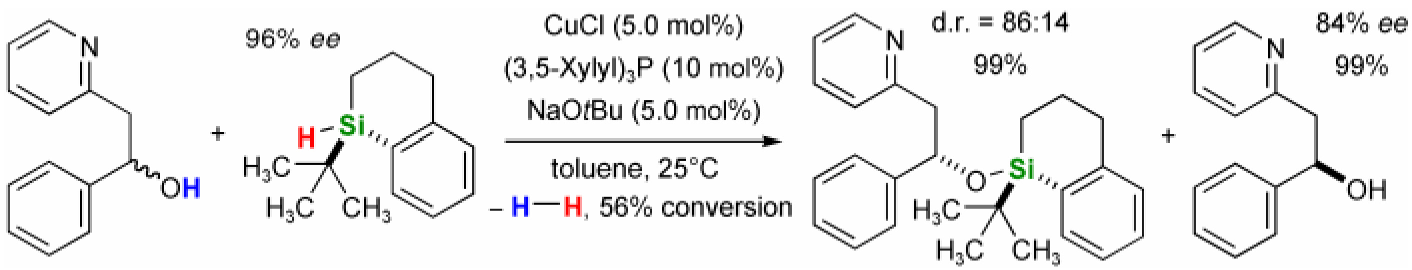
Recent Applications of Chiral Silicon Reagents

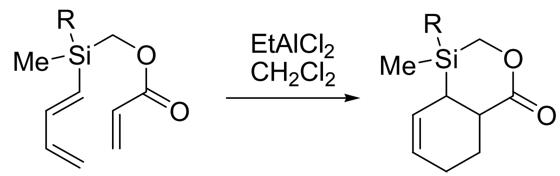


Leading Reference:

Kinetic Resolution of Chiral Secondary Alcohols by Dehydrogenative Coupling with Recyclable Silicon-Stereogenic Silanes, S. Rendler, G. Auer, M. Oestreich, *Angew. Chem. Int. Ed.* **2005**, *44*, 7620.

Maciej A. Walczak
Wipf Group
January 21st, 2006

Silicon to Carbon Chirality Transfer 1

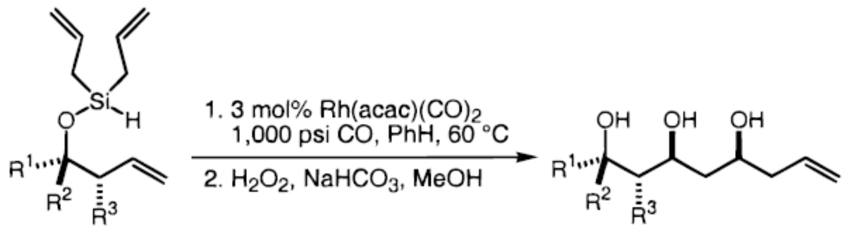


Entry	Time [h]	Yield %	dr
R = Ph	2	50	3:15:79:3
R = Ch	1	68	21:74:5
R = 2-MeOC$_6$H$_4$	1.5	74	4:5:90:1

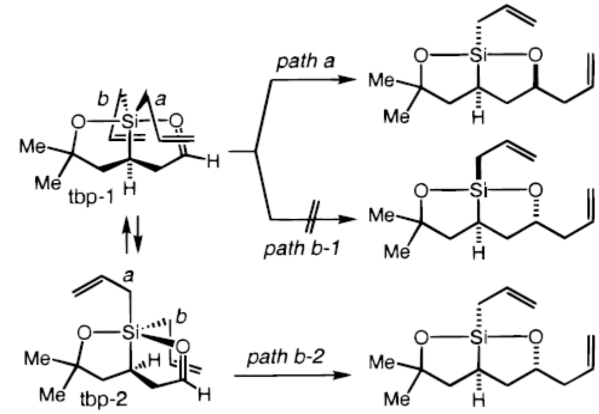
Coelho, P. J.; Blanco, L. *Tetrahedron* **2003**, *59*, 2451.

For more examples, see: Fleming *et al. Chem. Rev.* **1997**, *96*, 2059.

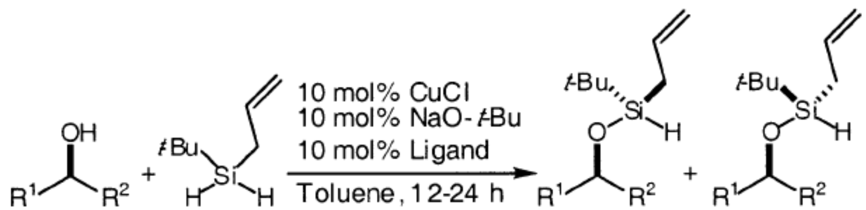
Silicon to Carbon Chirality Transfer 2



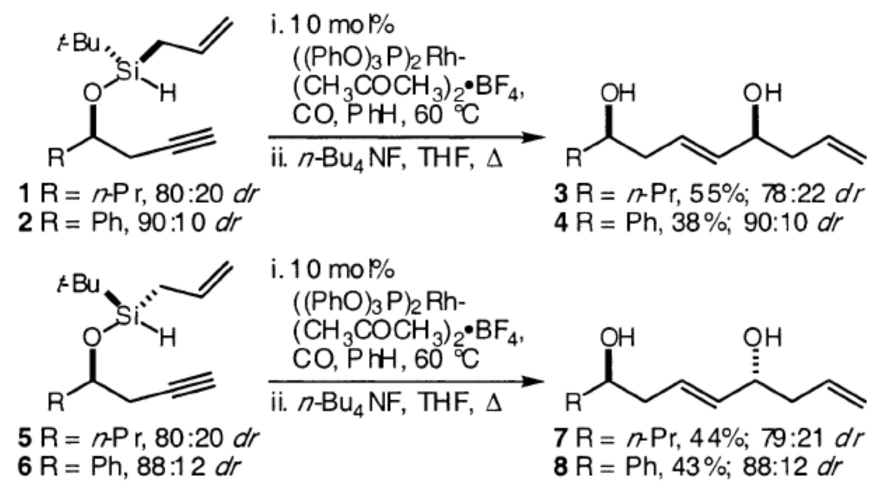
entry	R^1	R^2	R^3	d.s.[b]	*y* (%)[c]
1	H	*i*-Pr	H	77:23	59
2	H	$TBSOCH_2CH_2$	H	71:29	45
3	H	$CH_2{=}CHCH_2$	H	69:31	50
4	H	*i*-Pr	Me	92:8	59
5	Me	Me	H	93:7	65



Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

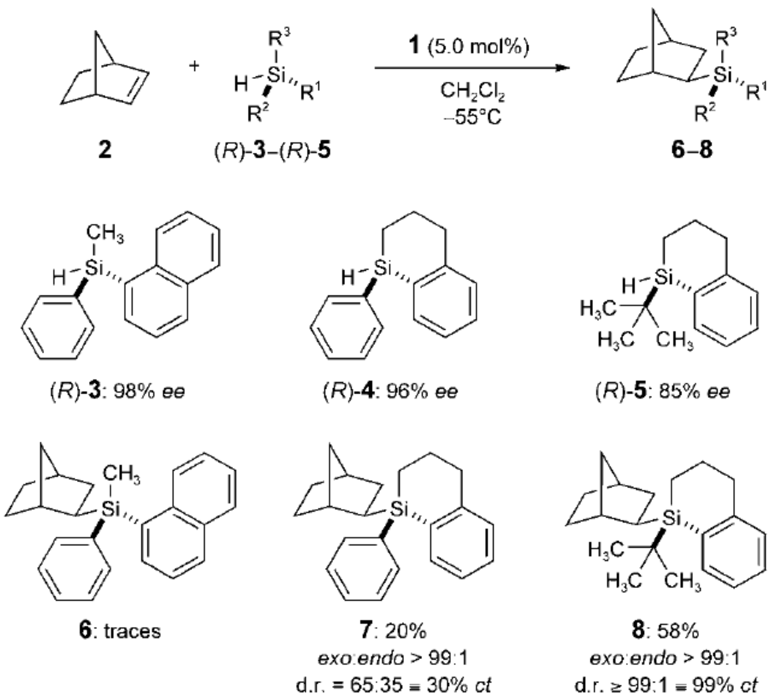


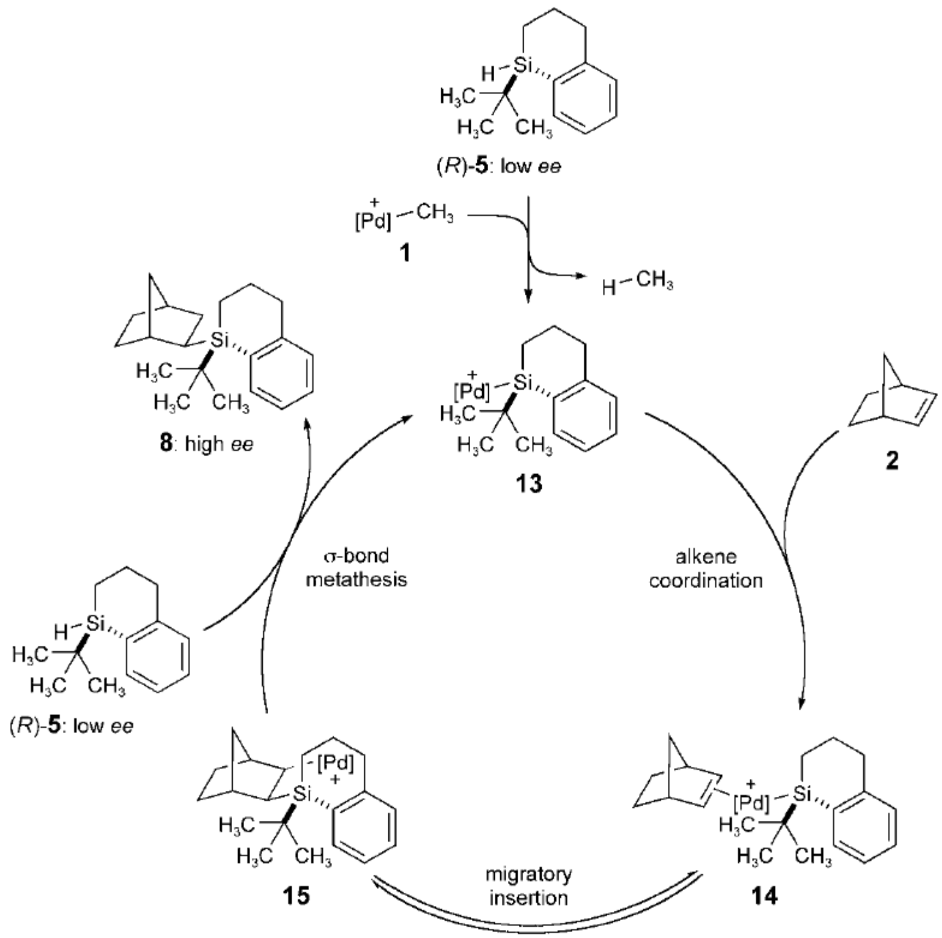
entry	R^1	R^2	ligand	yield (%)[a]	dr[b]
1	*n*-Pr	CH_2CCH	(*R*,*R*)-BDPP	75	80:20
2	*n*-Pr	CH_2CCH	(*S*,*S*)-BDPP	89	20:80
3	CH_2CCH	*i*-Pr	(*R*,*R*)-BDPP	91	82:18
4	CH_2CCH	*i*-Pr	(*S*,*S*)-BDPP	93	36:64
5[c]	Ph	CH_2CCH	(*R*,*R*)-BDPP	83	90:10
6[c]	Ph	CH_2CCH	(*S*,*S*)-BDPP	82	12:88
7[c]	Et	Ph	(*R*,*R*)-BDPP	99	78:22
8[c]	Et	Ph	(*S*,*S*)-BDPP	99	12:88

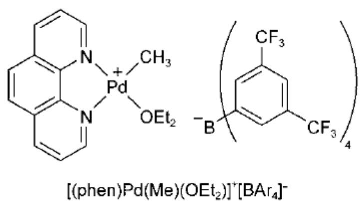


Leighton *et al. J. Am. Chem. Soc*. **2003**, *125*, 1190.

Silicon to Carbon Chirality Transfer 3





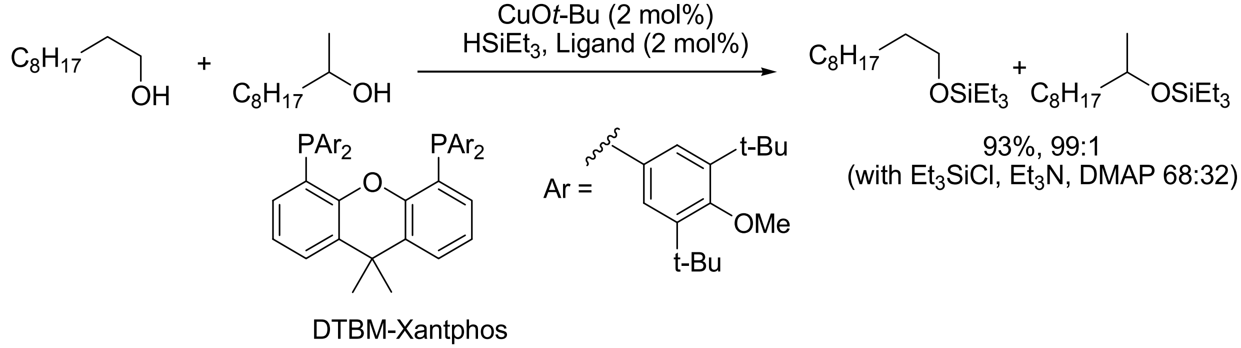


1

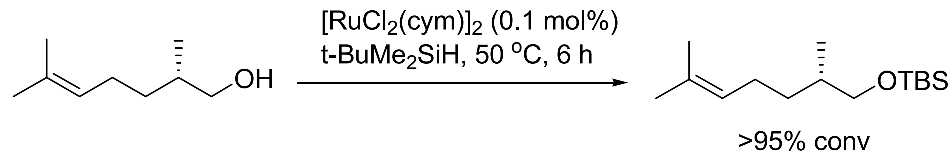
Oestreich, M.; Rendler S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1661.

Dehydrogenative Alcohol Silylation

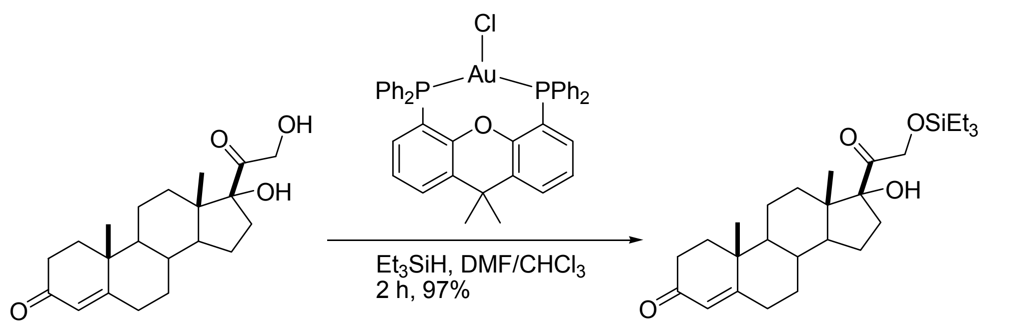
First efficient system: $[(Ph_3P)_3CuH]_6$ (Lorentz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267)



Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett.* **2005**, *7*, 1869.



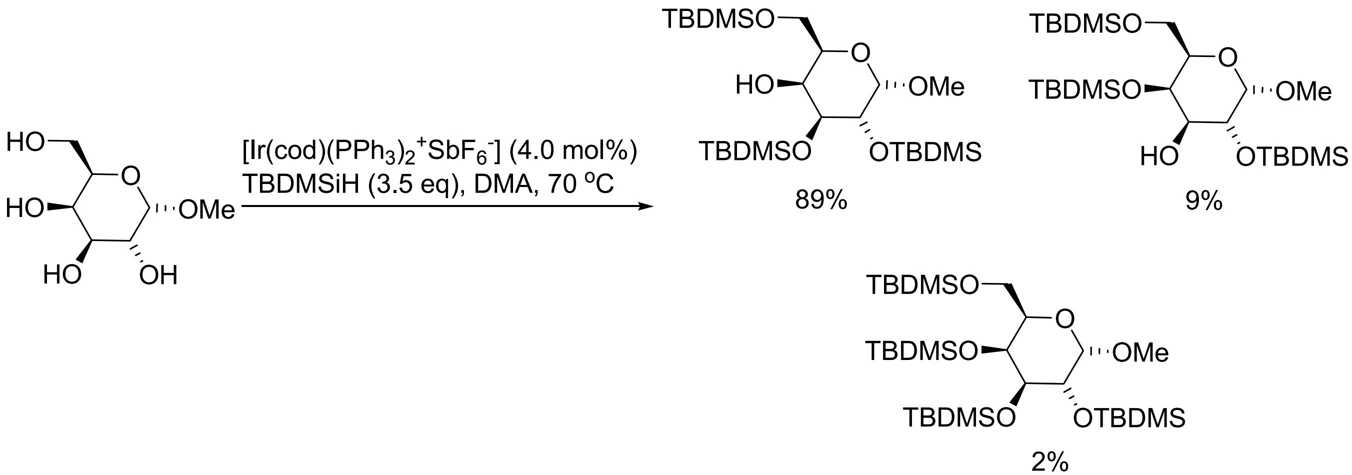
Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773.

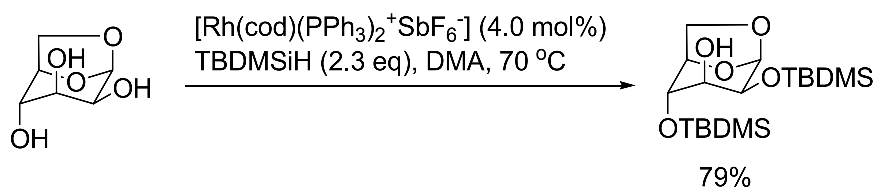


compatibile functional groups:
alkene, alkane, -Cl, -Br, ester,
ketone, aldehyde, carbamate, enone

Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* **2005**, *7*, 3001.

Dehydrogenative Alcohol Silylation



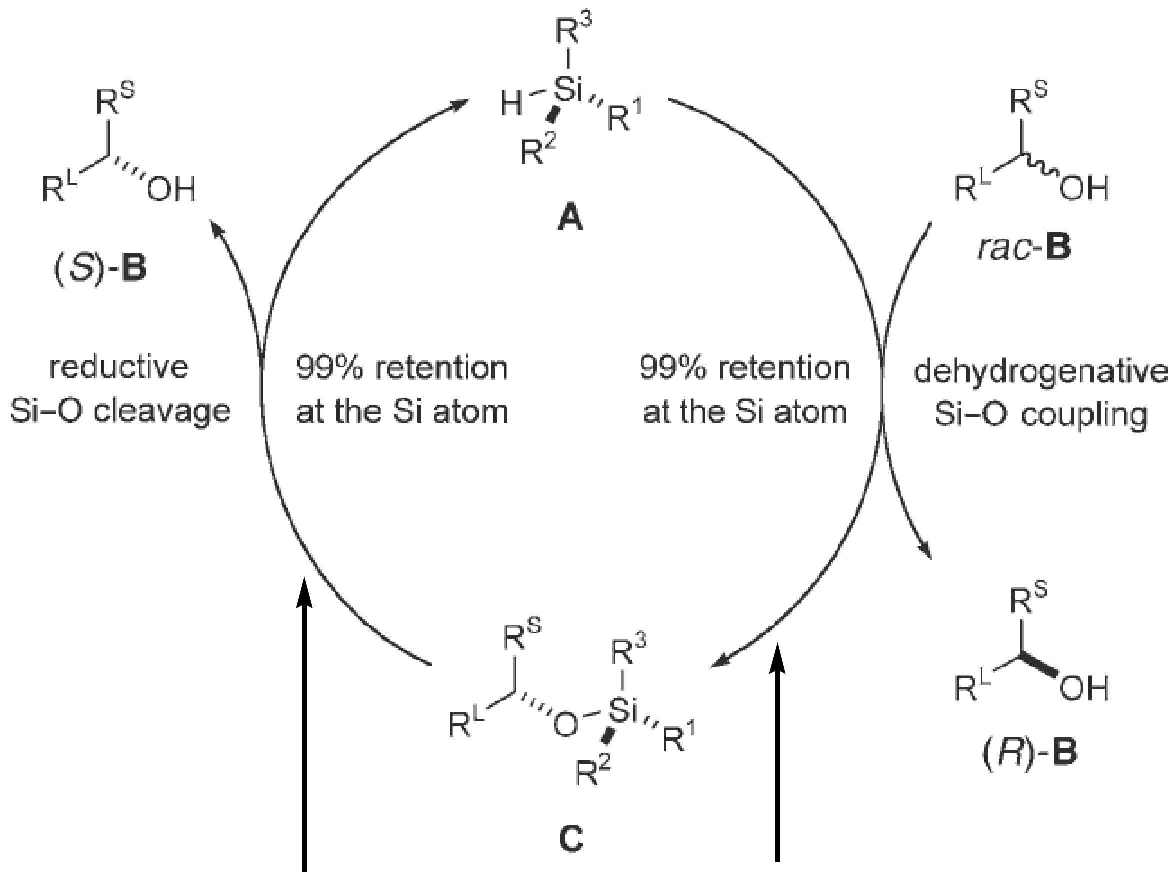


Chung, M.-K.; Schlaf, M. *J. Am. Chem. Soc.* **2005**, *127*, 18085.

Chung, M.-K.; Orlova, G.; Goddard, J. D.; Schlaf, M.;

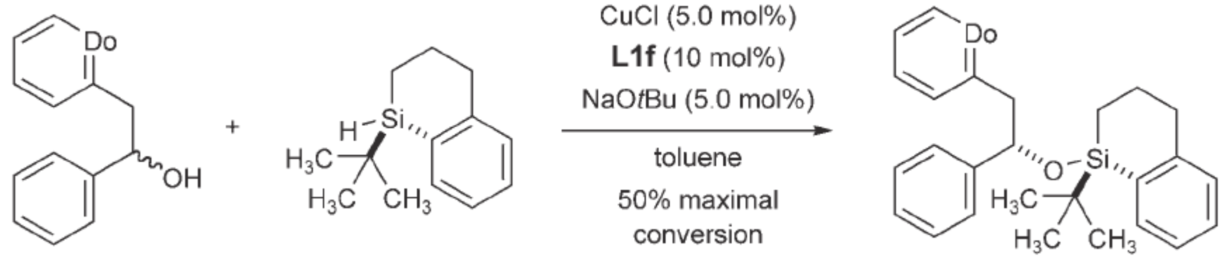
Harris, R.; Beveridge, T. J.; White, G.; Hallett, F. R. *J. Am. Chem. Soc.* **2002**, *124*, 10508.

The Concept



via *pentavalent Si* -
any scrambling of chirality?

Does always coupling of silanes proceed
with *retention* at the Si atom?

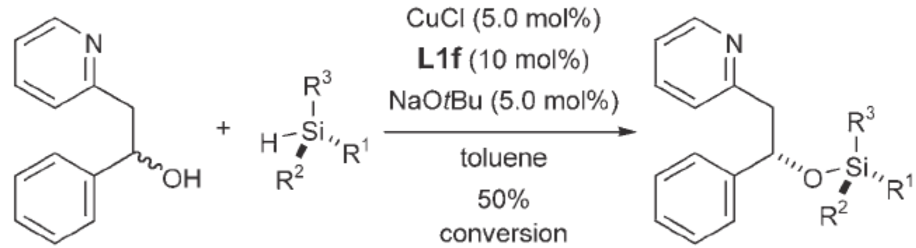


rac-**4** (Do = CH) *rac*-**6** (Do = N) — 1.0 equiv

(${}^{Si}R$)-**1** — 0.50 equiv

(${}^{Si}S,S$)-**5** (Do = CH): 30% conversion, 50°C for 30 h, d.r. = 60:40

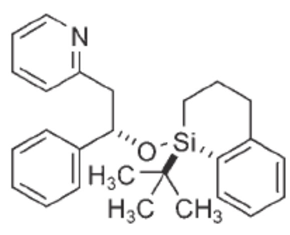
(${}^{Si}S,S$)-**7** (Do = N): 50% conversion, 20°C for 20 h, d.r. = 92:8



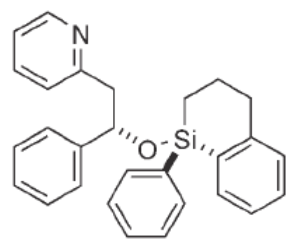
rac-**6** — 1.0 equiv

(${}^{Si}R$)-**1–3** — 0.50 equiv

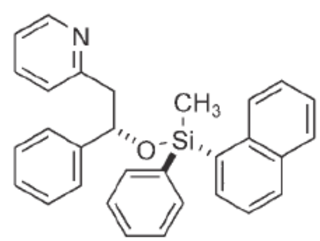
(${}^{Si}S,S$)-**7–9**



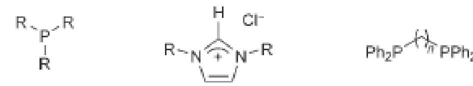
(${}^{Si}S,S$)-**7**: 99%
20°C for 8 h
d.r. = 92:8

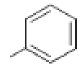
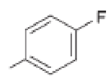
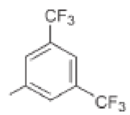
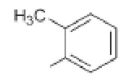
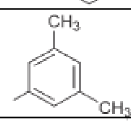
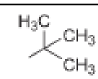
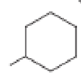
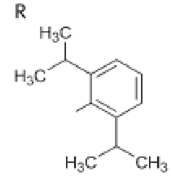
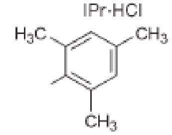


(${}^{Si}S,S$)-**8**: 99%
20°C for 4 h
d.r. = 66:34

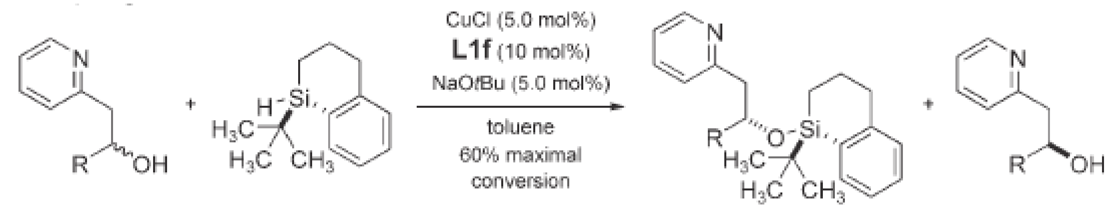


(${}^{Si}S,S$)-**9**: 99%
20°C for 3 h
d.r. = 57:43

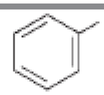
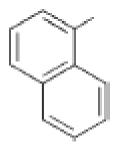
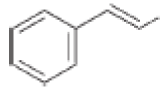
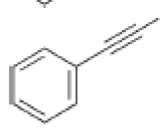
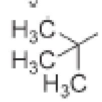


Entry	Ligand L			L/CuCl	T [°C]	t [h]	d.r.[b]	Conv. [%][c]
	L1	R						
1	**L1a**			2:1	20	48	90:10	42
2	**L1b**			2:1	50	48	89:11	37
3	**L1c**			2:1	70	60	83:17	38
4	**L1d**			2:1	70	60	86:14	34[d]
5	**L1e**			2:1	20	–	–	–[e]
6	**L1f**			2:1	20	20	92:8	50
7	**L1g**			1:1[f]	20	24	81:19	33
8	**L1h**			2:1	50	6	75:25	21[e]
	L2	R						
9[g]	**L2a**	 IPr·HCl		1:1	85	2	55:45	10
10[g]	**L2b**	 IMes·HCl		1:1	60	2	76:24	40
	L3[h]		n					
11	**L3a**	(dppm)	1	1:1	45	48	82:18	32
12	**L3b**	(dppe)	2	1:1	45	48	87:13	20
13	**L3c**	(dppp)	3	1:1	45	48	80:20	20
14	**L3d**	(dppb)	4	1:1	45	48	79:21	18

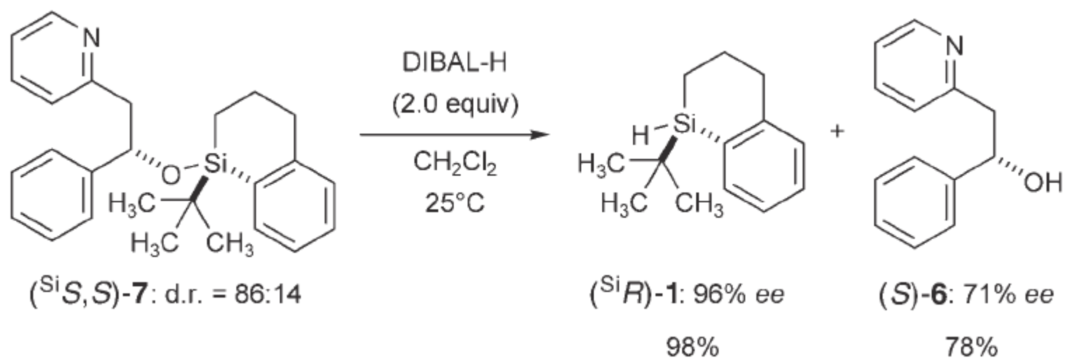
Scope of the Silane Resolution



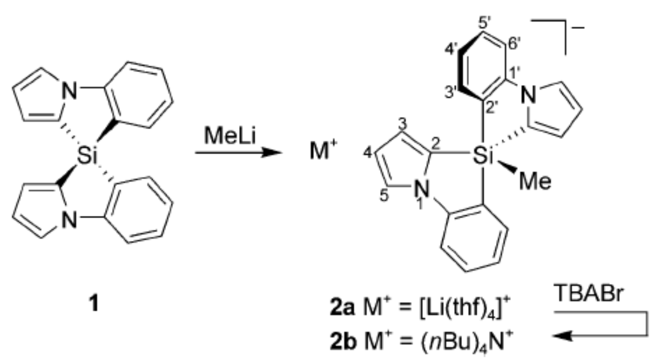
rac-**6**, *rac*-**10**–*rac*-**15** (1.0 equiv) + (^{Si}R)-**1** (0.60 equiv) → ($^{Si}S,S$)-**7**, ($^{Si}S,S$)-**16**–($^{Si}S,S$)-**19**, ($^{Si}S,R$)-**20**, ($^{Si}S,S$)-**21** + (*R*)-**6**, (*R*)-**10**–(*R*)-**13**, (*S*)-**14**, (*R*)-**15**

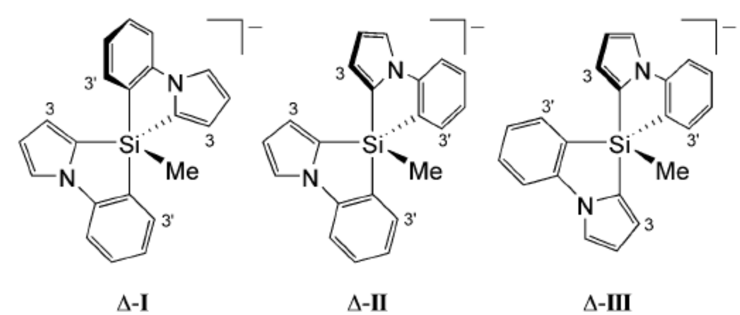
Entry	Alcohol	R	Silane (^{Si}R)-1 *ee* [%][b]	Silyl ether Product[c]	Silyl ether Yield [%][d]	d.r.[e]	Conv. [%][f]	Alcohol Product[c]	Alcohol Yield [%][d]	*ee* [%][g] ([α]D)[h]
1	*rac*-**6**		96	($^{Si}S,S$)-**7**	99	86:14	56	(*R*)-**6**	99	84 (+)
2	*rac*-**10**		93	($^{Si}S,S$)-**16**	97	84:16	58	(*R*)-**10**	99	80 (+)
3	*rac*-**11**		95	($^{Si}S,S$)-**17**	92	88:12	50	(*R*)-**11**	99	70 (+)
4	*rac*-**12**		93	($^{Si}S,S$)-**18**	99	87:13	57	(*R*)-**12**	99	74 (−)
5[i]	*rac*-**13**		93	($^{Si}S,S$)-**19**	99[i]	74:26	64[j]	(*R*)-**13**	84[i]	89 (−)
6	*rac*-**14**	H_3C	93	($^{Si}S,R$)-**20**	98	76:24	58	(*S*)-**14**	98	73 (+)
7[k]	*rac*-**15**		94	($^{Si}S,S$)-**21**	87	94:6[l]	46	(*R*)-**15**	99	68 (−)[l]

Final Deprotection



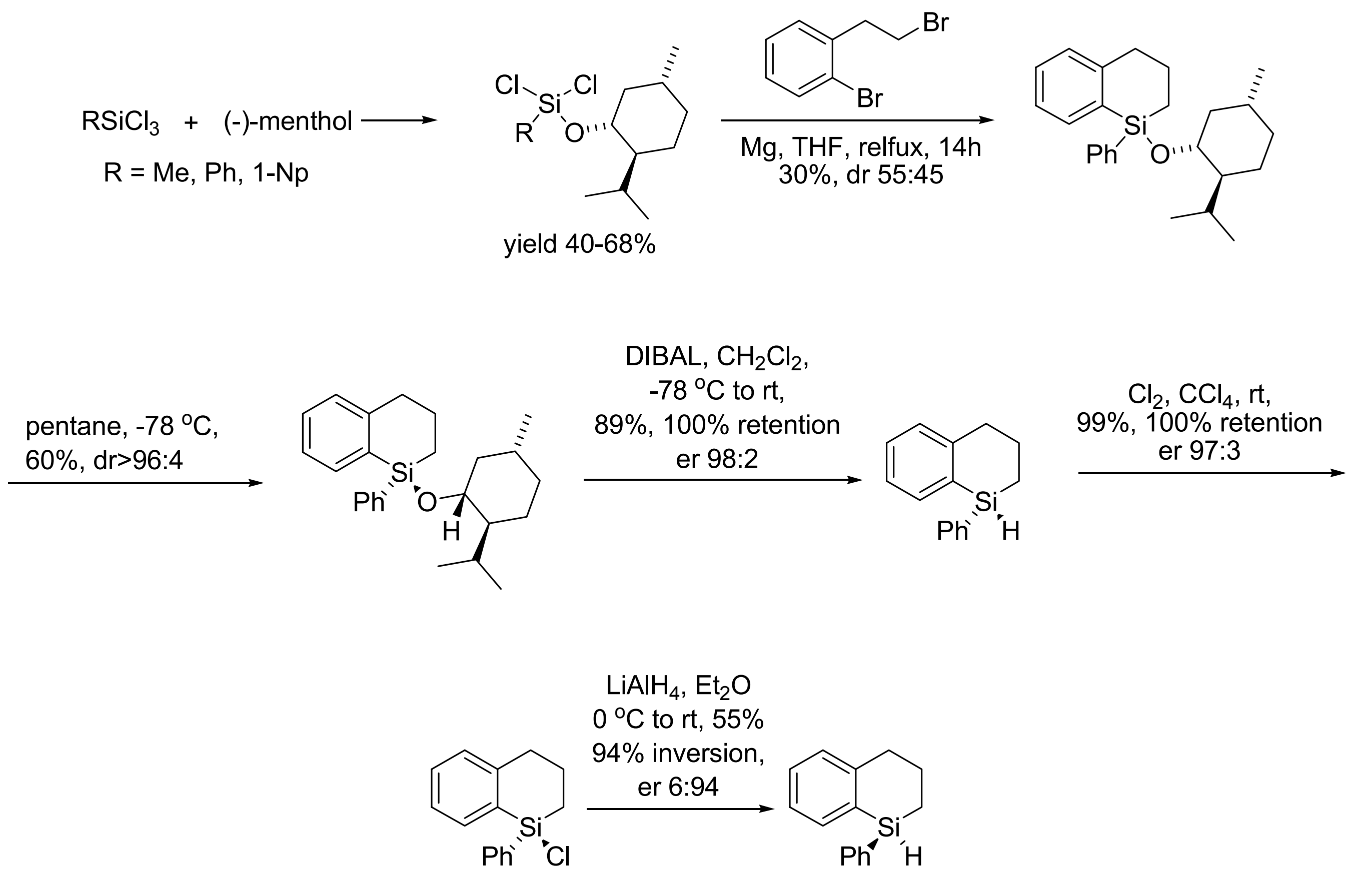
However, pentaorganosilicates are prone to undergo pseudorotation





See: Lammertsma *at al. Angew. Chem. Int. Ed.* **2004**, *43*, 3440.

Synthesis of Chiral Silanes



Oestreich, M.; Schmist, U. K.; Auer, G.; Keller, M. *Synthesis* **2003**, 2725.

See also: Sommer *at al. J. Am. Chem. Soc.* **1964**, *86*, 3271.

Conclusions

- Chiral silanes have been successfully applied in the kinetic resolution of secondary alcohols using Cu-catalyzed dehydrogenative coupling.

- Only cyclic silanes have been found to transfer chirality efficiently; the same observation is also true for the kinetic resolution process.

- Future developments may involve extension of the scope, applications in related reduction processes.