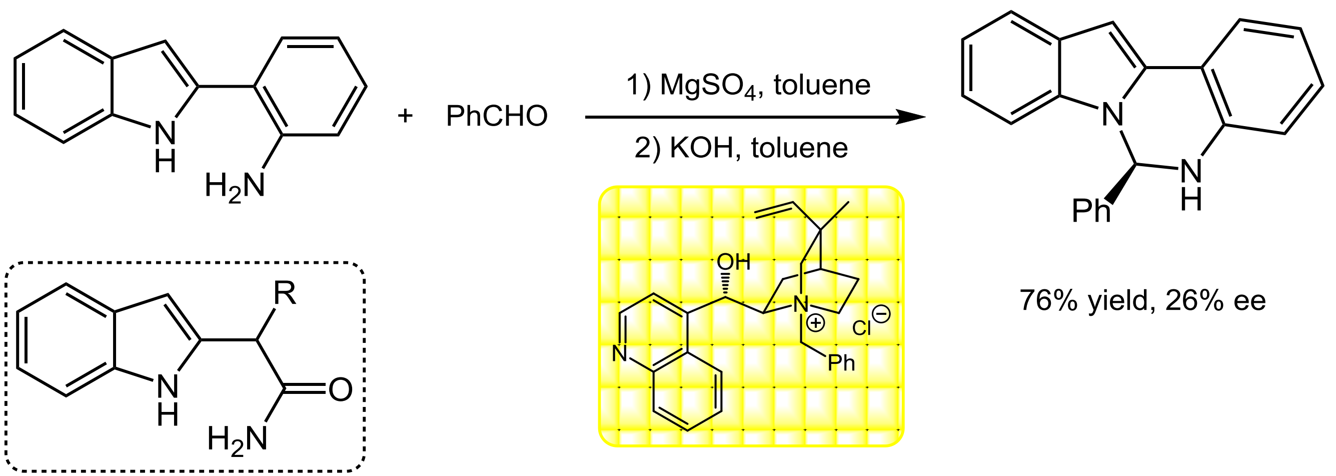
Also there are many methods available for the synthesis of *N*,*O*-aminals and utilized for several organic transformations. On the other hand, attempts to develop more traditional indole moieties containing asymmetric aminal syntheses have been less effective. These results may derive from the sensitivity of the aminal. In fact, a recent study in the stability of cyclic aminals synthesized asymmetrically noted that, “for the preparation and workup of these valuable intermediates and natural products, appropriate conditions have to be chosen and for application as drug molecules their sensitivity towards hydrolysis has to be taken into account.”

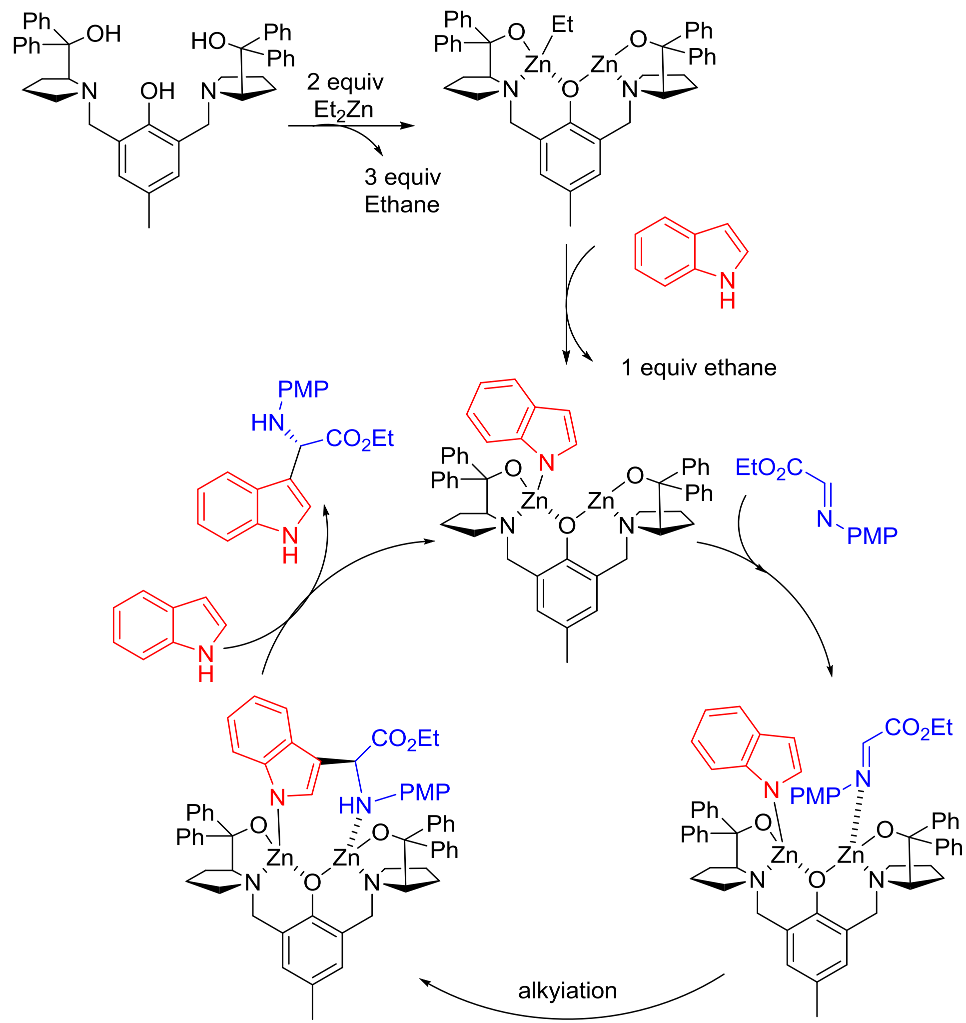
The Last Paragraph

In conclusion, we have developed the first enantioselective synthesis of *N*-alkylated indoles, which proceeds with good yields with excellent enantio-selectivity. Particularly noteworthy is the change in regioselectivity with Zn-ProPhenol catalysts in going from the *N*-sulfonylimines (favoring C3) to the *N*-alkoxyacylimines (favoring N1).



PG = CF_3, CO_2Et, $P(O)(O^iPr)_2$ PG = CO_2Et, $P(O)(O^iPr)_2$




2 equiv
Et_2Zn
3 equiv
Ethane
1 equiv ethane
alkyiation