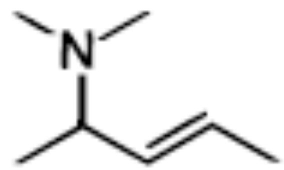
Synthesis of Chiral Allylic Amines via Coupling of Alkynes and Imines

Sato, F. *et al Org. Lett.* **2003,** *5*, 2145
Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367
Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944

Chunrui Wu

Aug 5, 2004



Important imtermediate: making α, or β amino acid
Aza-Claisen rearrangement
RCM etc

Auxiliaries

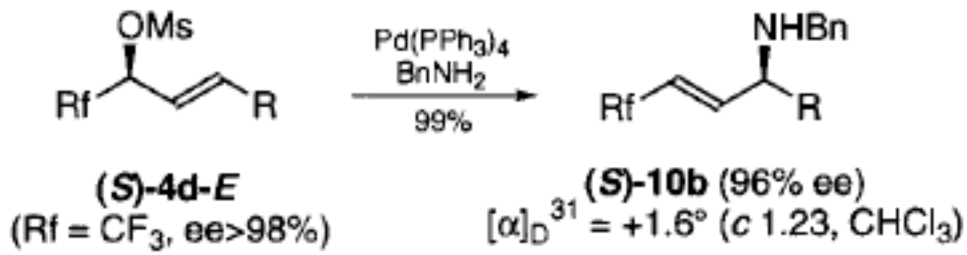
Resolving agents

Found in bioactive natural products

Methods to synthesis asymmetric allylic amination :
amination of chiral allylic alcohol,
asymmetric nucleophilic addition to C=N double bonds,
rearrangement of Allylic imidates,
asymmetric addition to alkynes

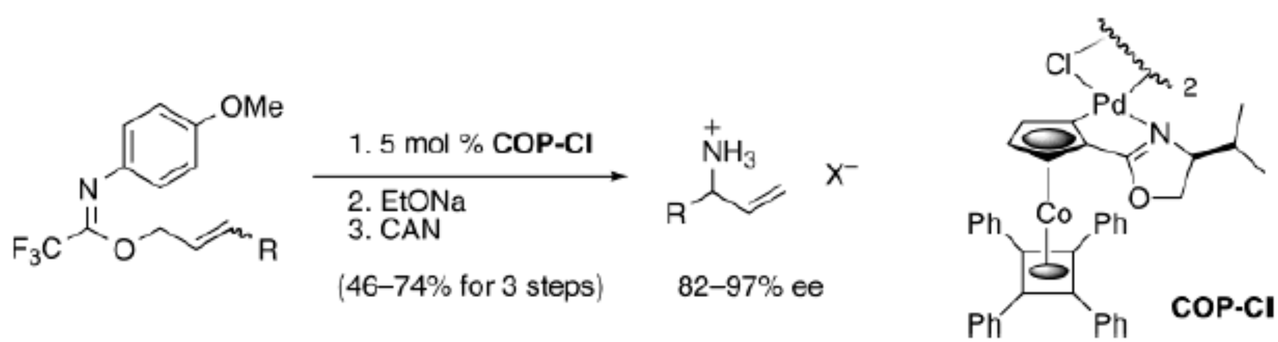
Some Methods to Prepare Chiral Allylamine

Pd catalyzed allylic substitution



J. Org. Chem. **2002**, *67*, 1768−1775

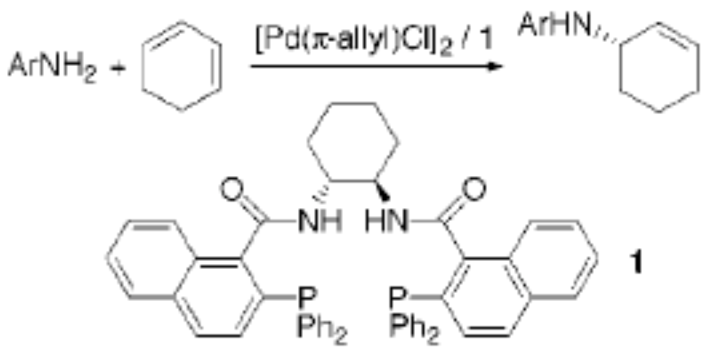
Rearrangement of Allylic N-Aryl Trifluoroacetimidates



Overman, L. E. *et al Org.Lett.* **2003**, *5*, 1809-12.

Some Methods to Prepare Chiral Allylamine

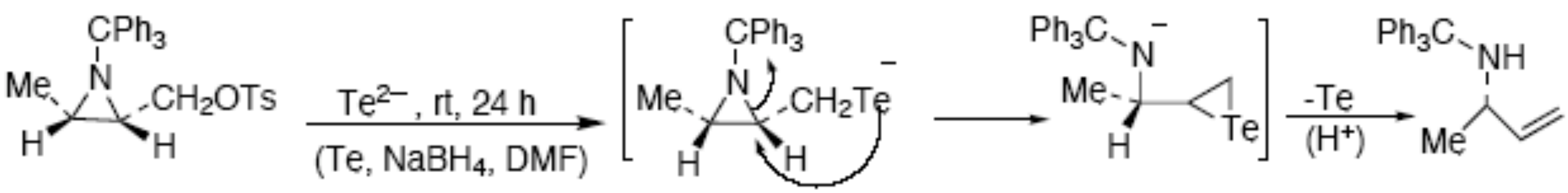
Pd catalyzed arylamines addition to cyclodienes



Yied 59-94%
ee. 50-95

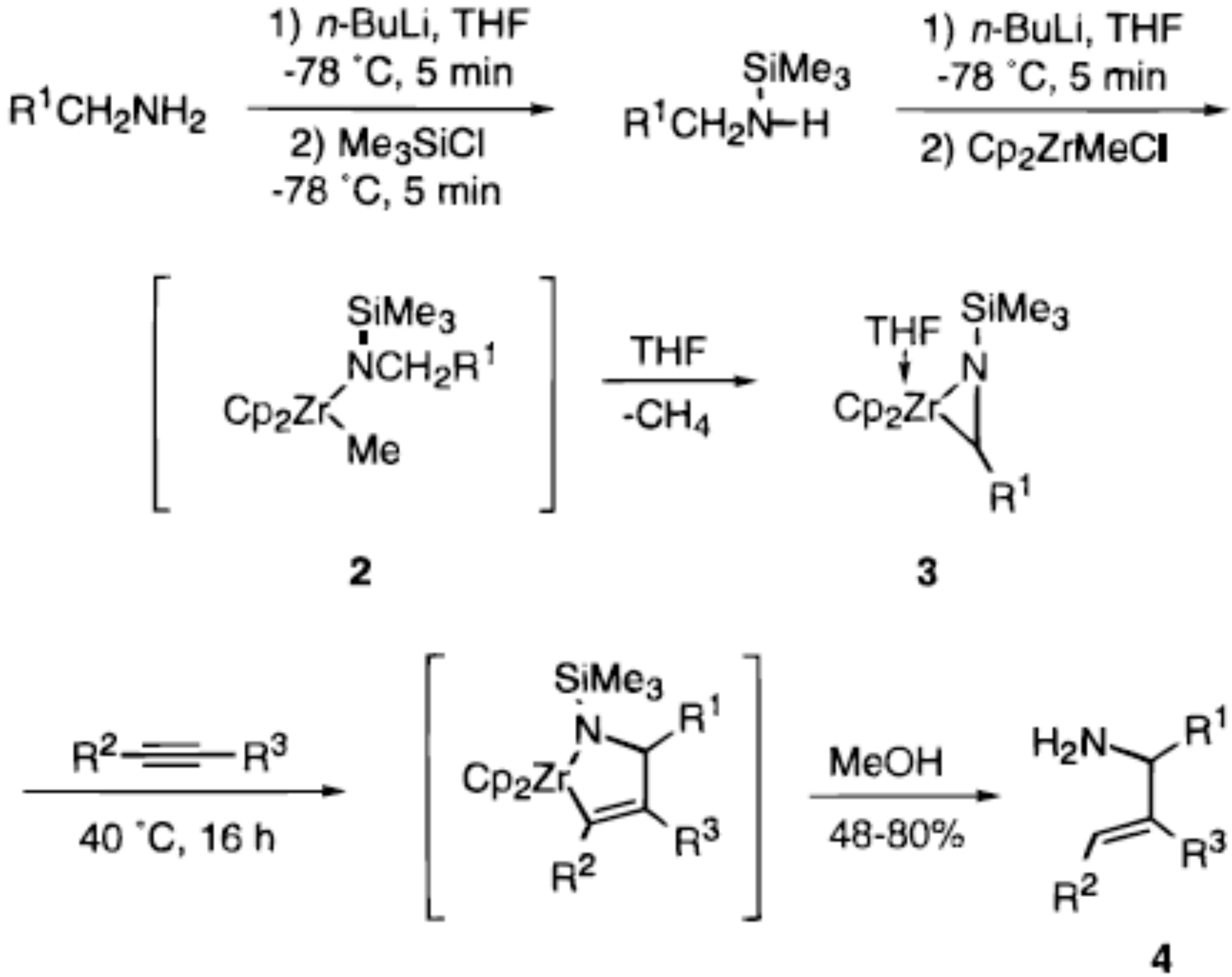
J. Am. Chem. Soc. **2001,** *123,* 4366−4367

allylic amine synthesis via tellurium.[1]



Tetrahedron Letters 42 (2001) 5789–5791

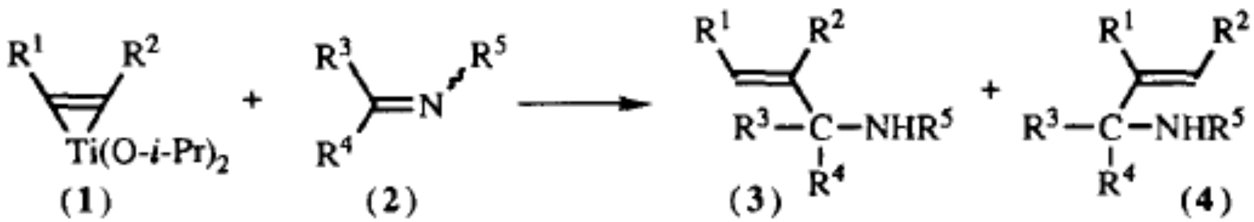
Coupling of Imines and Alkynes(I)



Buchwald, S. L. *JACS* **1989**, *111*, 4486

Coupling of Imines and Alkynes(II)

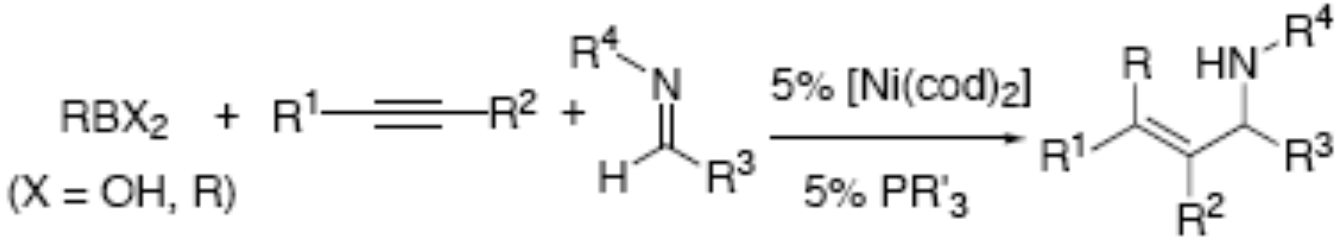
(propene)Ti(O-iPr)$_2$



Entry	1		2			3 and/or 4	
	R^1	R^2	R^3	R^4	R^5	Yield (%)	3/4[b]
1	Pr	Pr	*n*-Pr	H	CH_2Ph	75	—
2	Ph	Ph	"	"	"	82	—
3	Ph	Me	"	"	"	71	60/40
4	TMS	Ph	"	"	"	72	100/0[c]
5	TMS	Hex	"	"	"	83[d]	"
6	TMS	TMS	"	"	"	12	—
7	TMS	Hex	*n*-Pr	"	*n*-Pr	90	100/0
8	"	"	Ph	"	Ph	89	"
9	"	"	*c*-Hexyl	"	"	94	"
10	"	"	2-Furyl	"	"	82	"
11	"	"	*n*-Bu	Me	*n*-Pr	54	"

Sato, F. *et al Terahedron Lett*. **1995**, *36*, 5913.

Multi-component Coupling of Alkynes, Imines and Organoboron

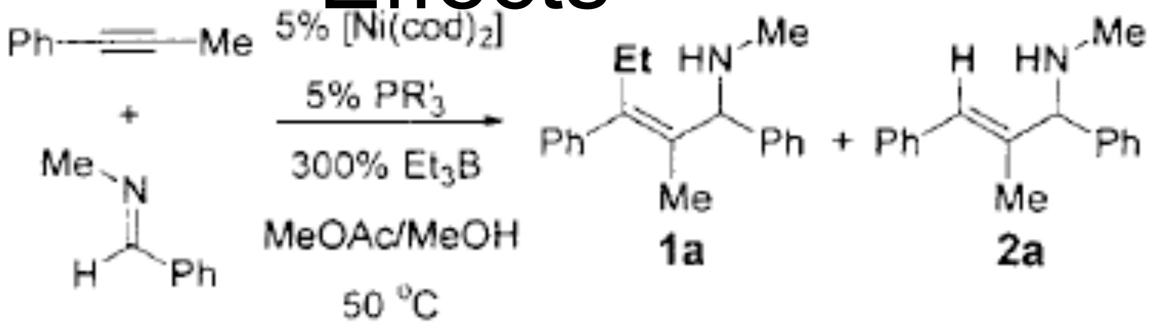


R^1 = aryl, alkyl; R^2 = alkyl, H; R^3 = aryl, alkyl
exclusive *cis* addition across alkyne (>97:3)
compatible with ketones, esters, and hydroxylic solvents

Scheme 1. Catalytic assembly of allylic amines from alkynes, imines, and organoboron reagents.

Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367

Ligand Effects



Entry	PR'$_3$[a]	Yield [%]	**1a**:**2a**[b]	Regioselectivity[c]
1	Bu_3P	80	94:6	96:4
2	Bn_3P	72	97:3	93:7
3	Cy_3P	88	89:11	91:9
4	Cyp_3P	85	92:8	91:9
5	$t$$Bu_3P$	9	93:7	80:20
6	Ph_3P	34	95:5	91:9

[a] $Cy_3P = (c\text{-}C_6H_{11})_3P$, $Cyp_3P = (c\text{-}C_5H_9)_3P$. [b] Ratio determined by ^1H NMR. [c] Regioselectivity of **1a** (determined by ^1H NMR).

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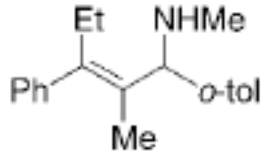
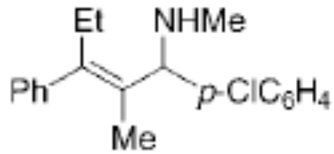
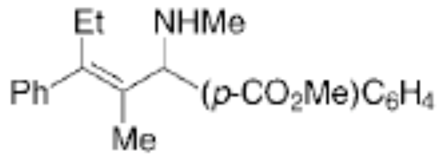
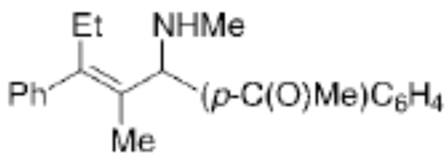
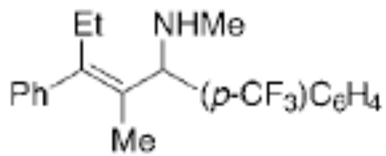
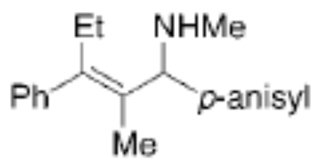
	Product	Yield [%][b]	1:2[c]	Regio-selectivity[c,d]
1b		85	94:6	90:10
1c		95	96:4	90:10
1d		82	>96:4	90:10
1e		78	>96:4	91:9
1f		98	96:4	89:11
1g		64	86:14	91:9

[a] $[Ni(cod)_2]$ (5 %) and $(c\text{-}C_5H_9)_3P$ (5 %) used in all cases.

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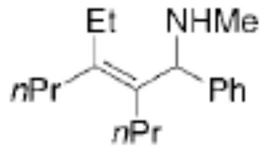
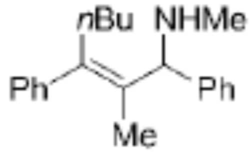
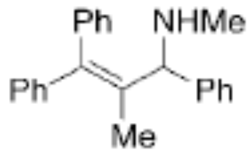
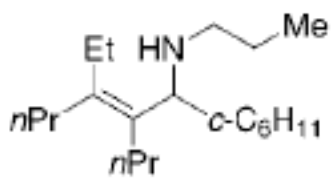
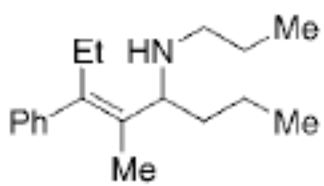
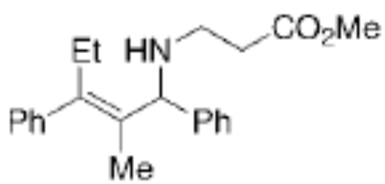
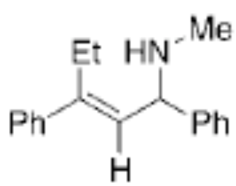
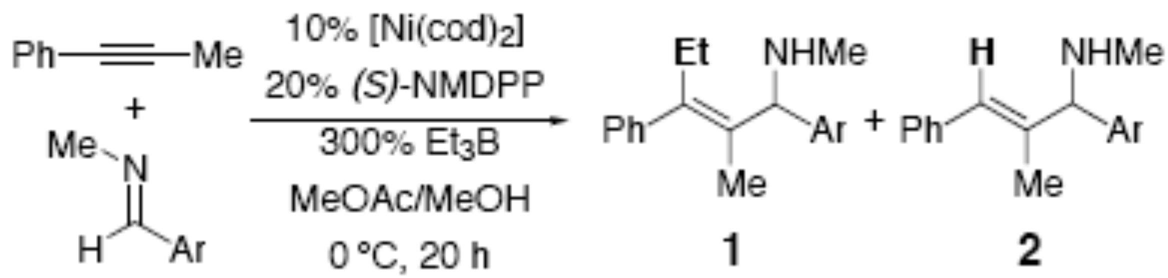
	Product	Yield [%][b]	1:2[c]	Regio-selectivity[c,d]
1h		91	94:6	–
1i		70	90:10	91:9
1j		65	–	93:7
1k		52	>96:4	–
1l		30	90:10	91:9
1m		75	94:6	91:9
1n		35[e]	>95:5	>98:2

Enantioselective Attemps



Entry	Ar	*ee* 1 [%][a]	*ee* 2 [%][a]
1	Ph	41	42
2	*p*-ClC_6H_4	33	33
3	(*p*-CF_3)C_6H_4	40	39

[a] Enantiomeric excess determined for the corresponding acetamides (Ac_2O, Et_3N, cat. DMAP), Chiralcel OD column.

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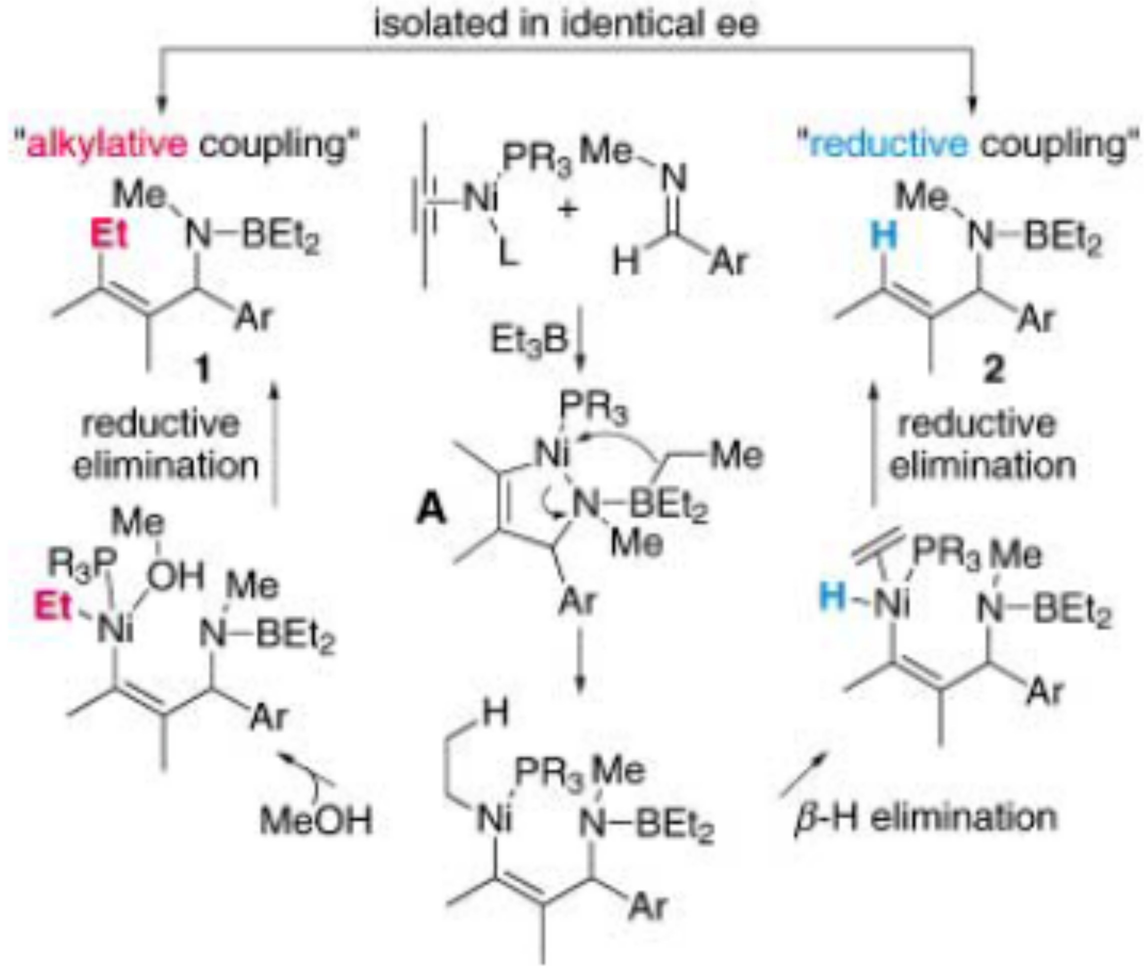
Proposed Mechanism



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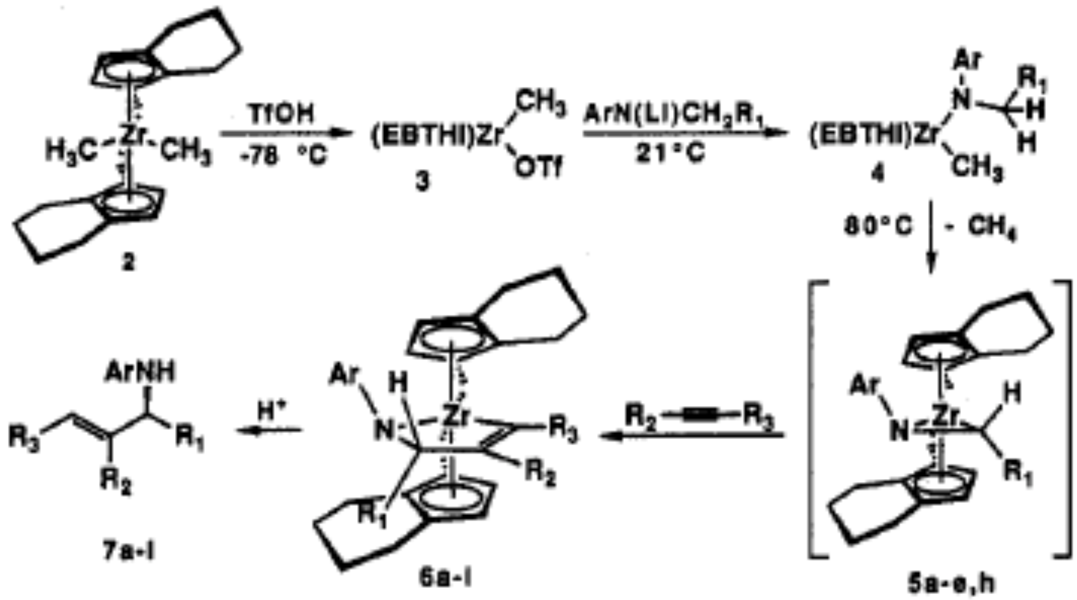
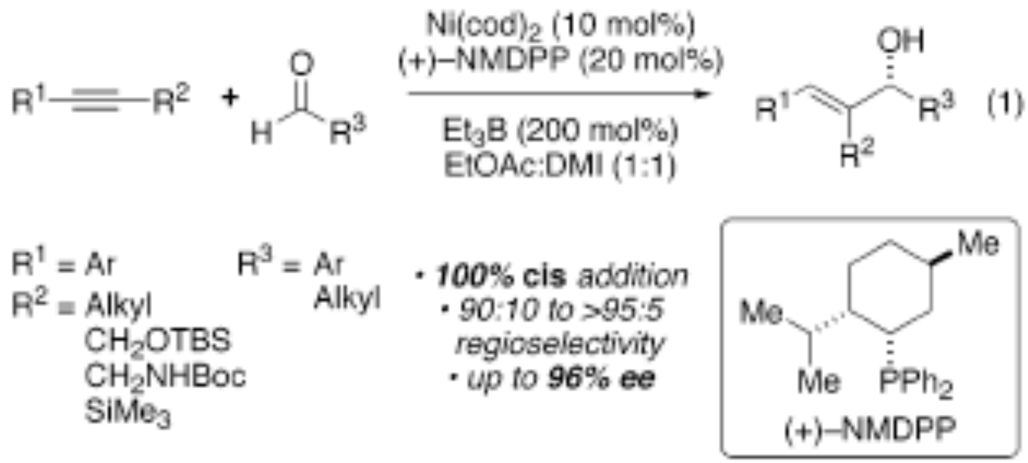
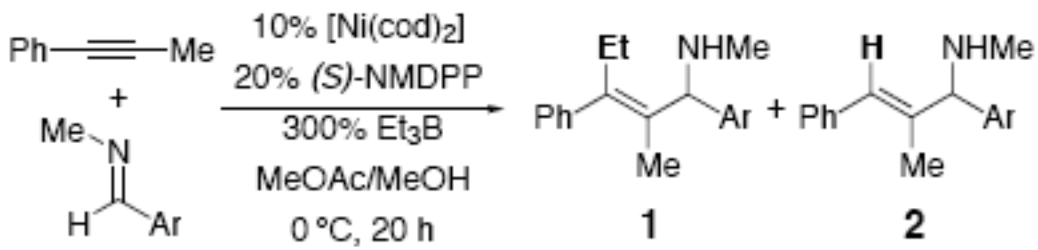
Stoichiometric Reactions



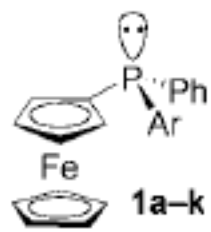
Excellent ee and moderate yields

Buchwald, S. L. *JACS*, **1991**, *113*, 2321-2322.



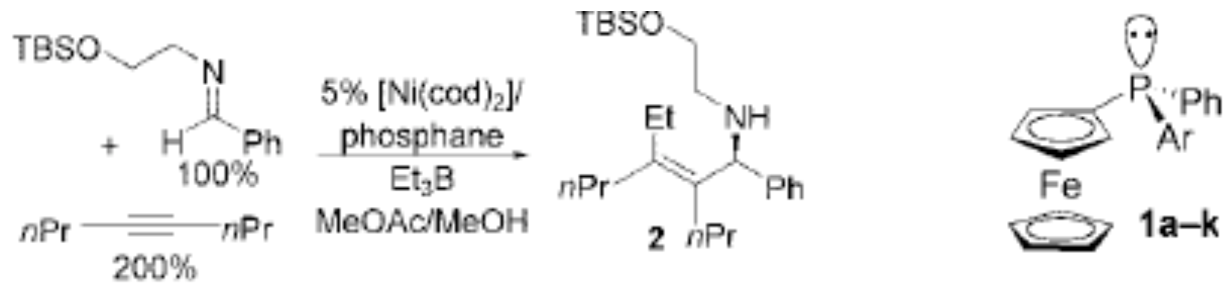


ee. Up to 41%, yield up to 36%



Only **1**
No Reductive coupling by products **2**

Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944



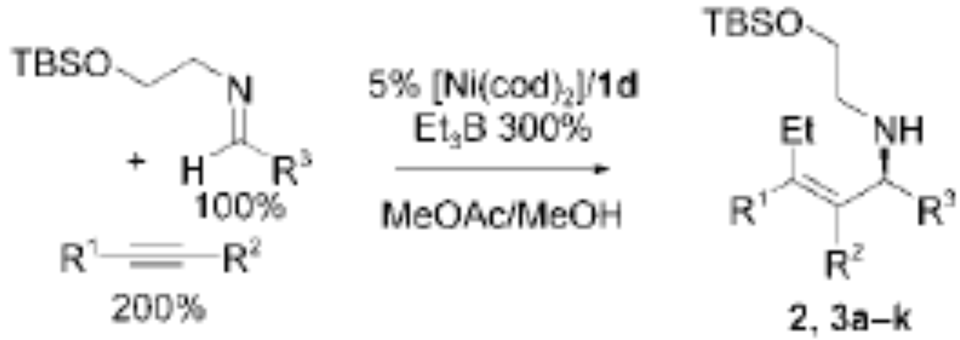
	Ar
a	*o*-tolyl
b	2-EtC_6H_4
c	2-*n*BuC_6H_4
d	2-*i*PrC_6H_4
e	*o*-biphenylyl
f	2,5-$Me_2C_6H_3$
g	2-*i*Pr-5-MeC_6H_3
h	3,5-*t*$Bu_2C_6H_3$
i	*o*-anisyl
j	2-EtOC_6H_4
k	2-*i*PrOC_6H_4

Entry	Phosphane	Yield [%]	ee[b]
1	**1a**	88	75
2	**1b**	90	80
3	**1c**	60	75
4	**1d**	**85**	**89**
5	**1e**	19	45
6	**1f**	85	75
7	**1g**	25	77
8	**1h**	20	45
9	**1i**	64	54
10	**1j**	41	41
11	**1k**	73	51

Failed to make catalysts with
Ar = 2-^{t}BuC_6H_4
2, 6-$Me_2C_6H_3$

Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944

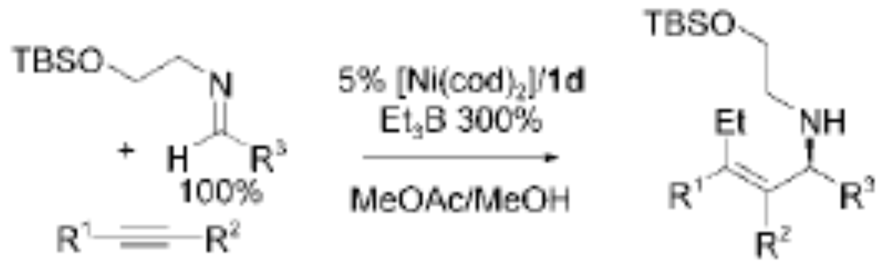
Enantiomeric Coupling with ligand **1d**



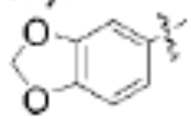
Entry	R^1	R^2	R^3	Product	Yield [%] (regio)[b]	*ee* [%][c]
1	*n*Pr	*n*Pr	Ph	**2**	85	89
2	*n*Bu	*n*Bu	Ph	**3a**	83	89
3	Et	Et	Ph	**3b**	89	83
4	*n*Pr	*n*Pr	*o*-tolyl	**3c**	74	85
5	*n*Pr	*n*Pr	*p*-anisyl	**3d**	75	82
6	*n*Pr	*n*Pr	*p*-$CF_3C_6H_4$	**3e**	91	85

Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944

Enantiomeric Coupling with ligand **1d**



2, 3a–k

Entry	R^1	R^2	R^3	Product	Yield [%] (regio)[b]	*ee* [%][c]
7	*n*Pr	*n*Pr	2-naph-thyl	**3f**	90	73
8	nPr	*n*Pr		**3g**	95	73
9	Et	Et	*c*-C_6H_{11}	**3h**	53	51
10	Ph	Me	Ph	**3i**	45 (80:20)	84
11	Ph	Et	Ph	**3j**	62 (>98:2)	71
12	2-naph-thyl	Me	Ph	**3k**	42 (85:15)	70

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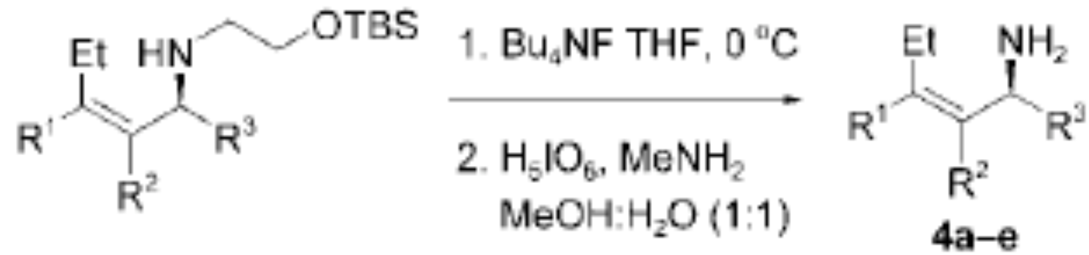
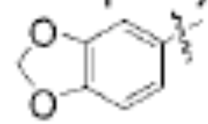
Deprotection of $TBSOCH_2CH_2$-Protected allylic amines



Entry	R^1	R^2	R^3	Product	Yield [%]	*ee* [%]
1	*n*Pr	*n*Pr	Ph	**4a**	73	89
2	*n*Pr	*n*Pr	o-tolyl	**4b**	66	85
3	*n*Pr	*n*Pr	2-naphthyl	**4c**	59	76
4	*n*Pr	*n*Pr		**4d**	68	73
5	Ph	Me	Ph	**4e**	63	84

[a] Enantiomeric excess of the major product, determined by HPLC.

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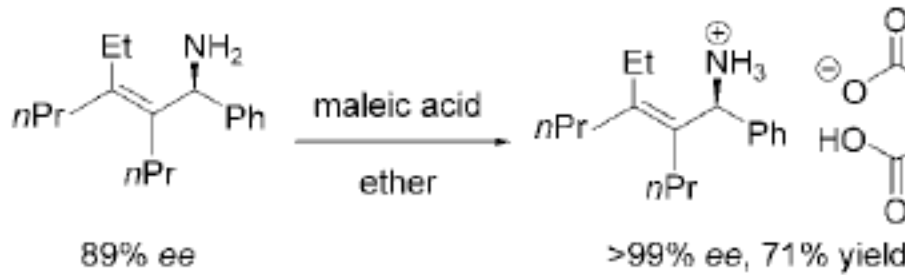
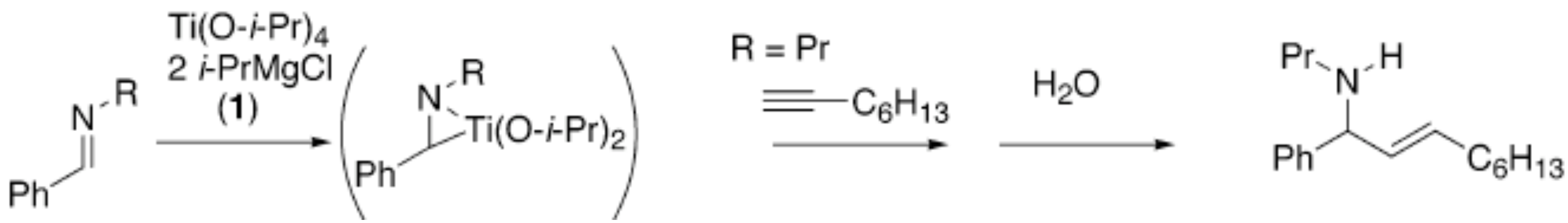
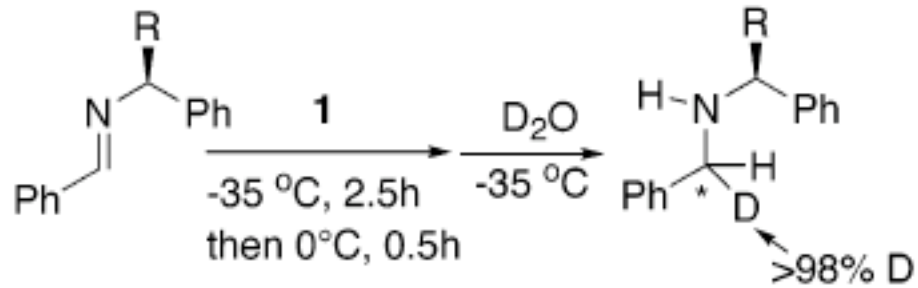


Jamison, T. F, Patel, S. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944

Diastereoselective Synthesis of Allylamine via Ti(II)

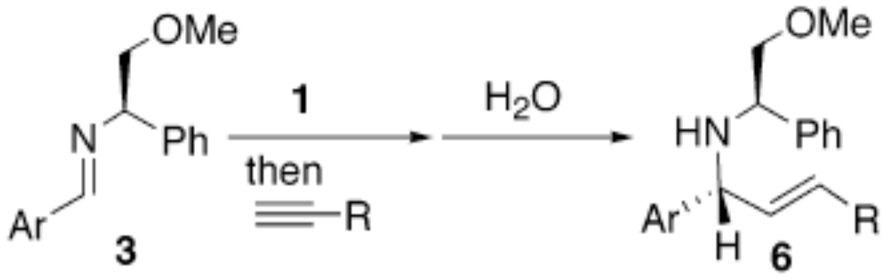


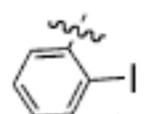


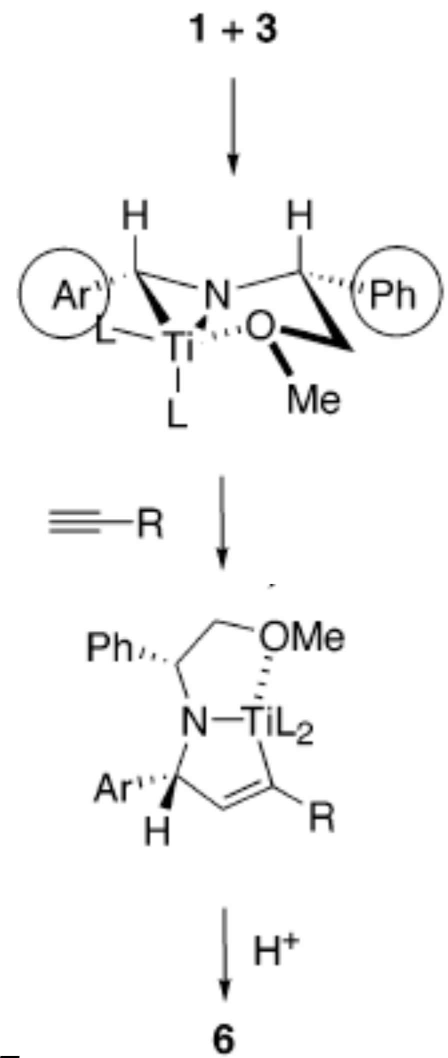
imine	d.r.[a]	yield, %
2a: R = Me	64:36	80
3a: R = CH_2OMe	>97 : 3	81
4a: R = $CH_2OSit\text{-}BuMe_2$	n.d.[b]	25
5a: R = CO_2Me	complex mixture[b]	

Sato, F. *et al Org. Lett.* **2003,** *5*, 2145

Proposed mechanism



entry	3	R-C≡CH	6		
	Ar			d.r.[a]	yield[b]
1	Ph (**3a**)	R = $SiMe_3$	**6a**	>97:3	81%
2	"	= n-C_6H_{13}	**6b**	>98:2	82%
3	"	= Ph	**6c**	>98:2	84%
4	"	= CO_2Et	**6d**	>96:4	63%
5	"	= SO_2Tol	**6e**	>94:6	28%
6	 (**3b**)	= $SiMe_3$	**6f**	>98:2	63%



Sato, F. *et al Org. Lett.* **2003,** *5*, 2145