Friedel-Crafts Alkylation Reaction
Asymmetric Versions

Keith A. Korthals

When Pepsi started marketing its products in China a few years back, they translated their slogan, "Pepsi Brings You Back to Life" pretty literally. The slogan in Chinese really meant, "Pepsi Brings Your Ancestors Back from the Grave."

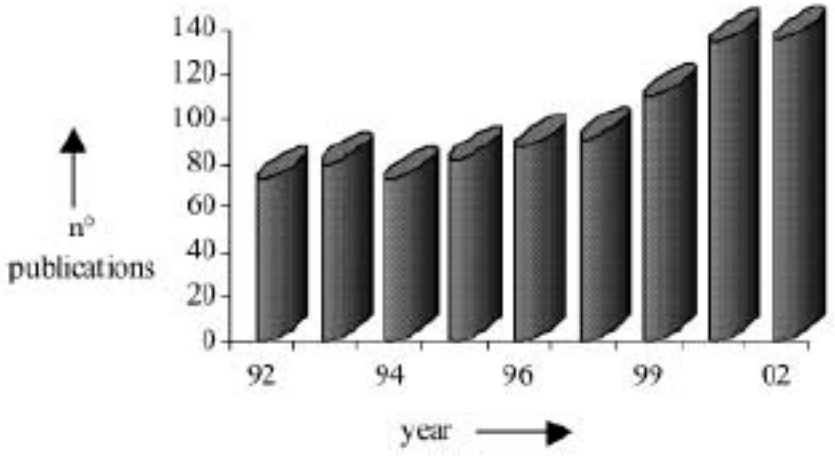
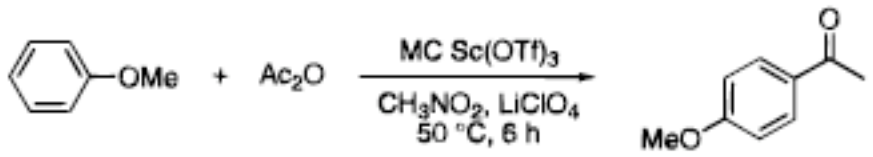


Figure 1. The increasing number of catalytic Friedel–Crafts procedures published from 1991 to date.

Marco Bandini,* Alfonso Melloni, and Achille Umani-Ronchi* *Angew. Chem. Int. Ed.* **2004**, 43, 550 –556.

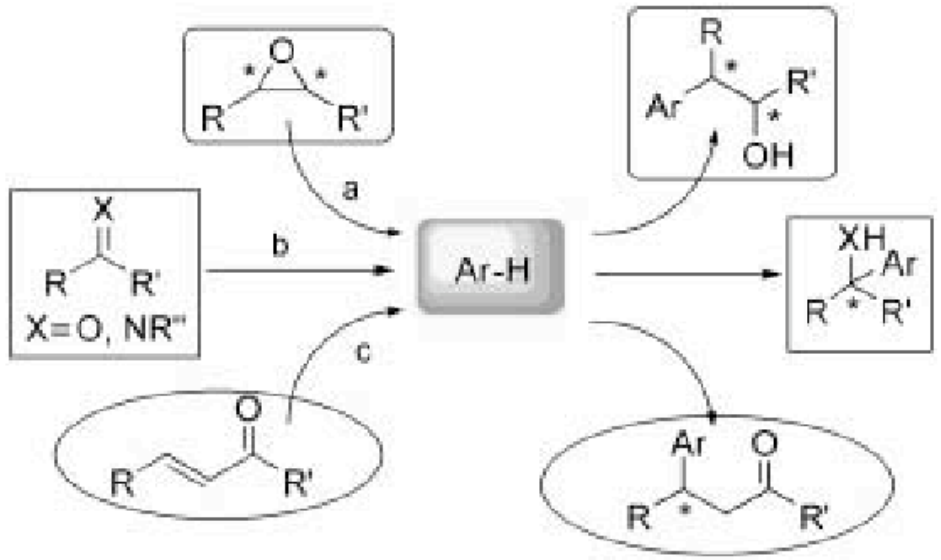
Approaches Used

Scheme 5. Friedel-Crafts Acylation (Batch System)



1st use, 76% yield; 2nd use, 76% yield; 3rd use, 81% yield

Polystyrene (1.000 g) was dissolved in cyclohexane (20 mL) at 40 °C, and to this solution was added powdered $Sc(OTf)_3$ (0.200 g) as a solid core. The mixture was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coacervates were found to envelop the solid core dispersed in the medium, and hexane (30 mL) was added to harden the capsule walls. The mixture was stirred at room temperature for 1 h, and the capsules were washed with acetonitrile several times and dried at 50 °C.13,14



Scheme 1. Possible approaches in the asymmetric Friedel–Crafts alkylation of aromatic compounds.

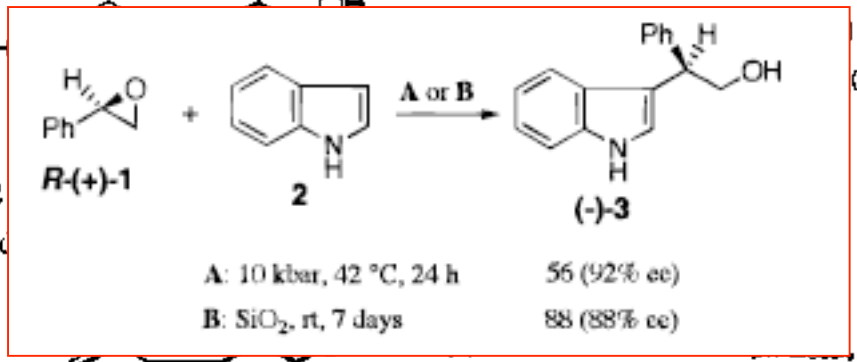
Shuj Kobayashi* and Satoshi Nagayama J. Am. Chem. Soc. **1998**, *120*, 2985-2986.

Epoxide Versions

Table 1. Reaction of Indoles with Epoxides[a]

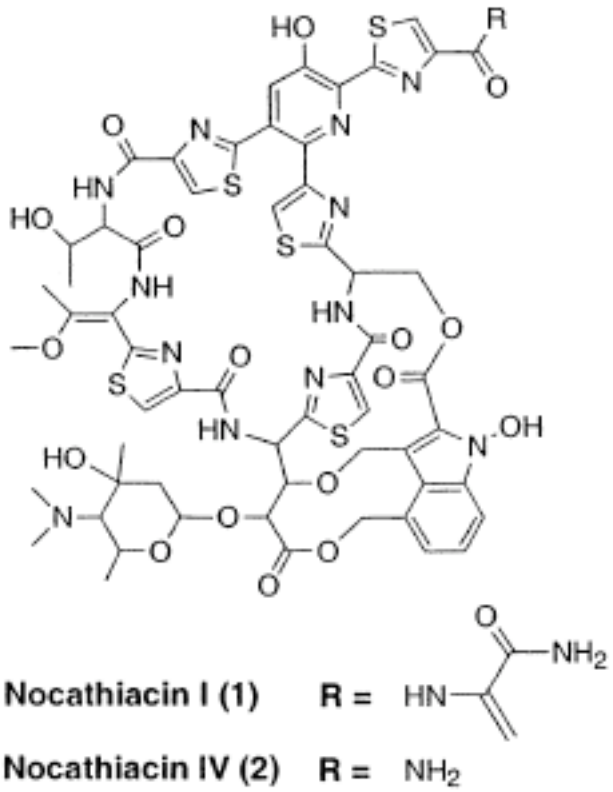
Run	Epoxide	Indole	Reaction Conditions	Product, Yield (%)[b]
1a	1	2	10 kbar, 42 °C, 24 h	58[c]
b			SiO_2, rt, 7 days	44
2a	1	4	10 kbar, 42 °C, 24 h	44[c]
b			SiO_2, rt, 7 days	70
			65 °C, 3 days	16
b			SiO_2, rt, 10 days	10
c			10 kbar, SiO_2,[d] 65 °C, 3 days	21
d			10 kbar, SiO_2,[e] 65 °C, 3 days	19
e			10 kbar, SiO_2,[f] 65 °C, 3 days	29

[a] All high-pressure reactions with 1 mmol of epoxide and 1 mmol of indole in ca. 1.5 mL of acetonitrile. All silica gel-catalyzed reactions with 1 mmol of epoxide, 1 mmol of indole, and 500 mg of Wakogel-C300. [b] Yields refer to pure isolated compounds. [c] See ref 6. [d] Wakogel C-300 (500 mg / mmol). [e] LC-5H (500 mg / mmol). [f] LC-5H (1000 mg / mmol).

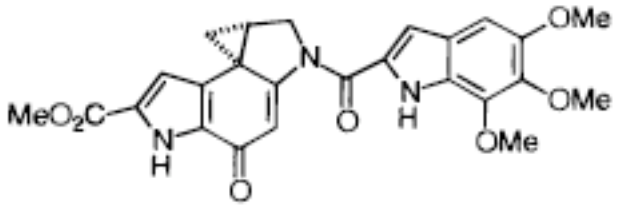


Hiyoshizo Kotsuki,* Katsunori Hayashida, Tomoyasu Shimanouchi, and Hitoshi Nishizawa
J. Org. Chem. **1996**, *61*, 984-990.

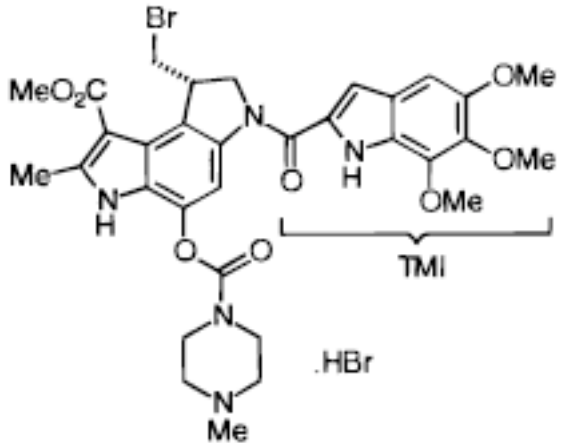
Why target indoles?



Peter Hrnciar,*,† Yasutsugu Ueda, Stella Huang, John E. Leet, and Joanne J. Bronson J. Org. Chem. **2002**, *67*, 8789-8793.



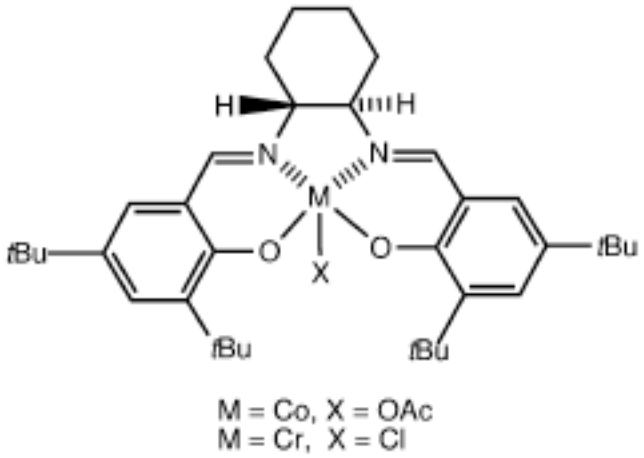
(+)-Duocarmycin SA

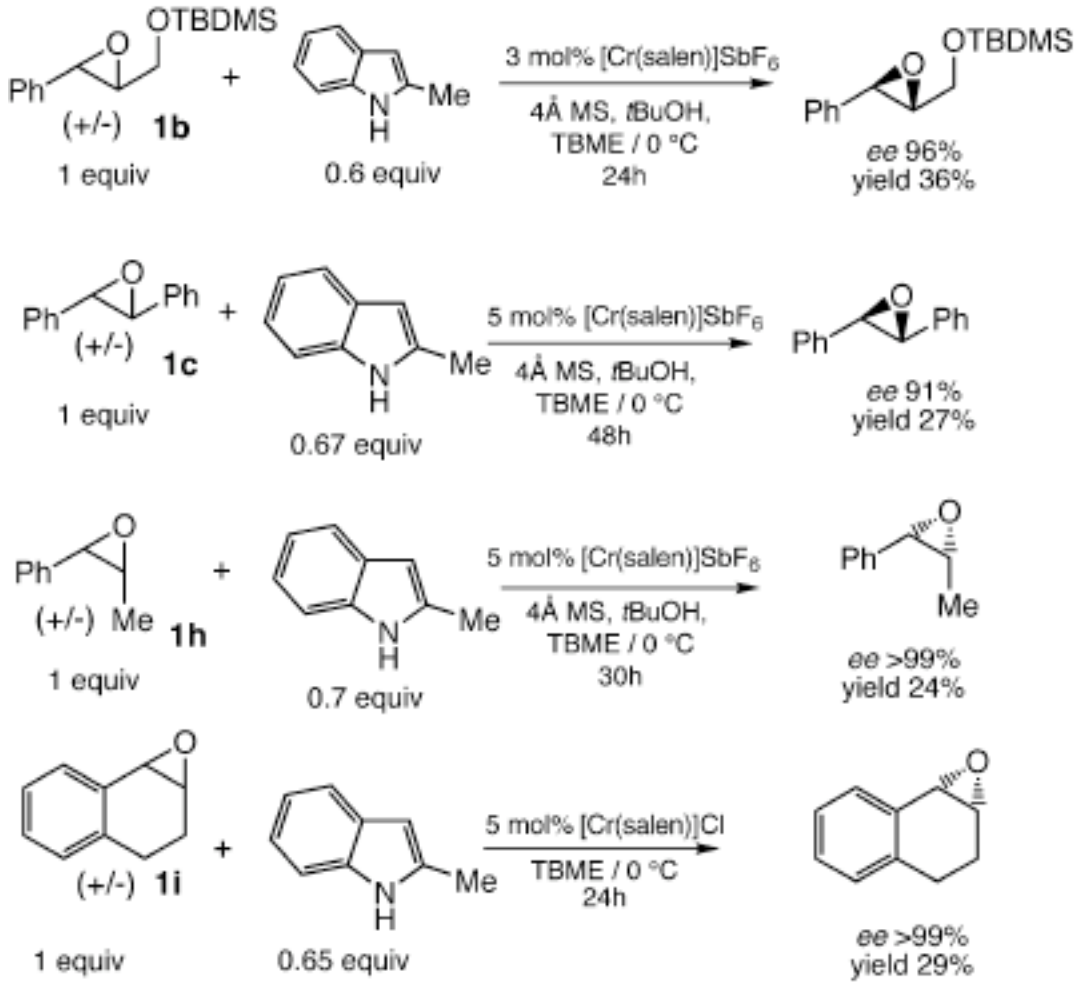


KW-2189

Moana Tercel,* Michael A. Gieseg, William A. Denny, and William R. Wilson J. Org. Chem. **1999**, *6*4, 5946-5953.

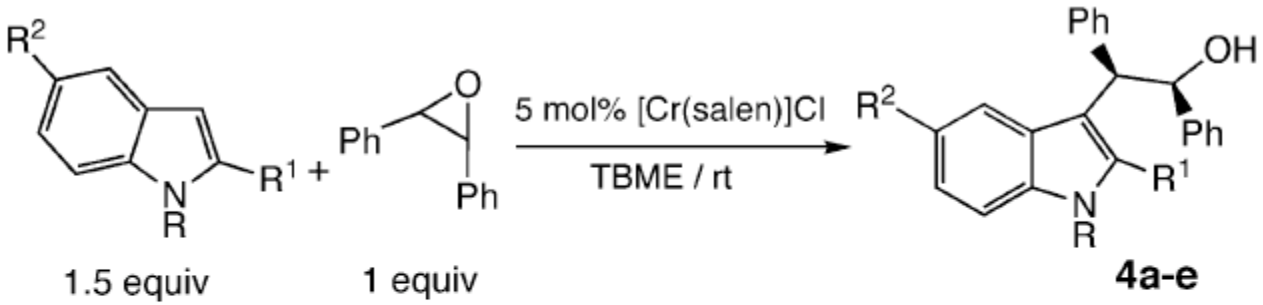
Kinetic Resolution





Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi*Angew. Chem. Int. Ed. **2004**, *43*, 84 –87.

Kinetic Formation of Alcohols



1.5 equiv 1 equiv

3a R = H, R^1 = H, R^2= H
3b R = Me, R^1 = H, R^2= H
3c R = H, R^1 = Me, R^2 = H
3d R = Me, R^1= Me, R^2 = H
3e R = H, R^1 = H, R^2 = OMe

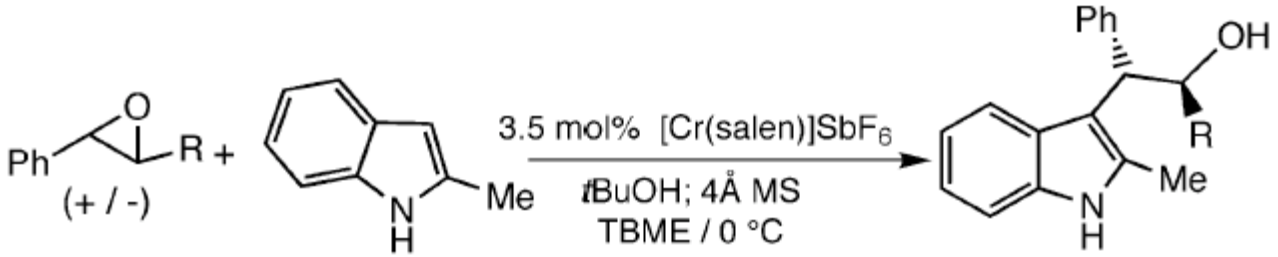
Table 2: ARO of *meso*-stilbene oxide with indoles.

Entry	Indole	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**3a**	36	98	93
2	**3b**	30	96	96
3	**3c**	36	98	98
4	**3d**	36	95	97
5	**3e**	36	95	90

[a] Yield of **4** after chromatographic purification; [b] Enantiomeric excesses were evaluated by HPLC; see Supporting Information.

Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi*Angew. Chem. Int. Ed. **2004**, *43*, 84 –87.

Kinetic Formation of Alcohols



1b R = $CH_2OTBDMS$
1c R = Ph
1d R = CH_2OH
1e R = CH_2OMe
1f R = Me
1g R = COOMe

2b-g

Table 1: Kinetic resolution of aromatic epoxides with 2-methylindole.[a]

Entry	Epoxide	*t* [h]	Yield [%][b]	*ee* of **2** [%][c]	*s*[d]
1	**1b**	16	96	91	30
2	**1c**	48	82	86	15
3	**1d**	40	93	87	25
4	**1e**	24	98	86	23
5	**1f**	36	99	72	10
6	**1g**	30	85	80	13
7	**1h**	18	95	80	13
8	**1i**[d]	24	97	83	16

[a] Reactions were carried out with 1 equiv of 2-methylindole, 3 equiv of racemic epoxide, 1 equiv of *t*BuOH, and 3.5 mol% [Cr(salen)]SbF_6 relative to the racemic epoxide. [b] Yield of **2** after chromatographic purification. [c] Enantiomeric excesses were evaluated by HPLC analysis; see Supporting Information. [d] Selectivity factor. [e] [Cr(salen)Cl] (3.5 mol% relative to the epoxide) was used as catalyst.

Lewis Acid Mediated Addition to Indole

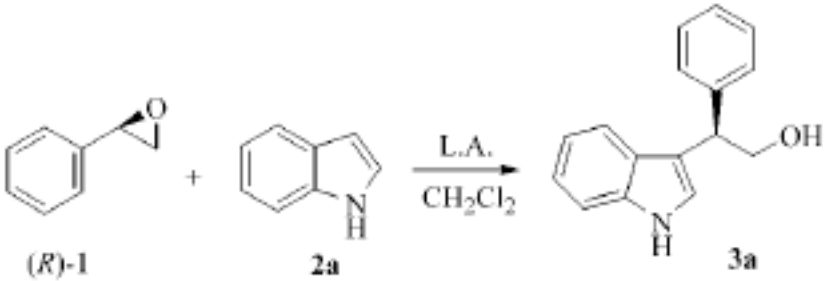


TABLE 1. Lewis Acid Mediated Addition of Indole to Styrene Oxide

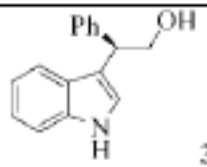
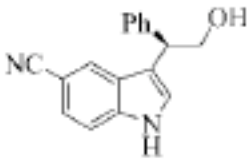
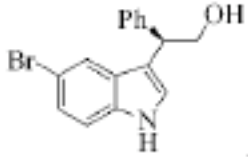
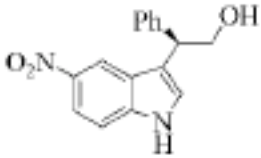
entry[a]	Lewis acid (mol %)	yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$ (10)	33[d]	*e*
2	$Zn(OTf)_2$ (10)	29	69
3	$Sc(OTf)_3$ (10)	54	99
4	$Sc(OTf)_3$ (1)	52	99
5	ZnI_2 (10)	57	90
6	$BF_3{\cdot}OEt_2$ (1)	54	99
7	$InCl_3$ (10)	55	99
8	$InBr_3$ (10)	60	75
9	$InBr_3$ (5)	64	99
10	$InBr_3$ (1)	70[f]	99
11	$InBr_3$ (1)	20[g]	*e*

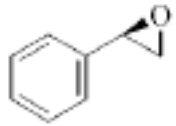
[a] All the reactions were carried out in anhydrous CH_2Cl_2 at 0 °C for 4 h unless otherwise specified. [b] The chemical yields are given on the isolated product after chromatographic purification. [c] The enantiomeric excess of the indolyl alcohol was determined by chiral HPLC analysis (column: Chiralcel OD). Racemic 3a was obtained starting from (±)-1a. [d] A 1:1 mixture of regioisomers was observed. [e] Not determined. [f] The reaction was performed at room temperature. [g] The reaction was carried out in THF (isolated yield after 5 days).

Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi* J. Org. Chem. **2002**, *67*, 5386-5389.

Lewis Acid Mediated Addition to Indole

TABLE 2. Addition of Indoles to Aromatic Epoxides Catalyzed by $InBr_3$[a]

Entry	Epoxide	Indole	Product	Yield (%)[b]	ee (%)[c]
1	1	2a	 **3a**	70	99
2	1	2b	 **3b**	41[d]	70
3	1	2c	 **3c**	54	
5	1	2e	 **3e**	24[e]	

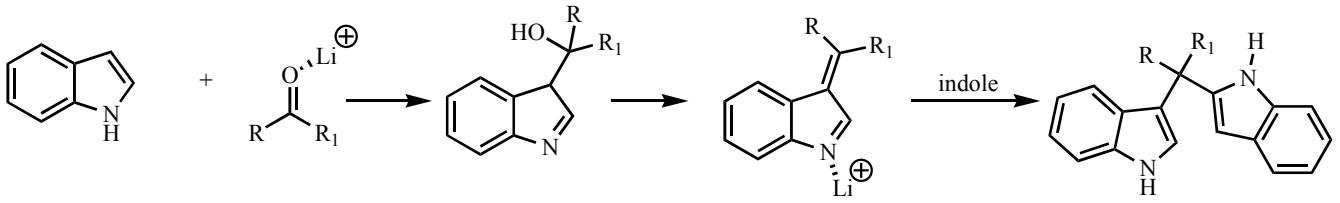


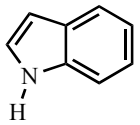
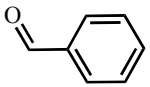
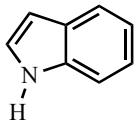
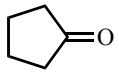
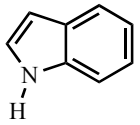
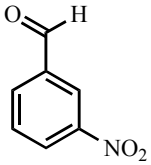
(*R*)-1

[a] All the reactions were carried out in anhydrous CH_2Cl_2 at room temperature, employing 1 mol % of $InBr_3$ for 8−16 h unless otherwise specified. [b] The chemical yields are given on the isolated product after chromatographic purification. [c] The enatiomeric excesses were determined by HPLC analysis with chiral column (Chiralcel OD). Racemic products were obtained performing the reaction on racemic epoxides with $InBr_3$. [d] The reaction was performed using 10 mol % of $InBr_3$ at room temperature for 16 h. [e] The reaction was performed using 10 mol % of $InBr_3$ at room temperature for 96 h. [f] The enantiomeric excess was not evaluated. [g] The optically active epoxide (1*R*,2*S*)-5 was prepared using the asymmetric Jacobsen epoxidation in 83% ee.[20]

Marco Bandini, Pier Giorgio Cozzi,* Paolo Melchiorre, and Achille Umani-Ronchi* J. Org. Chem. **2002**, *67*, 5386-5389.

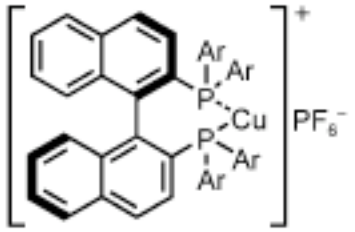
Bis(indolyl)methanes



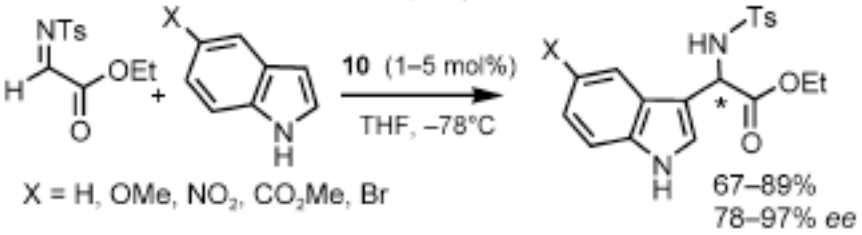
		5 M Lithium Perchlorate in diethyl ether		10 % $LiClO_4$	
		hours	yield	hours	yield
		2.5	95	5	90
		8	85	10	81
		10	75	10	67

Yadav, J.S.; Reddy, B.; Murthy, V.S.; Kumar, G.M.; Madan, Ch. *Sythesis* **2001**, 783 - 787.

Imine Examples



10 Ar = *p*-tolyl

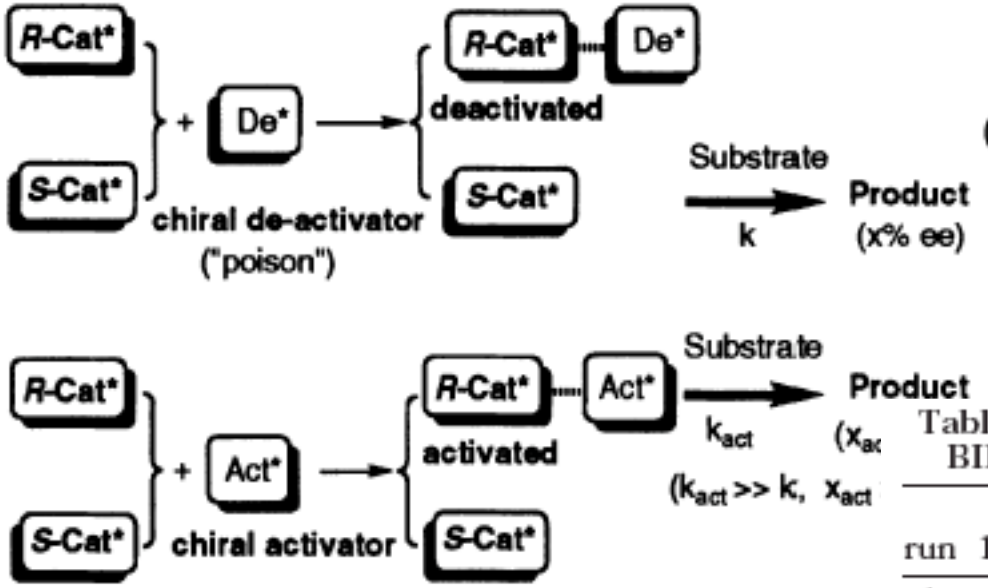


X = H, OMe, NO_2, CO_2Me, Br

Entry	Catalyst/ mol%	Solvent	T/ ºC	Yield (%)	ee
1	5	THF	RT	98	87
2	5	THF	-20	90	91
3	5	THF	-78	89	96
4	5	CH_2Cl_2	-78 to -10	57	78
5	1	THF	-78	89	94

Johannsen, M. Chem. Commun. **1999**, 2233-2234.

Chiral Activators



Scheme 1

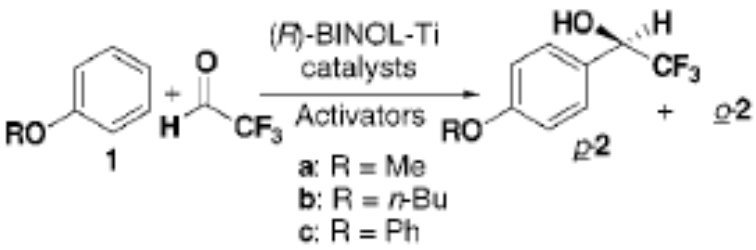


Table 2. The F−C Reactions with Fluoral Catalyzed by BINOL-Ti Complex through Asymmetric Activation[a]

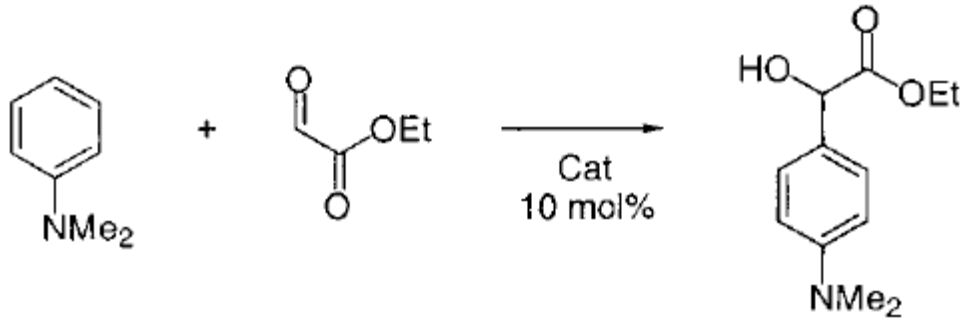
run	1	cat. (mol%)	additive	temp (°C)	yield (%)[c]	*p*-2:*o*-2[c]	ee (%)[d]
1	a	10	−	0	66	4:1	70 (*R*)
2	a	10	pentafluorophenol	0	94	3:1	68 (*R*)
3	a	10	(*R*)-BINOL	0	97	3:1	64 (*R*)
4	a	10	(*R*)-5-Cl-BIPOL[b]	0	88	4:1	78 (*R*)
5	a	10	(*R*)-6,6′-Br_2-BINOL	0	89	4:1	90 (*R*)
6	b	10	(*R*)-6,6′-Br_2-BINOL	0	90	8:1	90 (*R*)

[a] (*R*)-6,6′-Br_2-BINOL-Ti(OPr^i)$_2$ was activated by the additive in a molar ratio of 1:1 in dichloromethane (2 mL) at room temperature under an argon atomosphere for 1 h. The F−C reaction was carried out in situ by the addition of anisole (1 mmol) in dichloromethane (1 ml) and then passing an excess amount of fluoral. [b] 5,5′-Dichloro-4,4′,6,6′-tetramethyl-2,2′-biphenol. [c] Isolated yield after silica gel chromatography. [d] Refers to that of *p*-2.

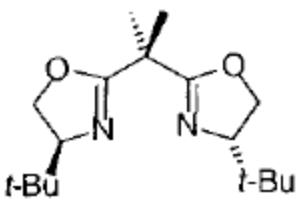
Mikami, K.; Matsukawa, S. Nature, 385, 613-615

Akihiro Ishii,† Vadim A. Soloshonok, and Koichi Mikami* *J. Org. Chem.* **2000**, ***65*** (5), 1597-1599.

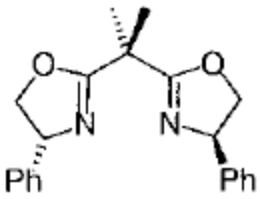
More Traditional Friedel-Crafts



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



(*S*)-**4a**



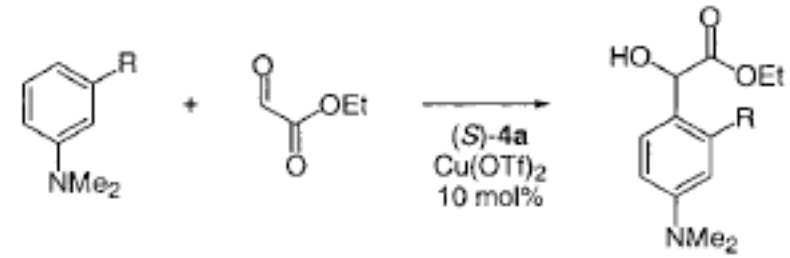
(*R*)-**4b**

entry	catalyst	solvent	temp (°C)	**2a** (equiv)	yield[b] (%)	ee[a] (%)
1	(*S*)-**4a**-$Cu(OTf)_2$	CH_2Cl_2	rt	1.5	81	80
2	(*S*)-**4a**-$Cu(OTf)_2$	Et_2O	rt	1.5	78	89
3	(*S*)-**4a**-$Cu(OTf)_2$	THF	rt	1.5	72	90
4	(*S*)-**4a**-$Cu(OTf)_2$	CH_2Cl_2	rt	10	90	82
5	(*S*)-**4a**-$Cu(OTf)_2$	THF	−30	5	71	74
6	(*S*)-**4a**-$Cu(OTf)_2$	$MeNO_2$	0	5	32	18
7	(*S*)-**4a**-$Cu(SbF_6)_2$	THF	rt	5	36	0
8	(*R*)-**4b**-$Cu(OTf)_2$	CH_2Cl_2	rt	1.5	70	54
9	(*R*)-**4b**-$Cu(OTf)_2$	Et_2O	rt	1.5	76	42
10	(*R*)-**4b**-$Cu(OTf)_2$	THF	rt	1.5	81	22
11	(*R*)-**4b**-$Zn(OTf)_2$	CH_2Cl_2	rt	1.5	41	12

[a] For experimental details see Supporting Information. [b] Isolated yield.

Nicholas Gathergood, Wei Zhuang, and Karl Anker Jørgensen*J. Am. Chem. Soc. **2000**, *122*, 12517-12522.

More Traditional Friedel-Crafts



1
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

2a

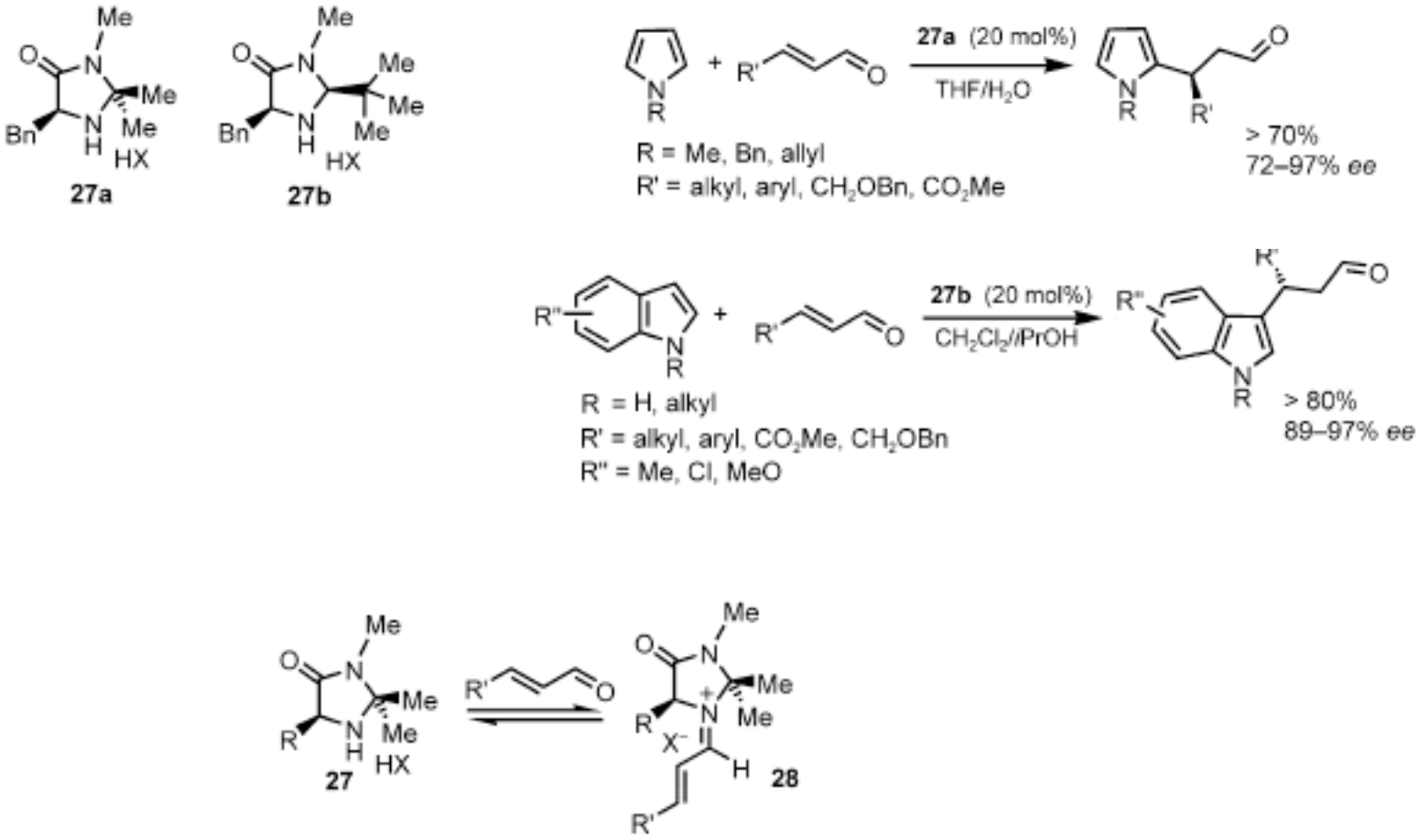
3
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

entry	subst	reaction time (d)	product	yield[b] CH_2Cl_2/THF (%)	ee[a] CH_2Cl_2/THF (%)
1[c]	**1a**	1	(+)-(*S*)-**3a**	81/72	80/90
2	**1b**	1	(+)-**3b**	80/58	85/81
3	**1c**	2	(+)-**3c**	84/41	93/95
4	**1d**	4	(+)-**3d**	68/36	88/89
5	**1e**	1	(+)-**3e**	77/76	80/92
6	**1f**	1	(+)-**3f**	21/19	77/86

[a] For experimental details see Supporting Information. [b] Isolated yield. [c] 1.5 equiv of ethyl glyoxylate.

Nicholas Gathergood, Wei Zhuang, and Karl Anker Jørgensen*J. Am. Chem. Soc. **2000**, *122*, 12517-12522.

α, β-Unsaturated Aldehyde



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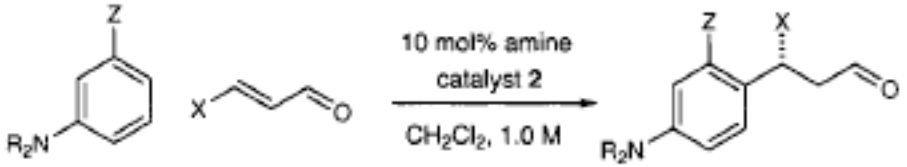
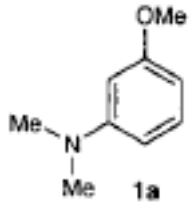
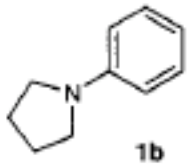
α, β-Unsaturated Aldehyde





1a



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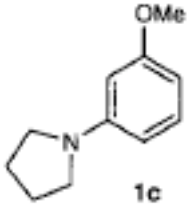
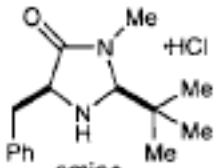


1c



amine
catalyst 2

entry	aniline	X	temp(°C)	time(h)	% yield	% ee[a]
1	**1a**	Me	–40	36	86	89[d]
2	**1b**	Me	–20	48	70[b]	87[d]
3	**1a**	Et	–50	48	68	88[d]
4	**1a**	CH_2OBz[c]	–20	24	89	92[d]
5	**1b**	CH_2OBz[c]	+20	24	73	90[d]
6	**1a**	CO_2Me[c]	–20	8	90	92[d]
7	**1c**	Ph	–50	36	82[b]	84
8	**1c**	*p*-Cl-Ph	–50	80	80[b]	92
9	**1a**	*p*-NO_2-Ph	–10	48	87	92
10	**1b**	*p*-NO_2-Ph	+20	48	82	90

[a] Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b] Using 20 mol % catalyst. [c] 1.0 M in $CHCl_3$. [d] Absolute configuration assigned by chemical correlation.

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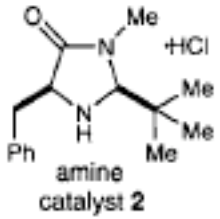
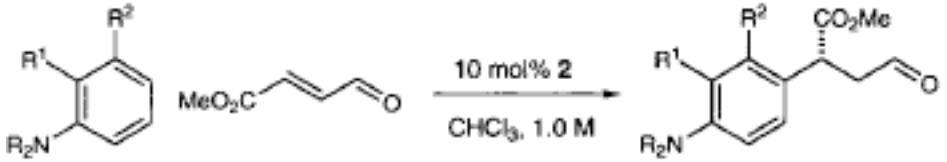
α, β-Unsaturated Aldehyde



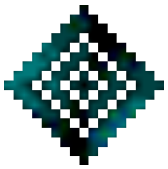
amine
catalyst **2**



entry	NR_2	R^1	R^2	temp(°C)	time(h)	% yield	% ee[a]
1	NMe_2	H	H	−10	48	86	96[b]
2	NMe_2	H	H	+20	5	77	94[b]
3	NBn_2	H	H	+20	24	65	96[b]
4	1-pyrrolidino	H	H	−20	8	97	97[b]
5	1-pyrrolidino	H	H	+20	0.3	96	95[b]
6	1-pyrrolidino	Ph	H	+20	12	94	99
7	$-N(Me)CH_2CH_2-$		H	−20	8	94	98

[a] Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b] Absolute configuration assigned by chemical correlation. [c] Using catalyst **2** (20 mol % amine, 15 mol % HCl).

Nick A. Paras and David W. C. MacMillan* J. AM. CHEM. SOC. **2002**, *124*, 7894-7895.



The End!

When Kentucky Fried Chicken entered the Chinese market, to their horror they discovered that their slogan "finger lickin' good" came out as "eat your fingers off"