Ni-Catalyzed Asymmetric Cross-Coupling with Alkyl Halides

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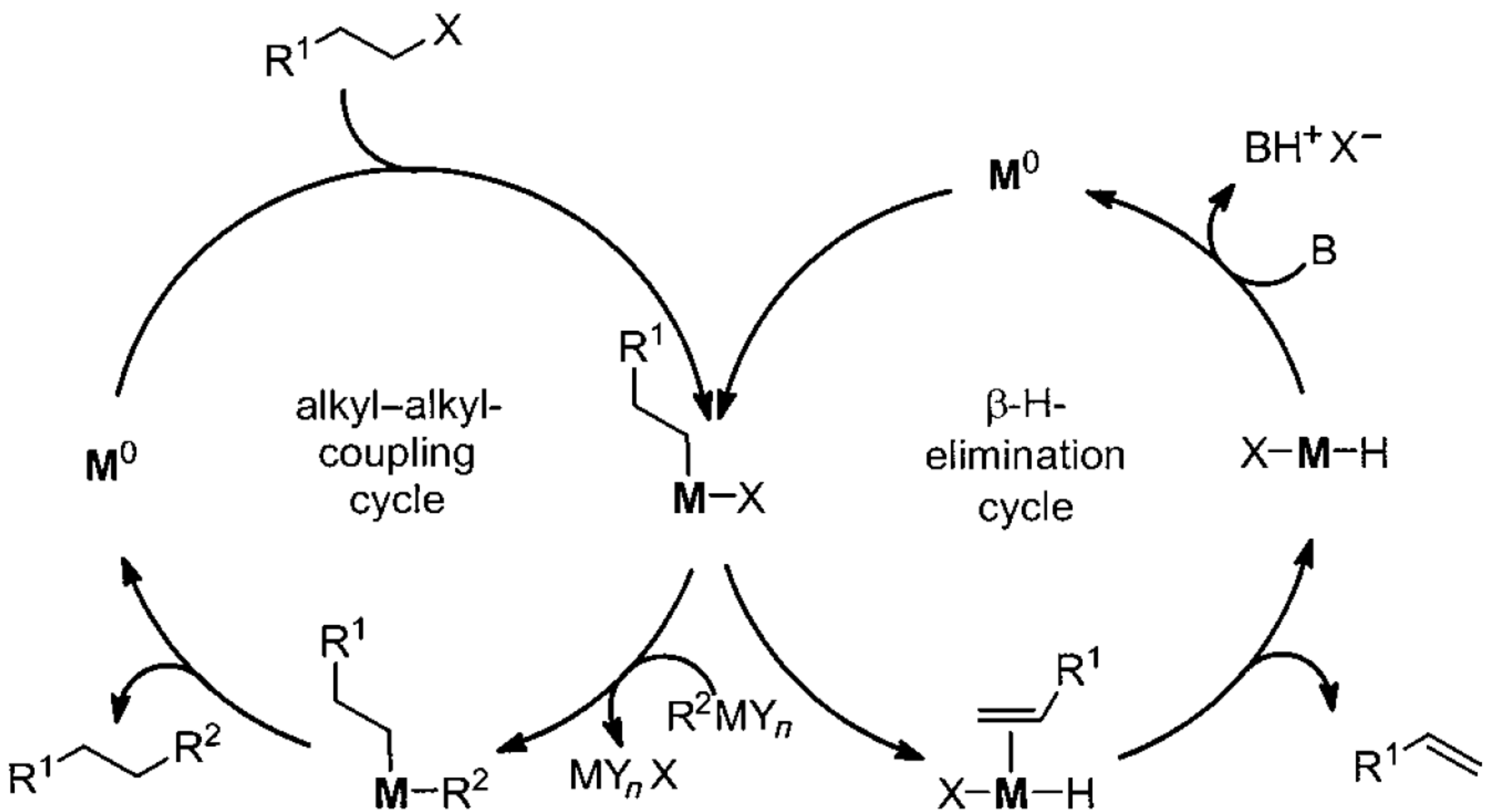
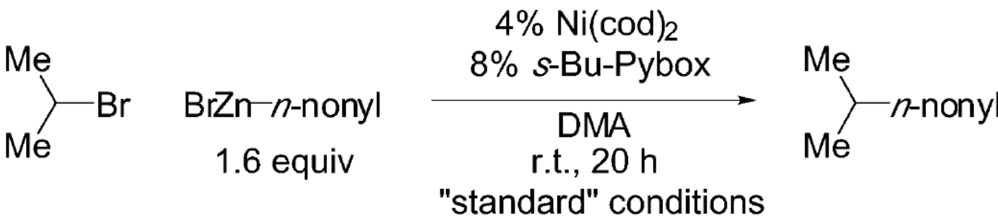
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.
Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.
Son, S.; Fu,G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756.
Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302.
Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**; ASAP Article; DOI: 10.1021/ja8013677

Mechanism of the Alkyl–Alkyl Cross-Coupling



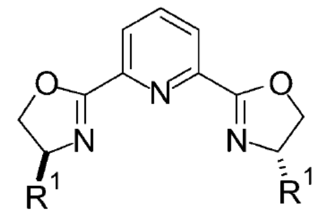
Frisch, A. C. ; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674.

Cross-Couplings of Unactivated Secondary Alkyl Halides

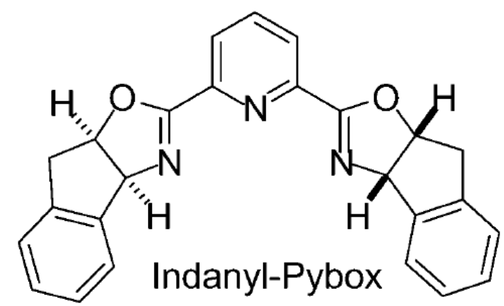


entry	change from the standard conditions	yield (%)[a]
1	none	91
2	no $Ni(cod)_2$	<5
3	$NiBr_2$	44
4	$Pd(OAc)_2$ or $Pd_2(dba)_3$	<5
5	*t*-Bu-Pybox	<5
6	*i*-Pr-Pybox	71
7	Ph-Pybox	80
8	Indanyl-Pybox	42
9	PPh_3	<5
10	P(*t*-Bu)$_3$	<5
11	P(*t*-Bu)$_2$Me	<5
12	PCy(1-pyrrolidinyl)$_2$	<5
13	1,3-bis(1-adamantyl)imidazol-2-ylidene	<5
14	4% *s*-Bu-Pybox	62
15	no *s*-Bu-Pybox	<5
16	2% $Ni(cod)_2$, 4% *s*-Bu-Pybox	80
17	1.2 equiv BrZn–*n*-nonyl	70

[a] Yield according to GC, versus a calibrated internal standard (average of two runs).



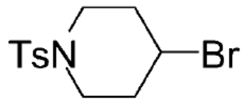
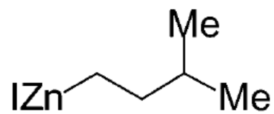
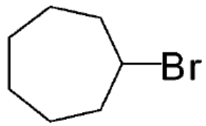
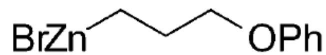
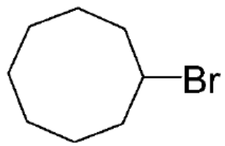
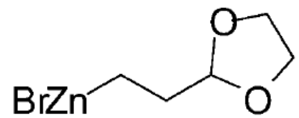
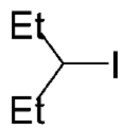
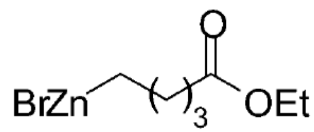
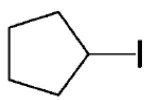
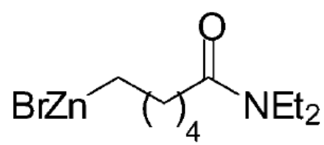
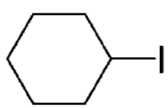
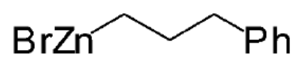
R^1-Pybox



Indanyl-Pybox

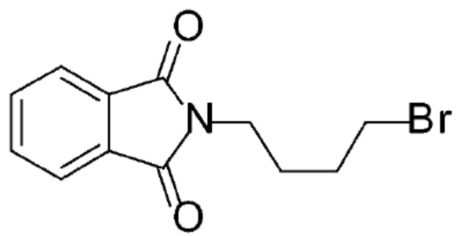
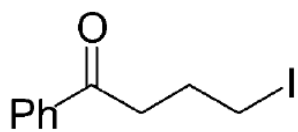
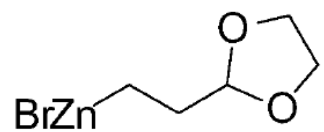
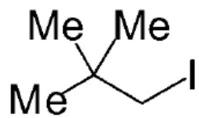
Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

Secondary Alkyl Bromides and Iodides

entry	R_{akyl}—X	YZn—R^{1}_{alkyl}	yield (%)
1			66
2			62
3			68
4			62
5			78
6			88

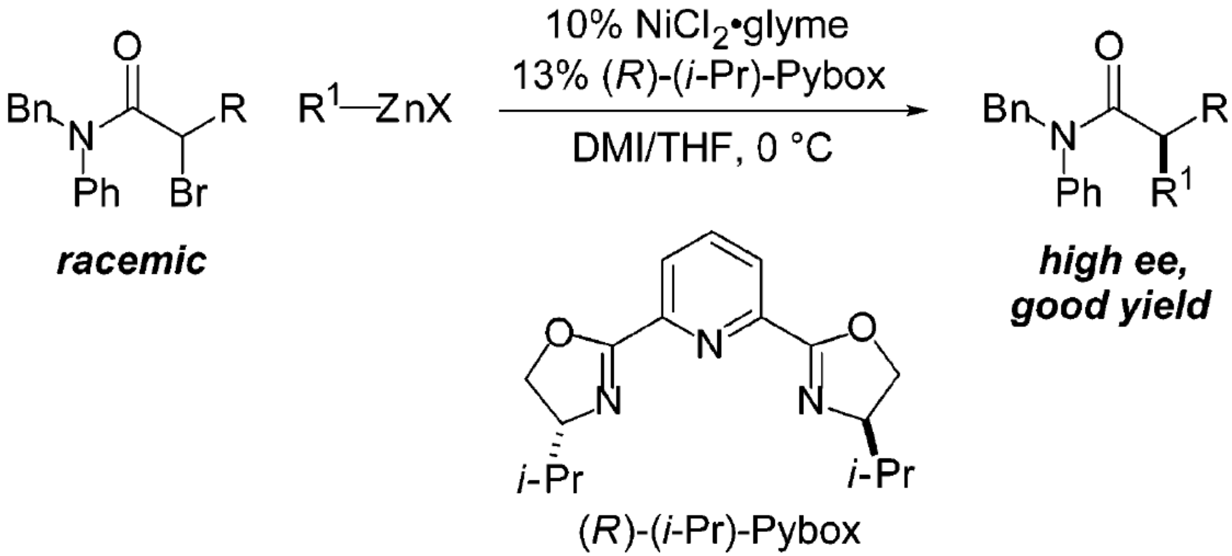
Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

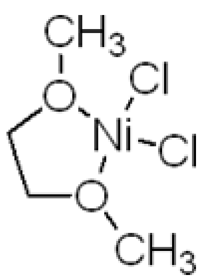
Primary Alkyl Bromides and Iodides

entry	R_{alkyl}—X	YZn—R^1_{alkyl}	yield (%)
1			65
2			74
3			73

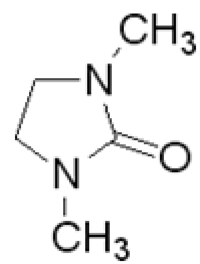
Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

Negishi Cross-Couplings of Racemic Secondary α-Bromo Amides





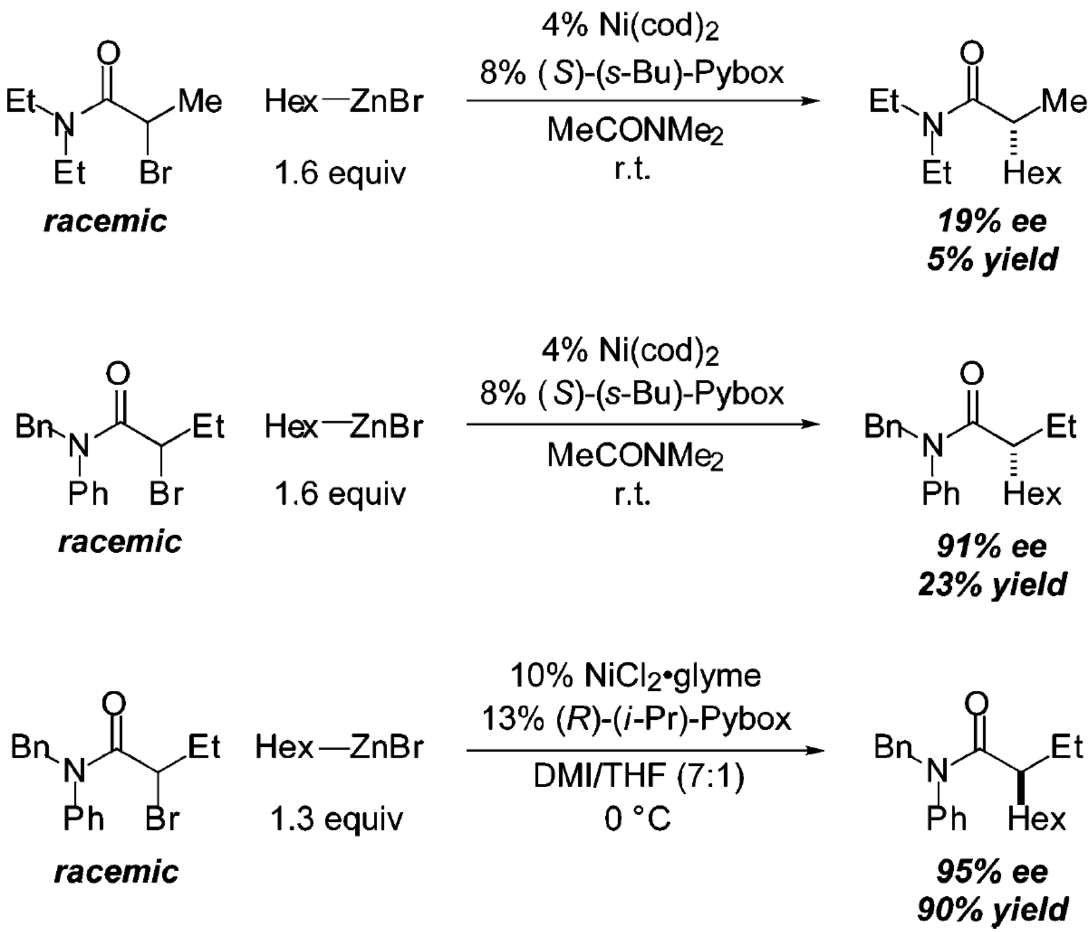
Nickel(II) chloride ethylene glycol dimethyl ether complex



DMI =1,3-dimethyl--2-imidazolidinone

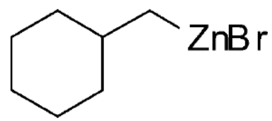
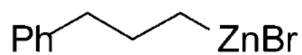
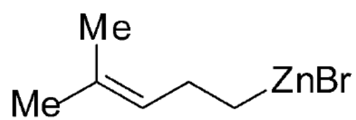
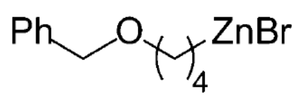
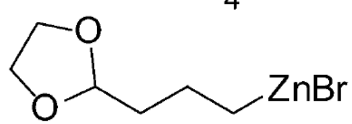
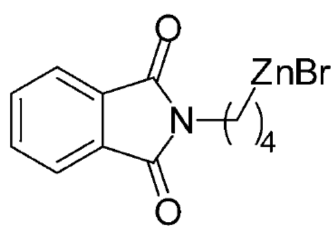
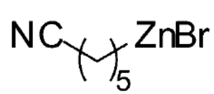
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

Optimization



At room temperature, the product is generated in 91% *ee*.
At -20 ℃, the cross-coupling process is slow.

Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

entry	R	R1—ZnX	yield (%)[a]	ee (%)
1	Et	Hex—ZnBr	90	96
2	Et	MeZnI	90	91
3	Et		84	96
4[b]	Et		58	92
5	*n*-Bu	Hex—ZnBr	85	96
6	*n*-Bu		79	96
7	*i*-Bu	MeZnI	78	87
8	Et		78	95
9	Et		77	96
10[c]	Me		66 (60)	77 (>98)
11	Et		51	96
12	Et		70	93

Notes

- (a) The yield of the reaction is sensitive to the steric demand of the coupling partners. Thus, they have not been able to efficiently crosscouple a secondary organozinc reagent or an α-isopropyl-α-bromo amide.
- (b) Under the standard conditions, benzylzinc reagents are not suitable substrates.
- (c) For the cross-coupling illustrated in entry 1 of Table 1, when the reaction is run on a 10 mmol scale, they obtain the product in 88% yield (3.0 g) and 95% *ee*.
- (d) The process is not highly sensitive to oxygen or moisture; when they conduct a coupling under air in a closed vial with 1.6 equiv of the organozinc reagent, they obtain essentially identical yield and *ee*.
- (e) Under identical conditions, α-bromoesters furnish lower yield and lower enantiomeric excess.

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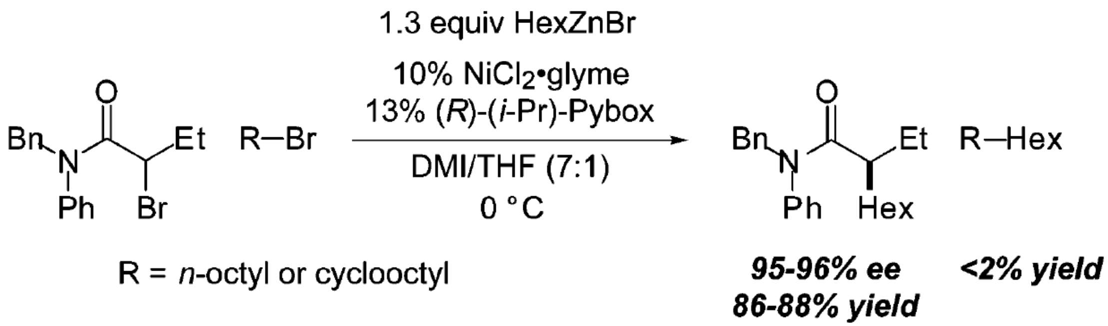
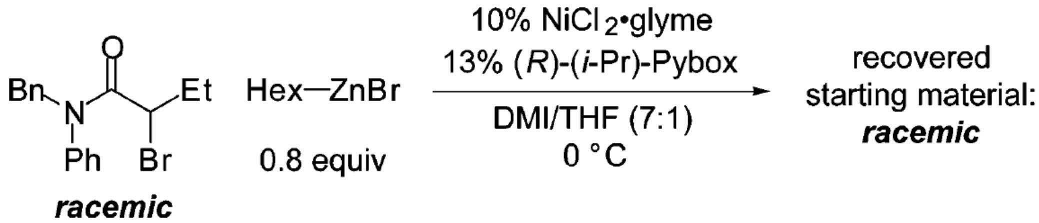
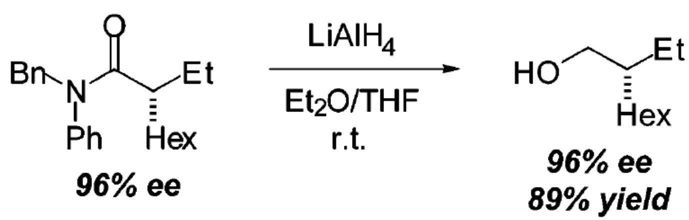
Control Experiments and Transformation







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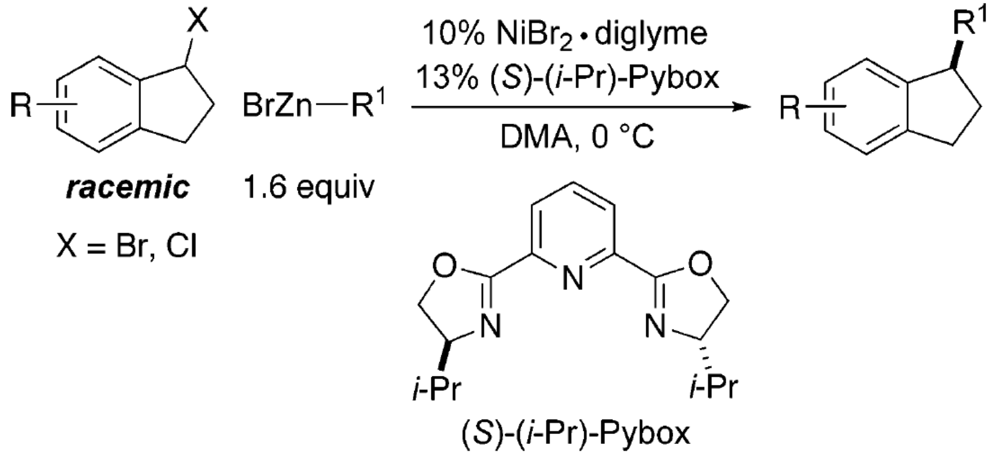
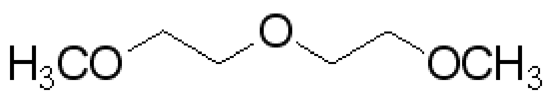
Negishi Cross-Couplings of Racemic Secondary Benzylic Halides



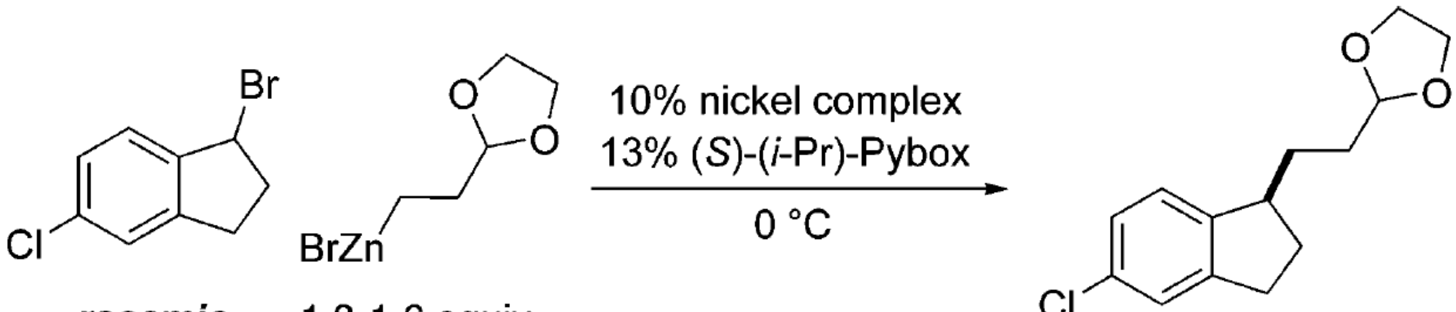


Diglyme
Diethylene glycol dimethyl ether

DMA = *N*,*N*-dimethylacetamide

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

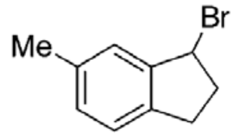
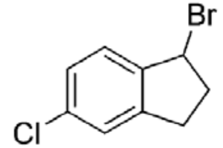
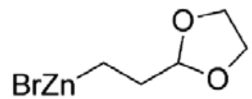
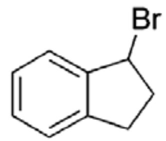
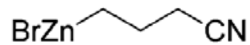
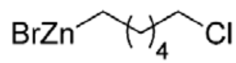
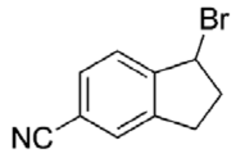
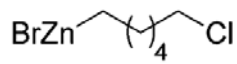
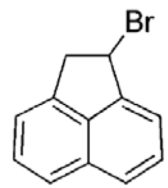
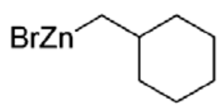
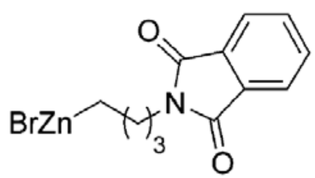
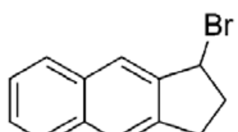
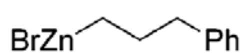
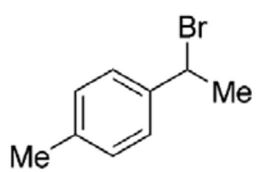
Optimization



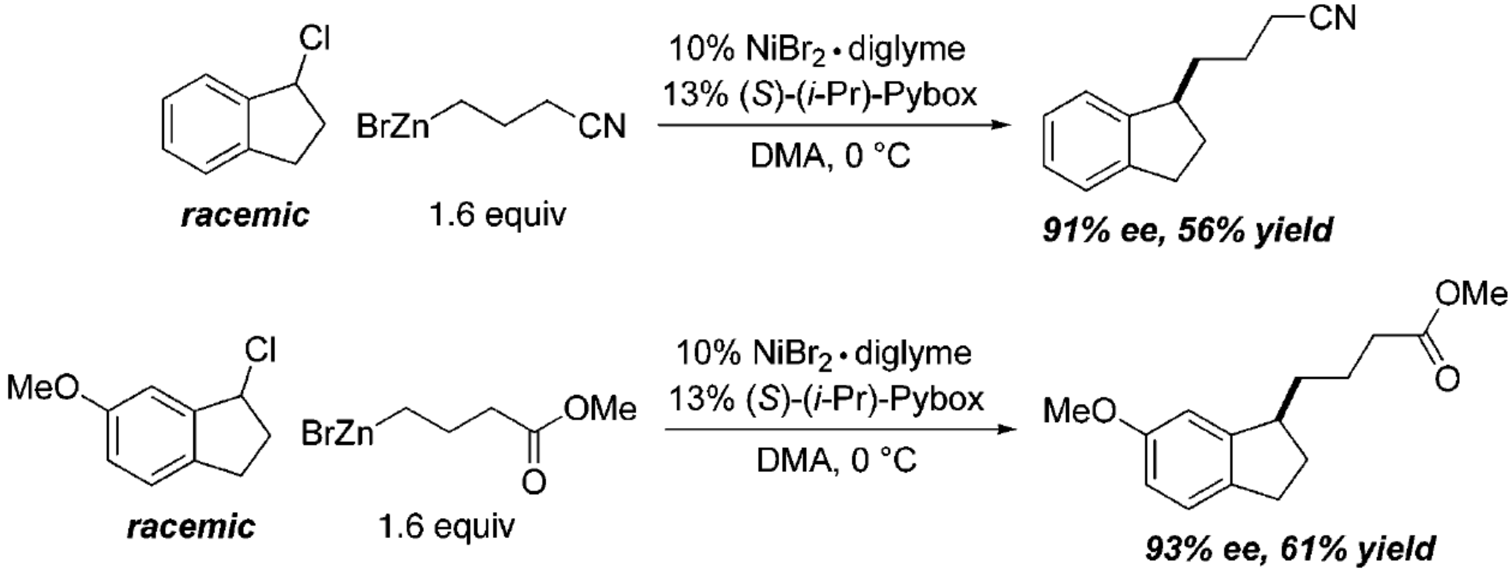
racemic 1.3-1.6 equiv

NiBr$_2$•diglyme, DMA ***91% ee, 82% yield***
NiCl$_2$•glyme, DMI/THF ***87% ee, 72% yield***

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

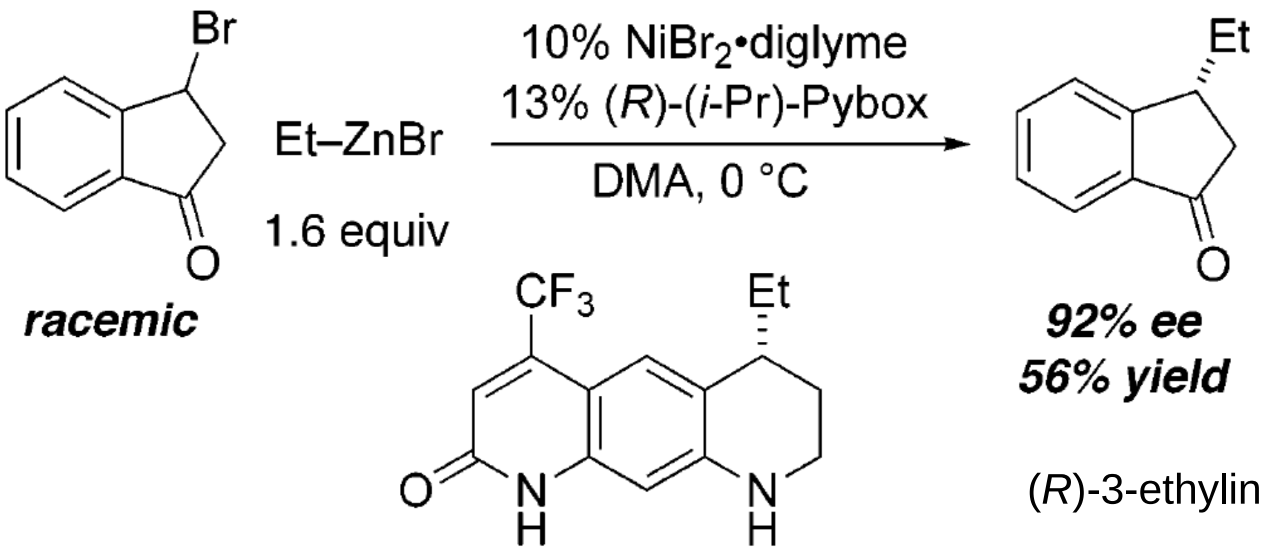
entry	R–X	R^1–ZnBr	yield (%)	ee (%)
1		BrZn–Hex	89	96
2			82	91
3			64	91
4			69	94
5			47	91
6		BrZn–Bu	72	98
7[b]			39	96
8[b]			41	99
9			76	98
10			63	75

Secondary Benzylic Chlorides



Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

Application



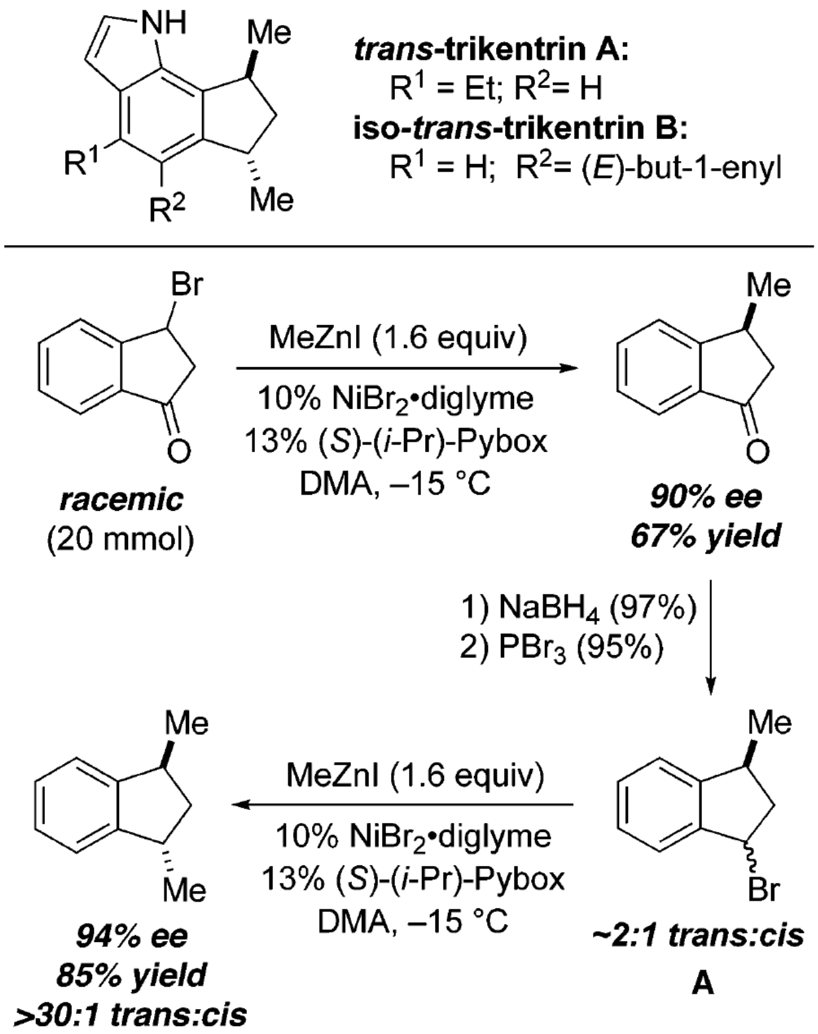
LG 121071

(*R*)-3-ethylindanone

LG 121071: the first orally active,
nonsteroidal androgen receptor agonist

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

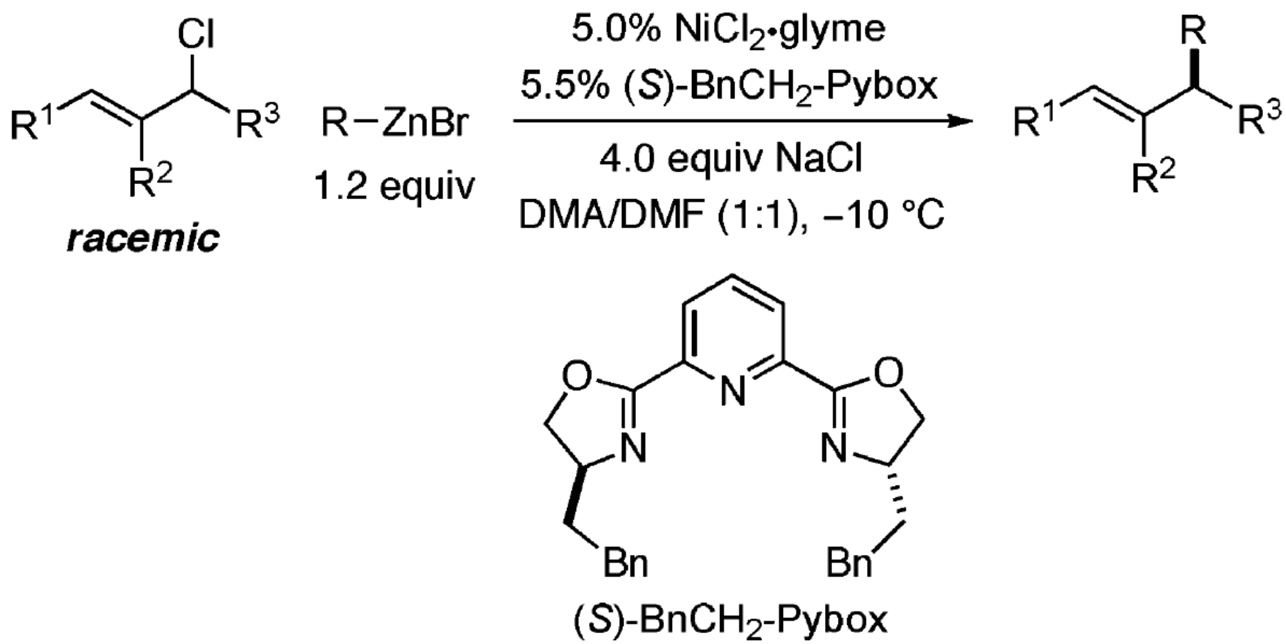
Application

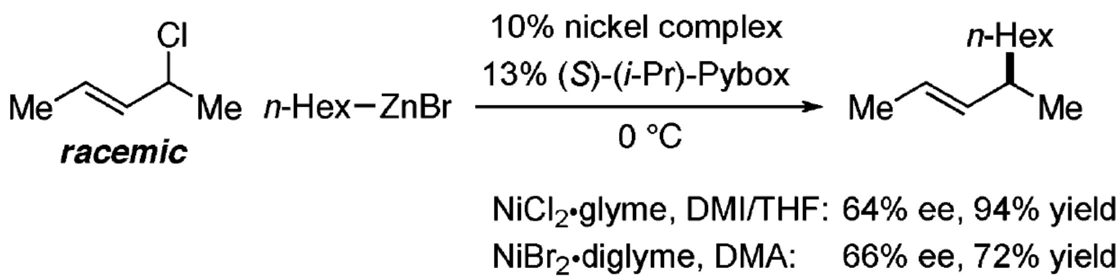


***trans*-trikentrin A**
iso-*trans*-trikentrin B
isolated from the marine sponge *Trikentrion flabelliforme* and exhibit antibacterial activity.

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

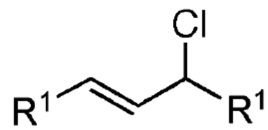
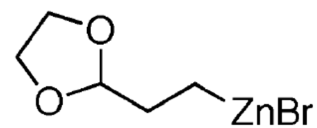
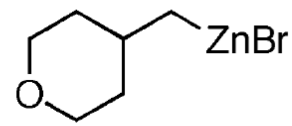
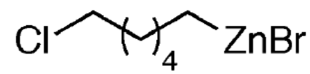
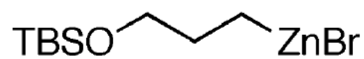
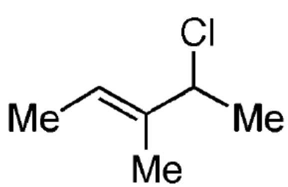
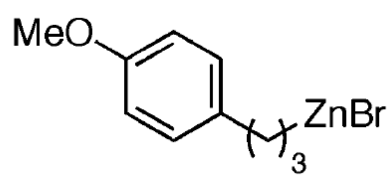
Negishi Cross-Couplings of Racemic Secondary Allylic Chlorides





Son, S.; Fu,G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756.

Substrate Scope

entry	allylic chloride	R−ZnBr	ee (%)	yield (%)[a]
1	 R^1 = Me	*n*-Hex−ZnBr	87	95[b]
2	Me		90	93
3[c]	*n*-Pr		85	81
4	*n*-Pr		79	81
5	*i*-Pr		69	57
6			98	54

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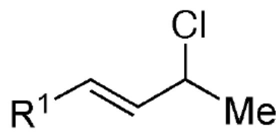
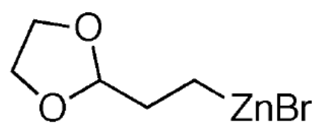
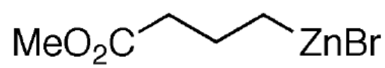
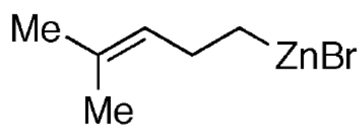
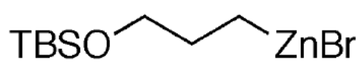
Substrate Scope

entry	allylic chloride	R−ZnBr	ee (%)	yield (%)[a]
1[b,c]	 R^1 = *n*-Bu		83	97
2[c]	*i*-Pr		84	95
3[c]	*t*-Bu		81	85
4	CO_2Et		96	86
5	$CONEt_2$	Et−ZnBr	91	57
6	CON(OMe)Me		93	91
7	$PO(OEt)_2$	*n*-Hex−ZnBr	90	63

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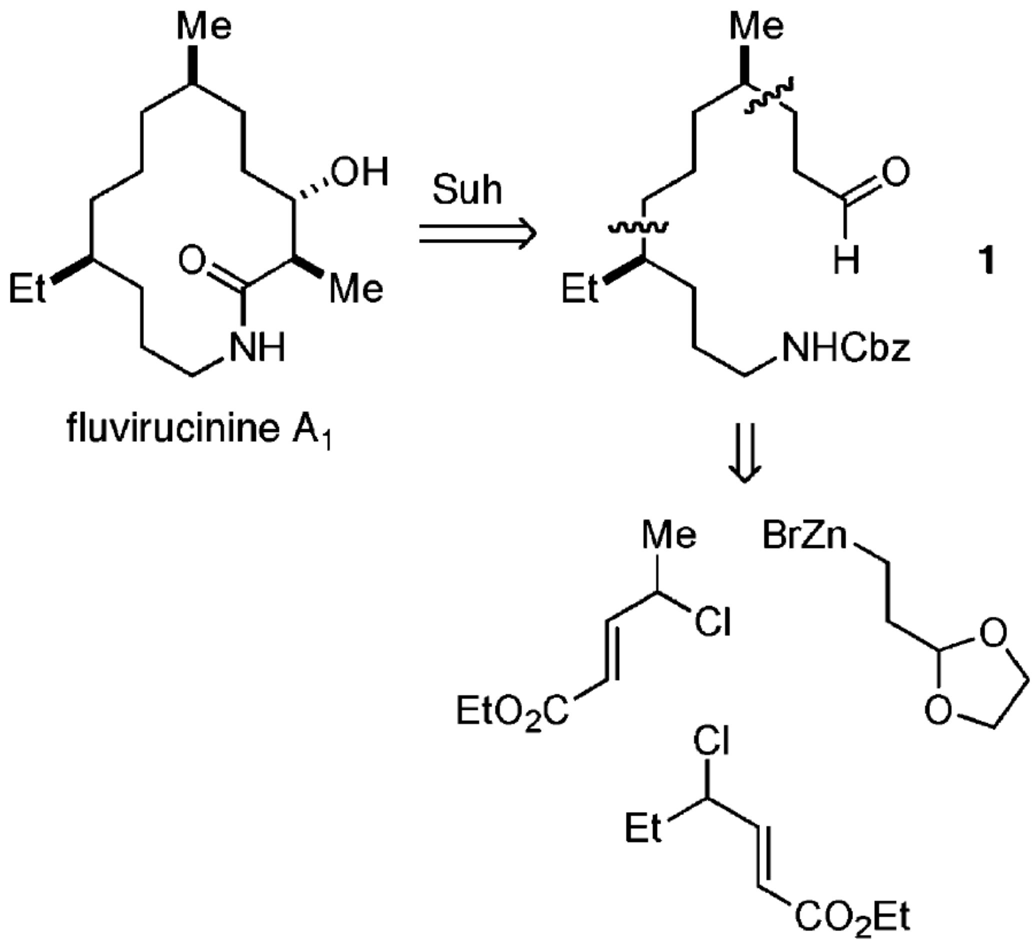
Application



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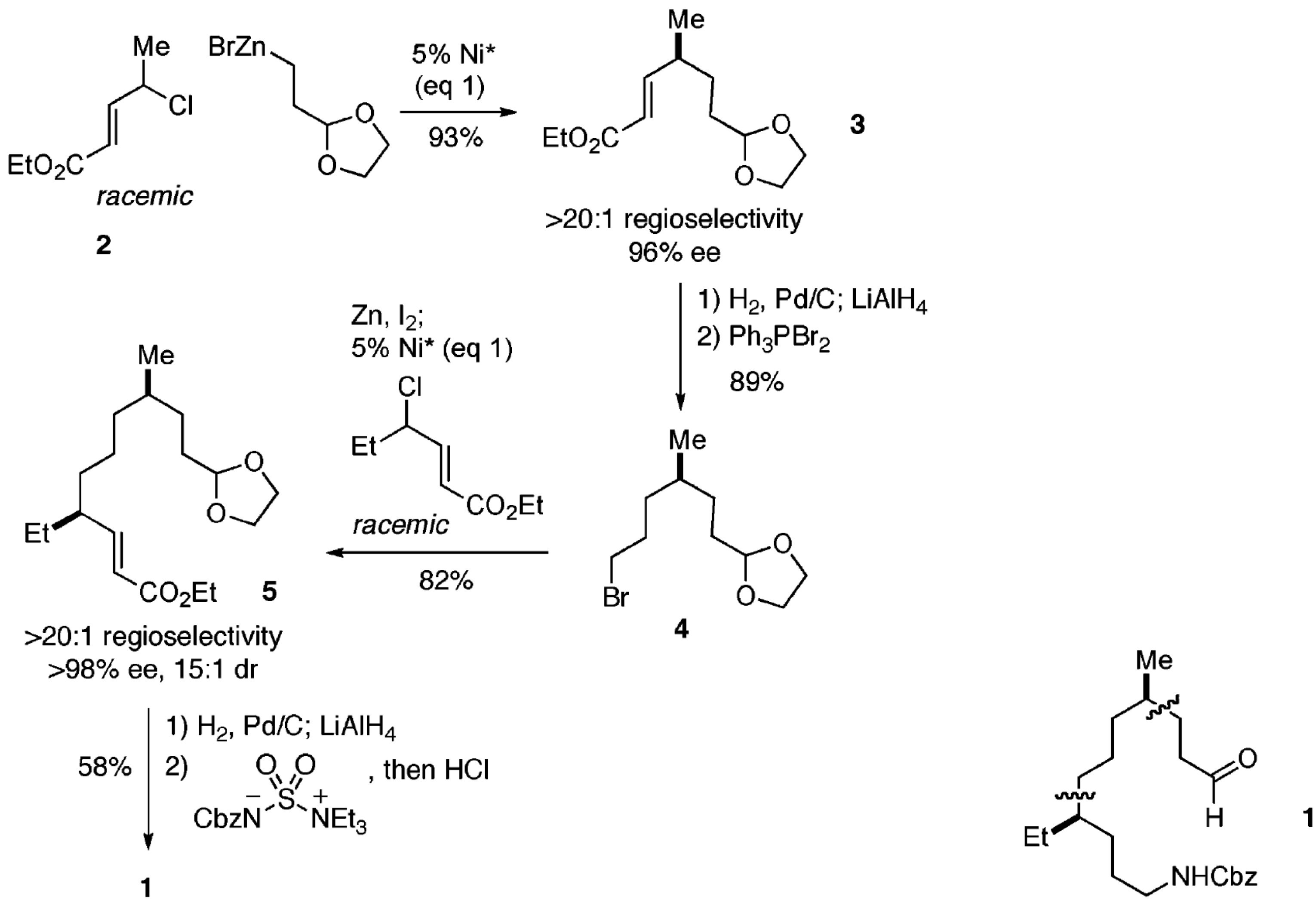
Application



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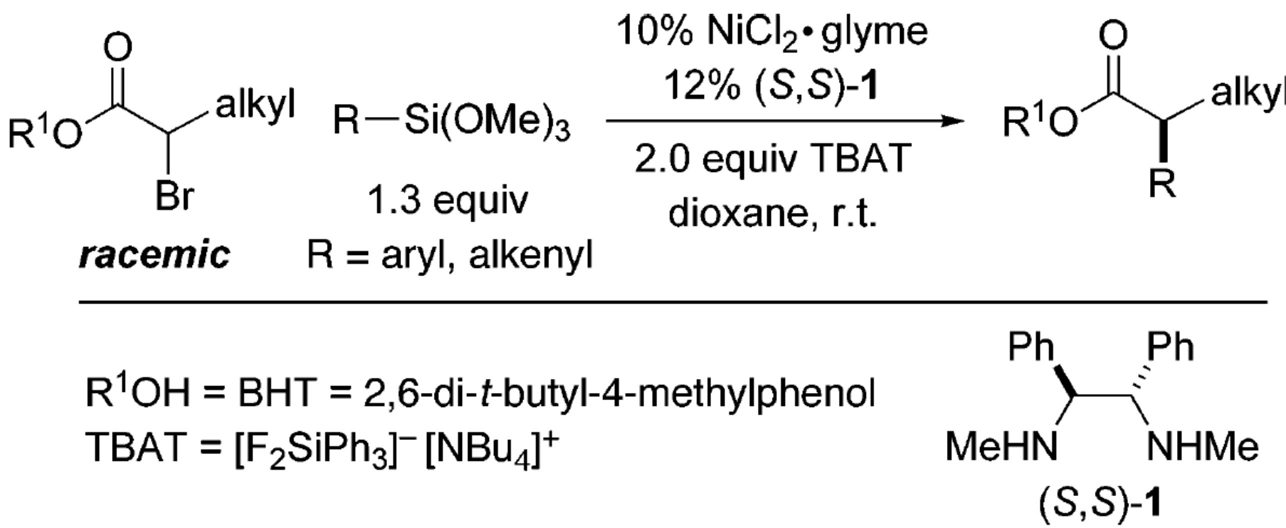
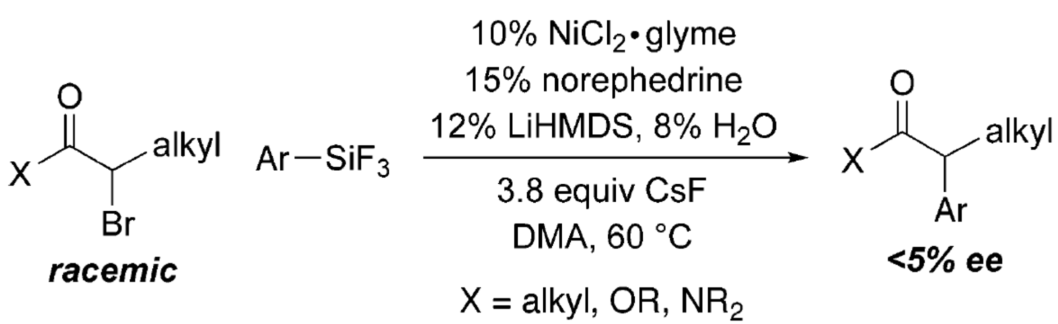
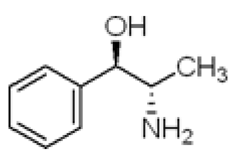
Hiyama Cross-Couplings of Racemic α-Bromo Esters







L-(−)-Norephedrine

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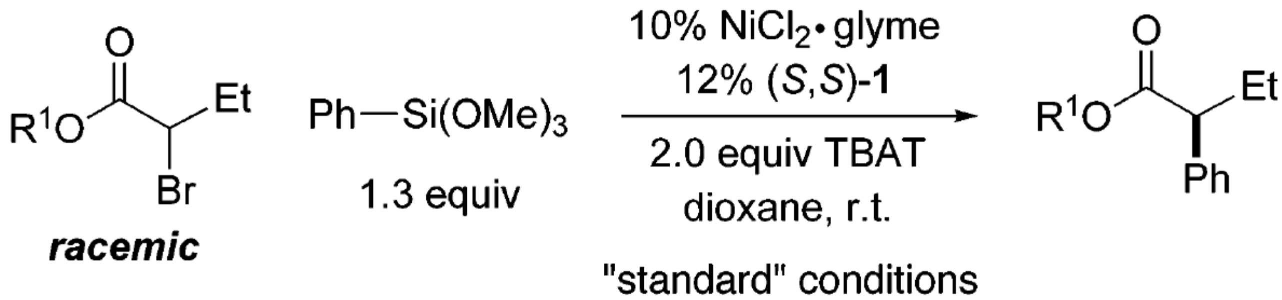
Optimization



R^1 = 2,6-di-*t*-butyl-4-methylphenyl

entry	variation from the "standard" conditions	ee (%)	yield (%)
1	none	99	80
2	(–)–norephedrine, instead of (*S*,*S*)-**1**	–	9
3	CsF, instead of TBAT	–	<2
4	TBAF, instead of TBAT	–	<2
5	$PhSiF_3$, instead of $PhSi(OMe)_3$	98	60
6	R_1 = Et	23	92
7	R_1 = *t*-Bu	33	85
8	R_1 = 2,4,6-trimethylphenyl	13	78
9	R_1 = 2,6-diisopropylphenyl	73	75
10	R_1 = 2,6-di-*t*-butyl-4-methoxyphenyl	95	82
11	5% $NiCl_2$•glyme, 6% (*S*,*S*)-**1**, instead of 10%/12%	98	70

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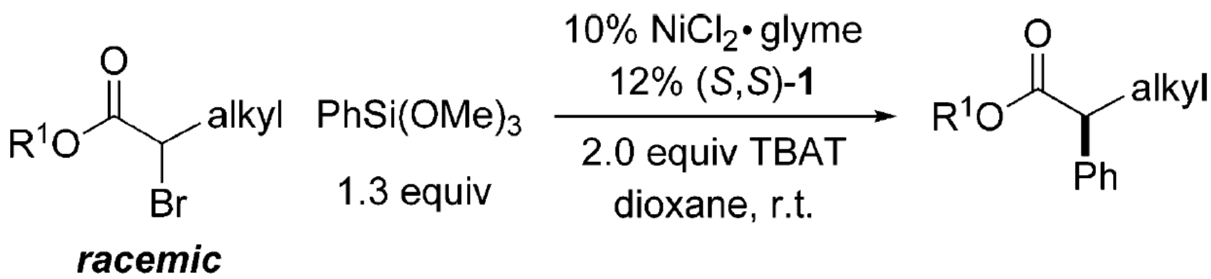
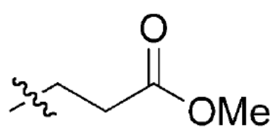
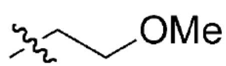
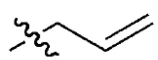
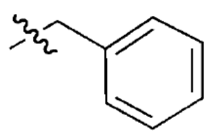
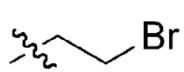


R^1OH = BHT = 2,6-di-*t*-butyl-4-methylphenol

entry	alkyl	ee (%)	yield (%)
1	Me	89	84
2	Et	99	80
3	Bu	92	76
4	*i*-Bu	93	64
5[b]	*i*-Pr	75	72
6		92	80
7		99	68
8		80	78
9		84	72
10		86	70

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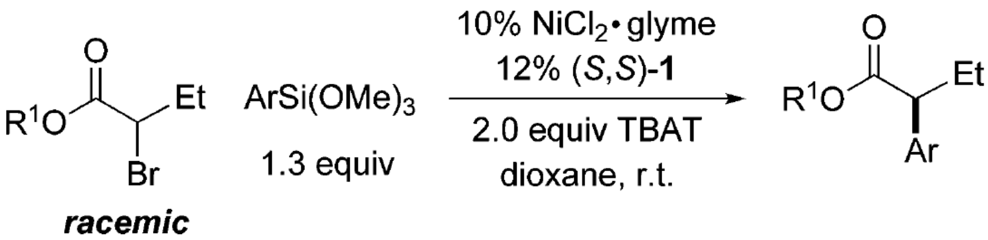
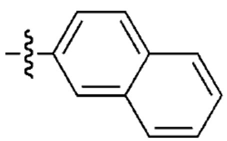
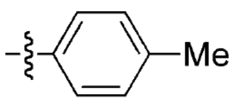
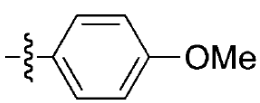
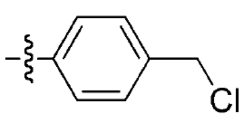
Arylations of α-Bromo Esters



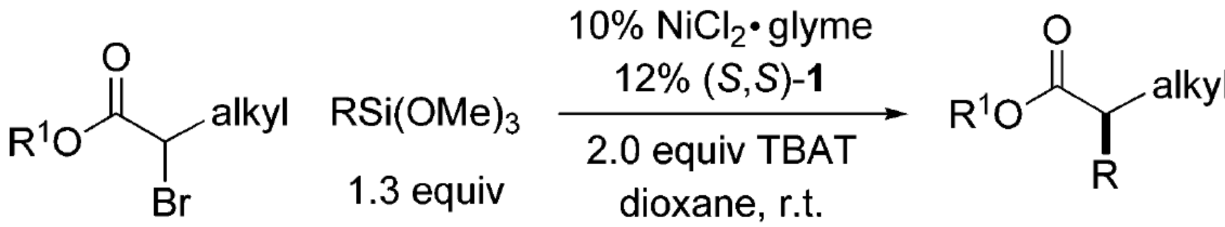
R^1OH = BHT = 2,6-di-*t*-butyl-4-methylphenol

entry	Ar	ee (%)	yield (%)
1		89	74
2		92	76
3		87	64
4		94	72

(a) $(4\text{-}CF_3)C_6H_4Si(OMe)_3$ furnished racemic product
(b) a reaction with (1-naphthyl)$Si(OMe)_3$ was unsuccessful;
(c) $(4\text{-}F)C_6H_4Si(OMe)_3$ underwent cross-coupling in moderate yield (44%) and *ee* (63%).

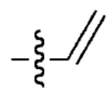
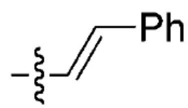
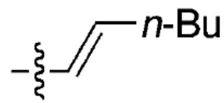
Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302.

Alkenylations of α-Bromo Esters



racemic

R^1OH = BHT = 2,6-di-*t*-butyl-4-methylphenol

entry	alkyl	R	ee (%)	yield (%)
1	*n*-Bu		93	66
2	*n*-Bu		92	72
3	Et		91	70

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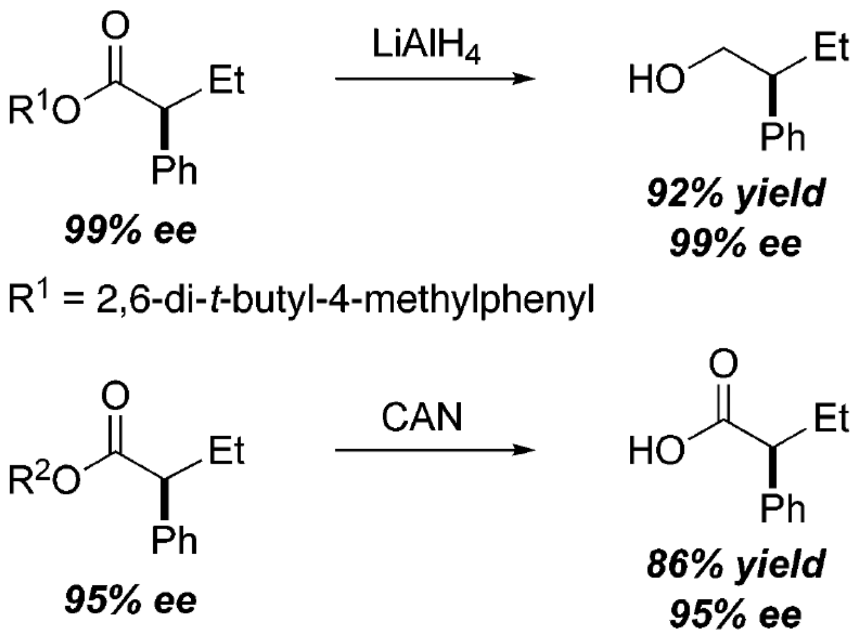
Transformations



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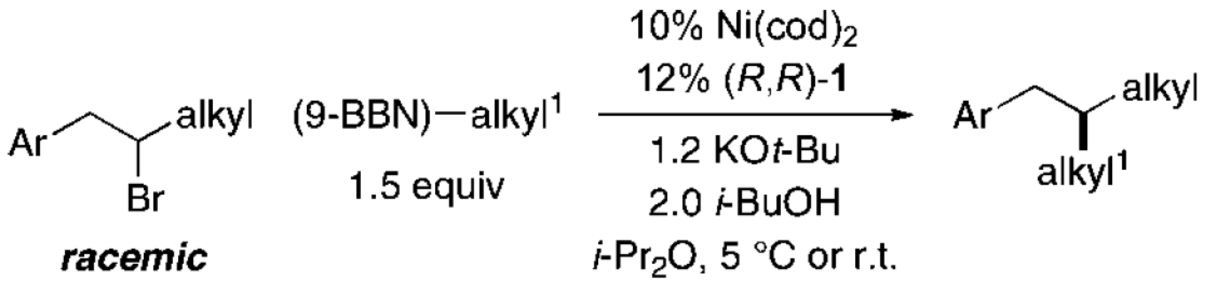
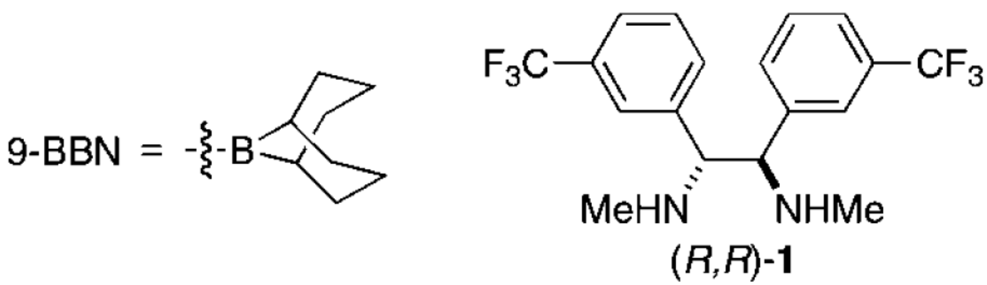
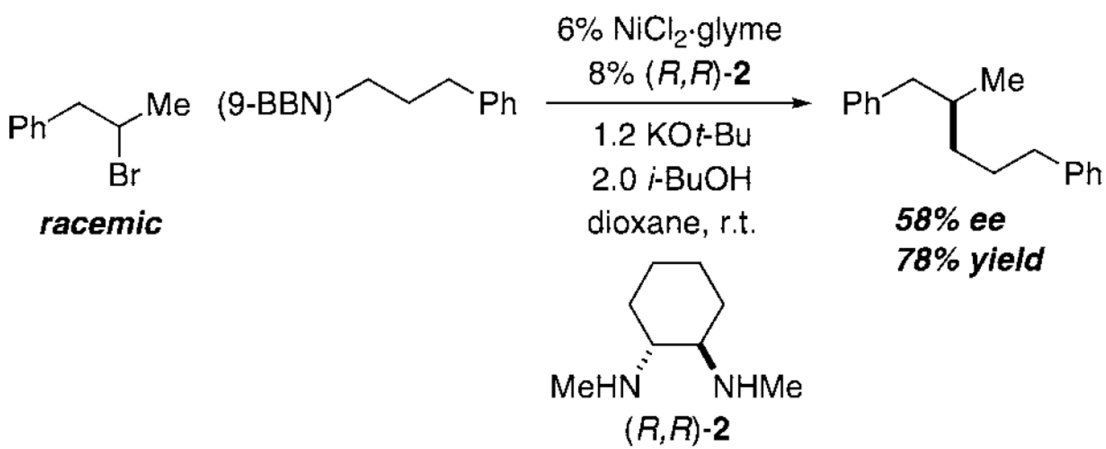
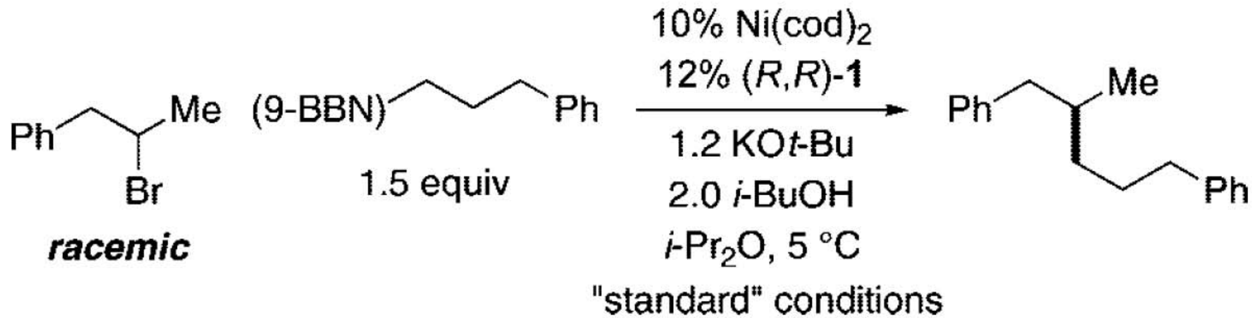
Suzuki Cross-Couplings of Unactivated Homobenzylic Halides



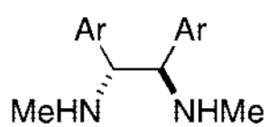




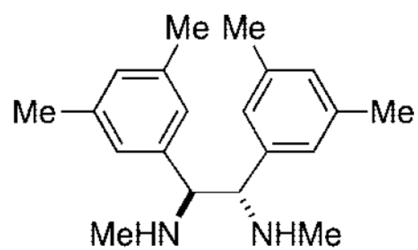
Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* 2008; ASAP Article; DOI: 10.1021/ja8013677



entry	variation from the standard conditions	ee (%)	yield (%)
1	none	89	85
2	no (*R*,*R*)-**1**	–	<2
3	(*R*,*R*)-**3**, instead of (*R*,*R*)-**1**	85	76
4	(*R*,*R*)-**4**, instead of (*R*,*R*)-**1**	88	66
5	(*R*,*R*)-**5**, instead of (*R*,*R*)-**1**	−6	46
6	(*S*,*S*)-**6**, instead of (*R*,*R*)-**1**	−80	72
7	rt, instead of 5 °C	87	76
8	dioxane at rt, instead of *i*-Pr_2O at 5 °C	60	32
9	5% $Ni(cod)_2$ and 6% (*R*,*R*)-**1**, instead of 10%/12%	89	70



Ar = Ph: (*R*,*R*)-**3**
= 4-(trifluoromethyl)phenyl: (*R*,*R*)-**4**
= mesityl: (*R*,*R*)-**5**



(*S*,*S*)-**6**

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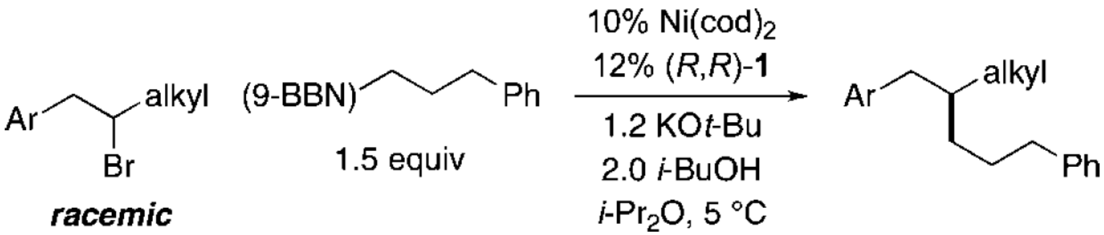
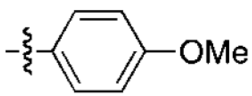
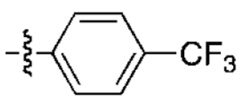
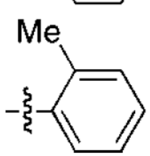
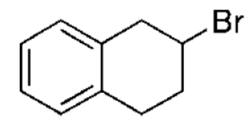
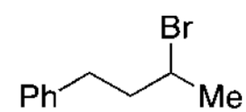
Substrate Scope



entry	Ar	alkyl	ee (%)	yield (%)[a]
1	Ph	Me	90	78
2	Ph	*n*-Bu	94	84
3	Ph	CH_2CH_2Ph	90	68
4	Ph	*i*-Pr	88	74
5		Me	90	84
6		Me	70	82
7		Me	86	86



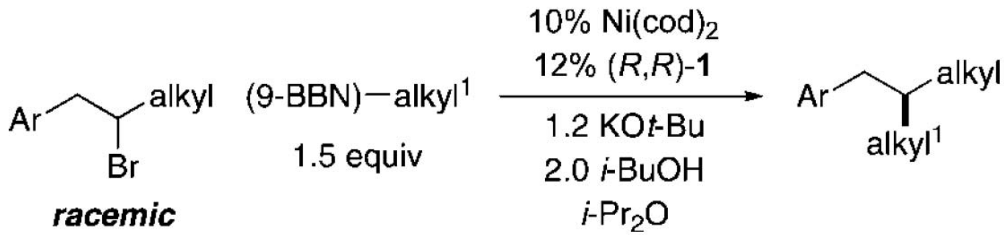
7
5% ee

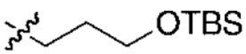
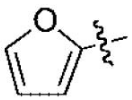
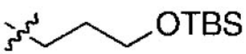
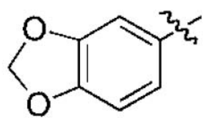
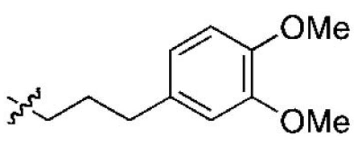
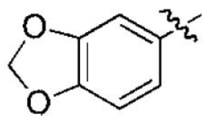
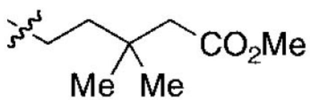


8
14% ee

Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* 2008; ASAP Article; DOI: 10.1021/ja8013677

Substrate Scope



entry	Ar	alkyl	alkyl[1]	ee (%)	yield (%)[a]
1[b]	Ph	Me		80	68
2[c]	Ph	Me		78	68
3[c]	Ph	*n*-Bu		82	64
4[b]	Ph	CH_2OBn	*n*-Hex	40	69
5[c]		Me		66	62
6[c]		Et		85	74
7[c]		Et		76	73

Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* 2008; ASAP Article; DOI: 10.1021/ja8013677

Conclusions

- Neigishi Cross-Couplings (α-bromo amide; benzylic bromides and chlorides; allylic chlorides)
- Hiyama Cross-Couplings (α-bromo ester)
- Suzuki Cross-Couplings
- Other Cross-Couplings……

Thank You