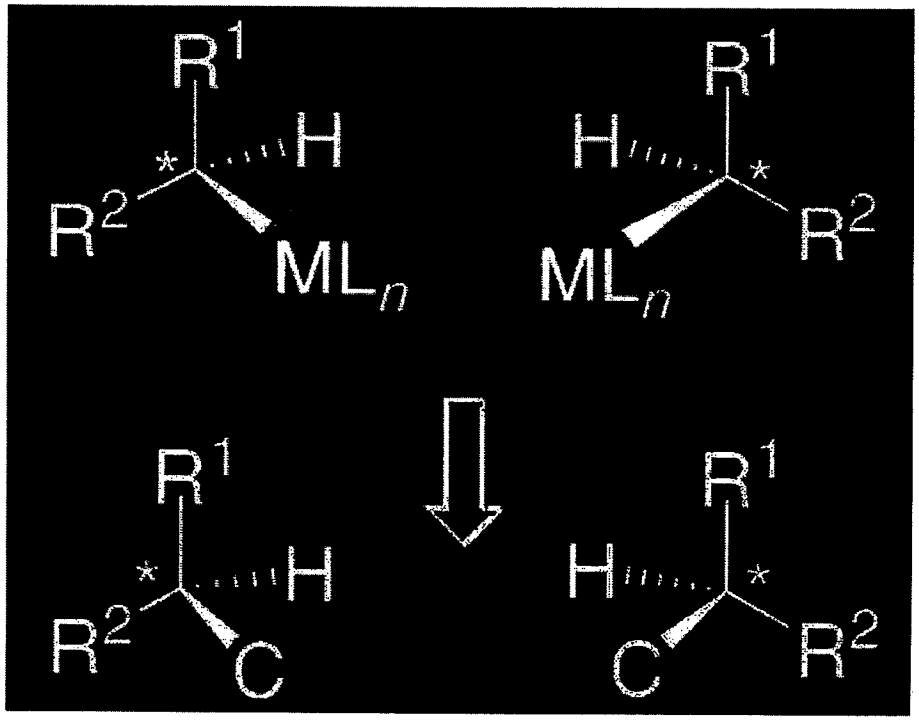
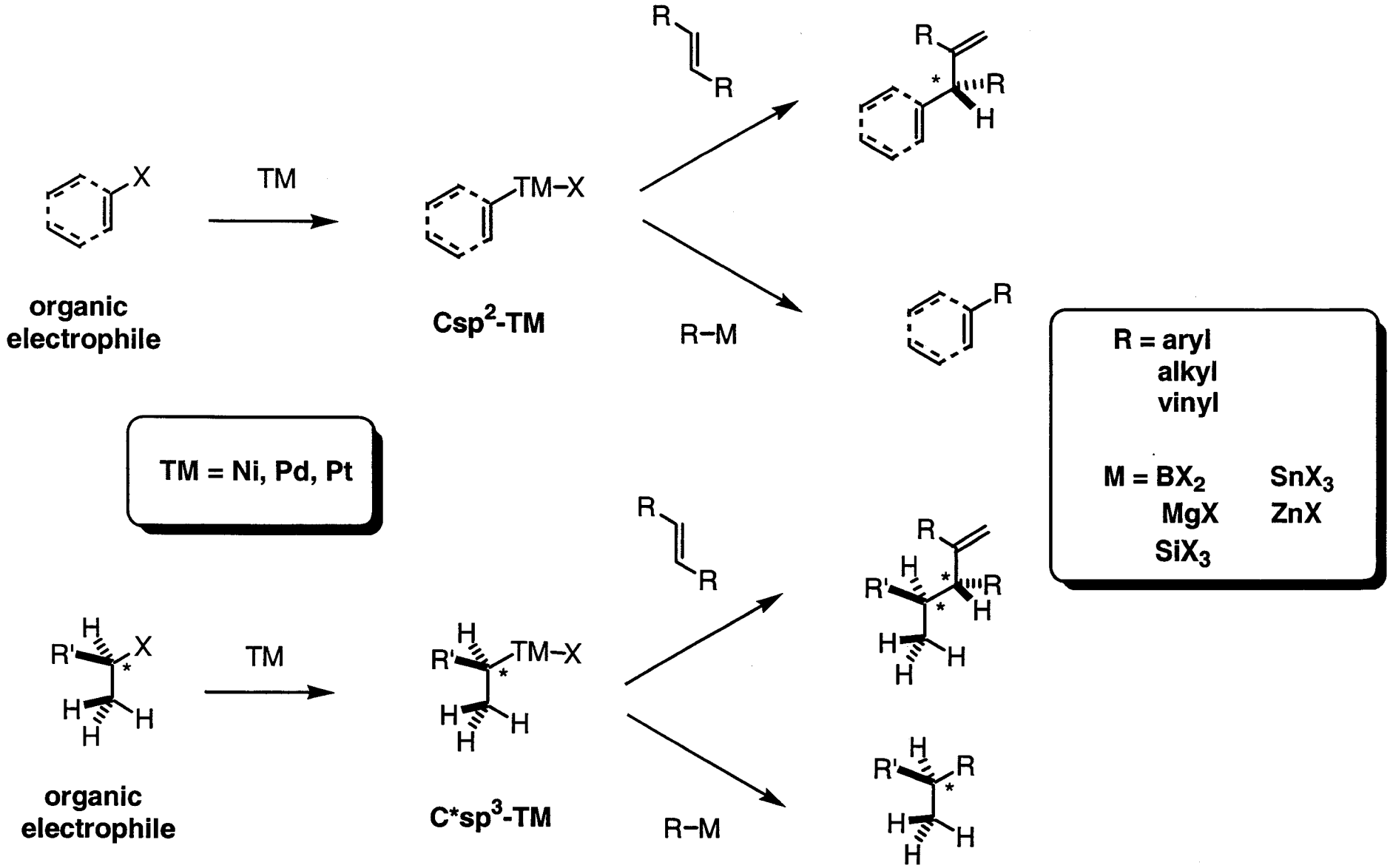
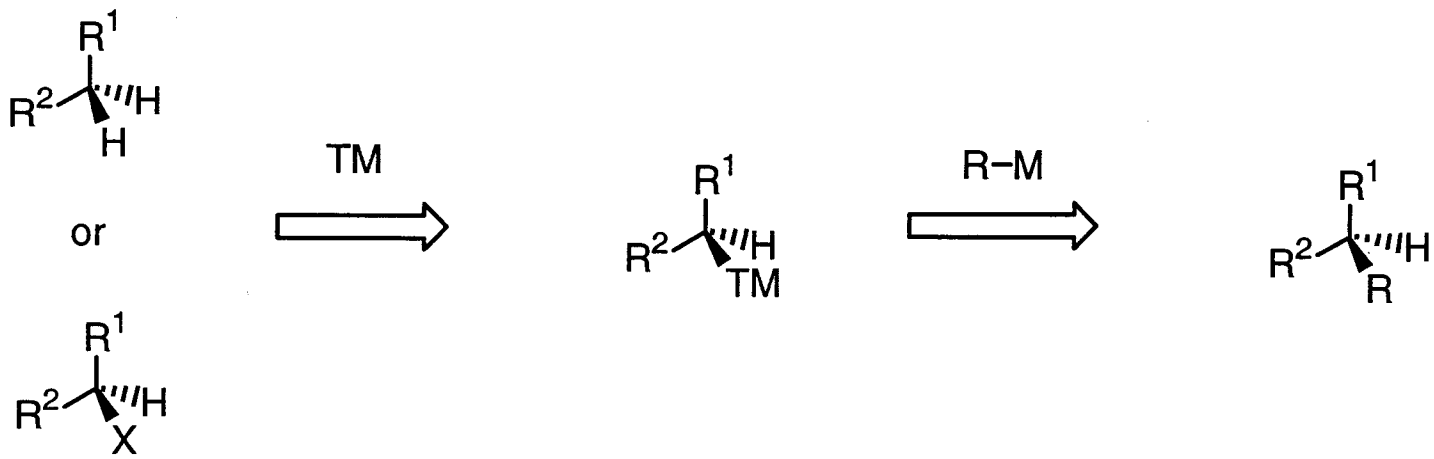
Organometallics With a Transition Metal-Bonded sp^3-Hybridized Stereogenic Carbon Atom: Development of New Tools For Asymmetric Synthesis



John R. Heemstra Jr.
SED Group Meeting
July 7, 2004


organic electrophile
TM
Csp2-TM
R–M
TM = Ni, Pd, Pt
organic electrophile
TM
C*sp3-TM
R–M
R = aryl
alkyl
vinyl
M = BX2
SnX3
MgX
ZnX
SiX3

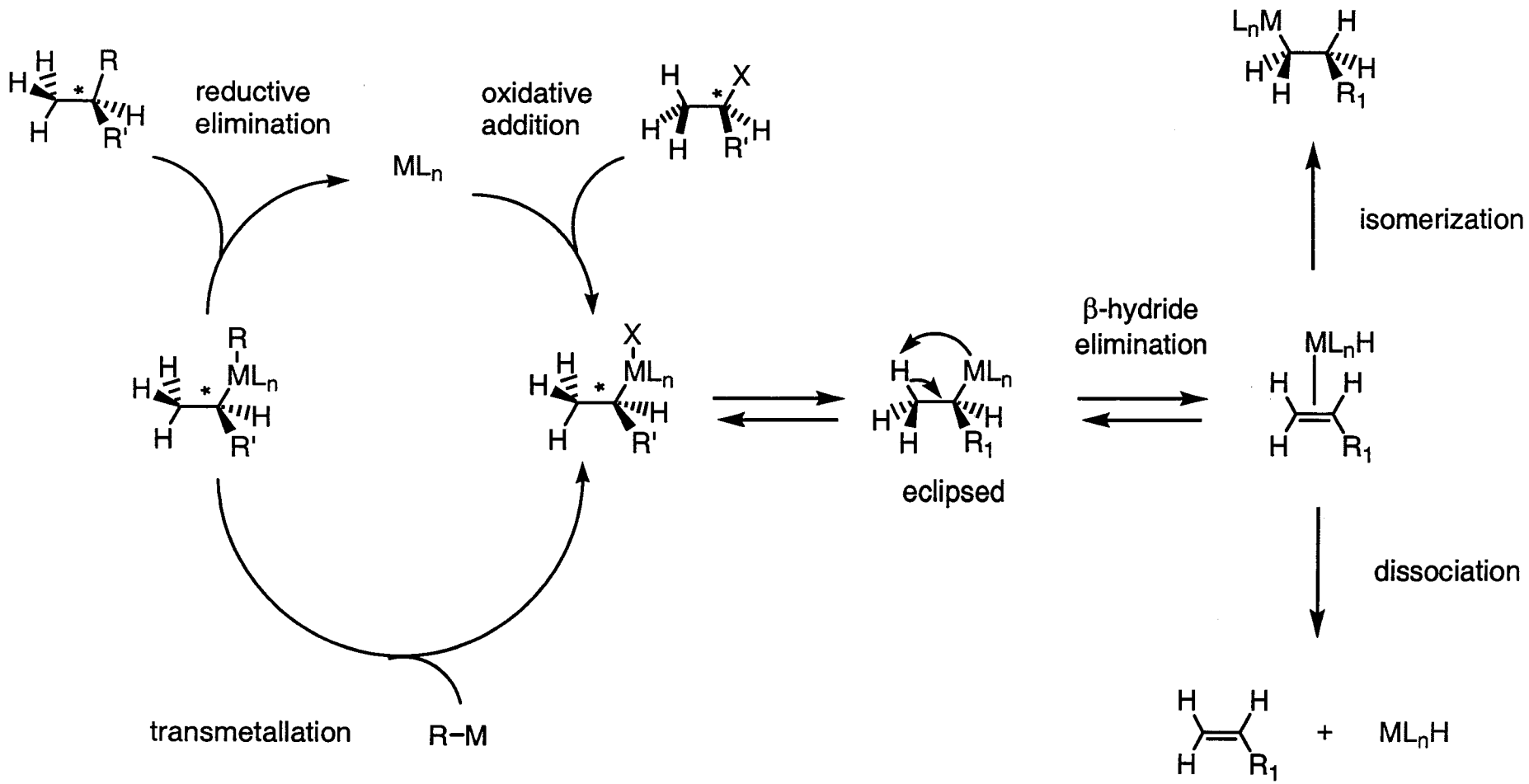


Stability of C*sp^3-TM center

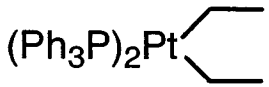
Stereochemical Course of Csp^3-TM Bond Formation

Stereochemical Course Of Csp^3-C Bond Formation

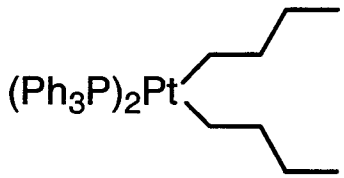
Methodology For Asymmetry Transfer


reductive elimination
oxidative addition
ML$_n$
transmetallation
R–M
eclipsed
β-hydride elimination
isomerization
dissociation
+ ML$_n$H

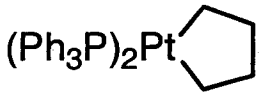
Thermal Decomposition of Bis(phosphine)platinum(II) Metallocycles



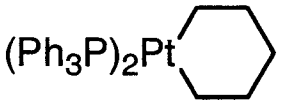
$4.5 \times 10^4\ s^{-1}$
at 60 °C



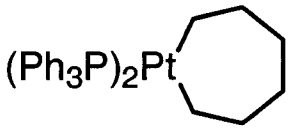
$4.1 \times 10^4\ s^{-1}$
at 60 °C



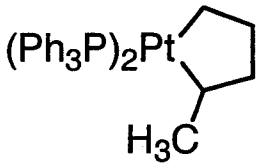
$0.54 \times 10^4\ s^{-1}$
at 120 °C



$0.40 \times 10^4\ s^{-1}$
at 120 °C



$1.7 \times 10^4\ s^{-1}$
at 60 °C

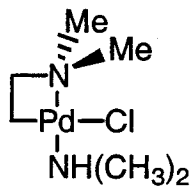


$1.0 \times 10^4\ s^{-1}$
at 120 °C

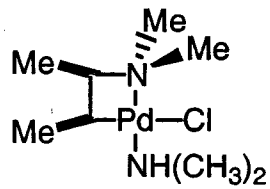
Rigid metallocycle does not allow Platinum and β-hydrogen to reach cisoid conformation

Whitesides, G. M. et.al. *J. Am. Chem. Soc.*, **1976**, *98*, 6521

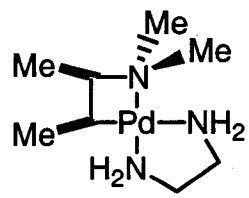
Geometrical Rigidity Around a Transition Metal Center



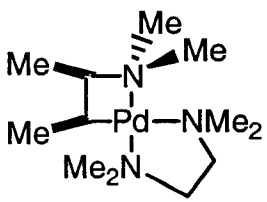
1



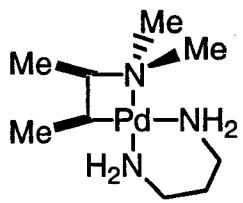
2



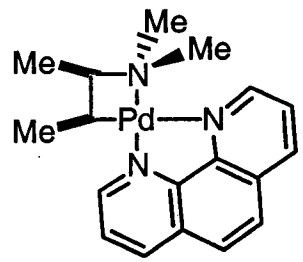
3



4



5



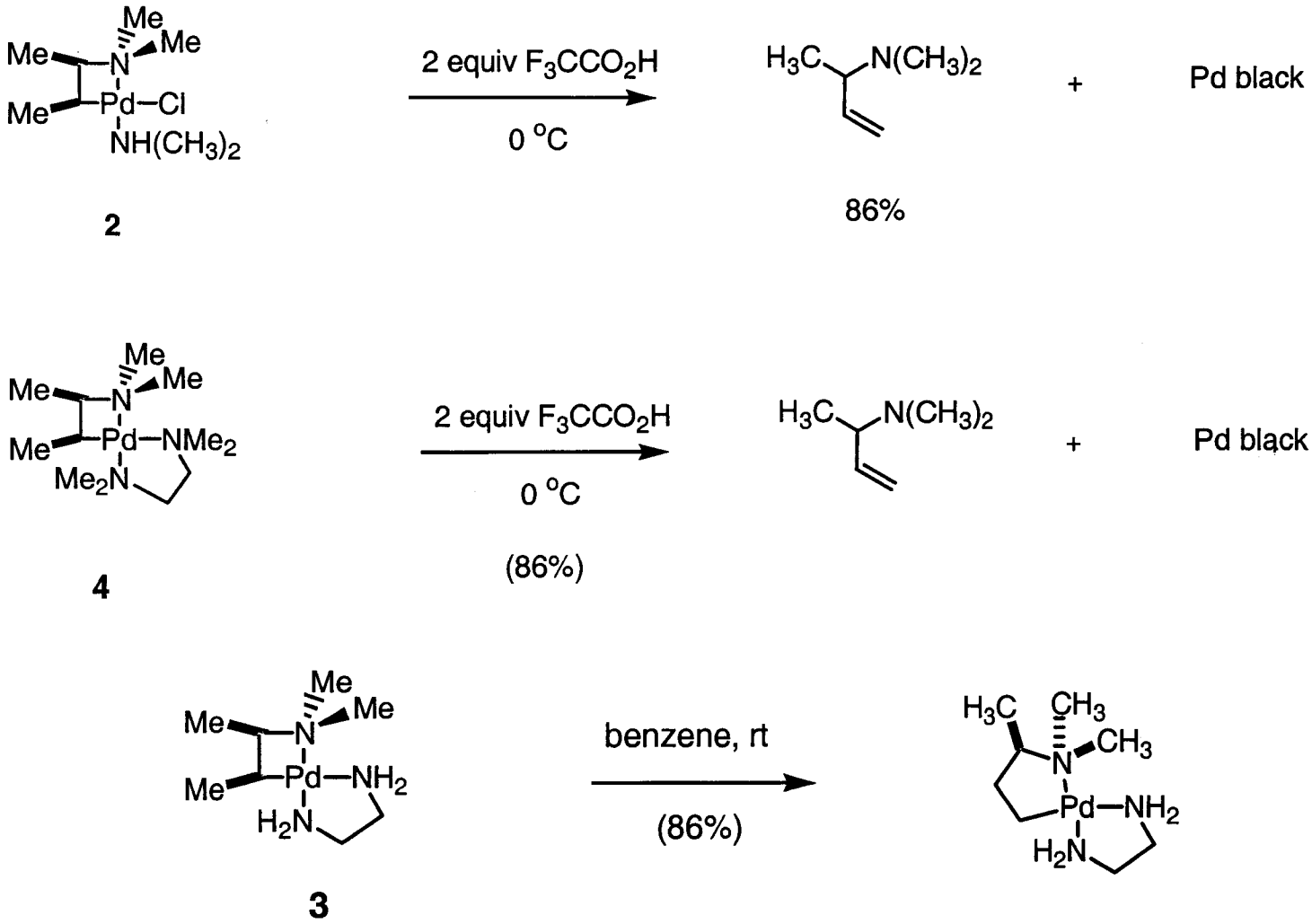
6

complex	decomposition temp, °C
1	<rt
2	68
3	80-85
4	108-109
5	76-79
5	149

<u>Stablization by geometrical rigidity around the metal center:</u>
Reluctance for the complex to undergo changes of
the bonding angles between rigid ligands and the metal

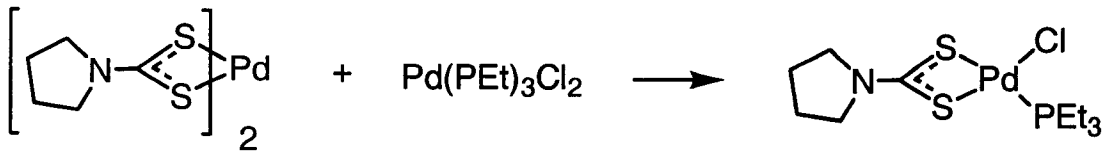
Zetterberg, K. et.al. *Organometallics*, **1991**, *10*. 3806

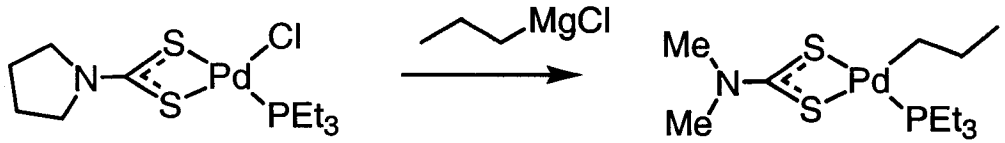
Geometrical Rigidity Around a Transition Metal Center



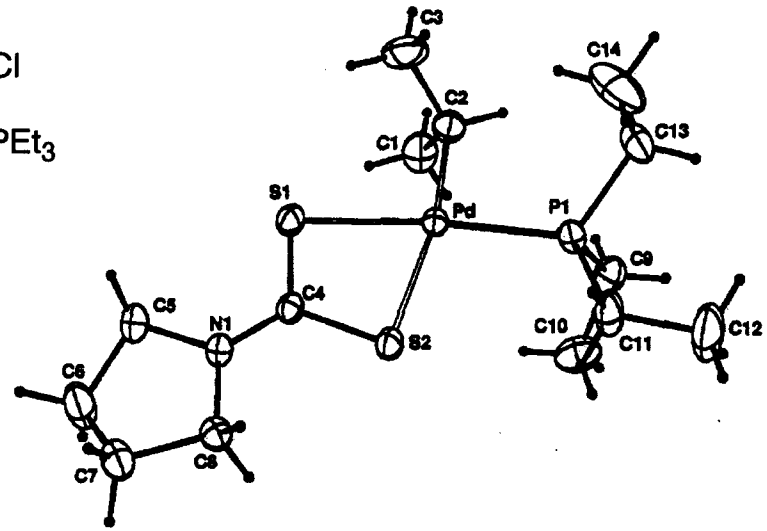
Zetterberg, K. et.al. *Organometallics*, **1991**, *10*, 3806

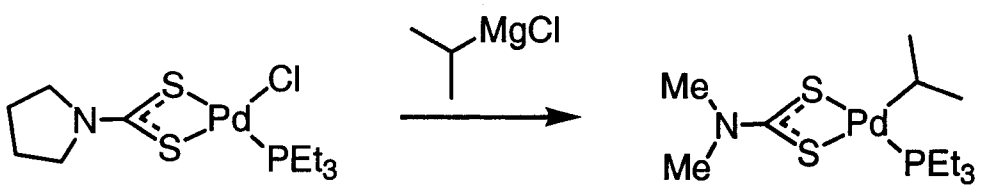
Thermally Stable Complexes Containing Acyclic Alkyl Ligands



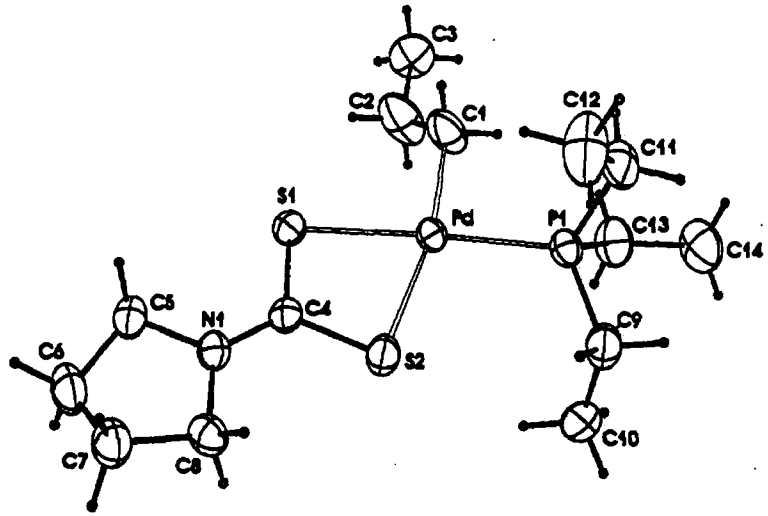


demposition in hexane at 75 °C



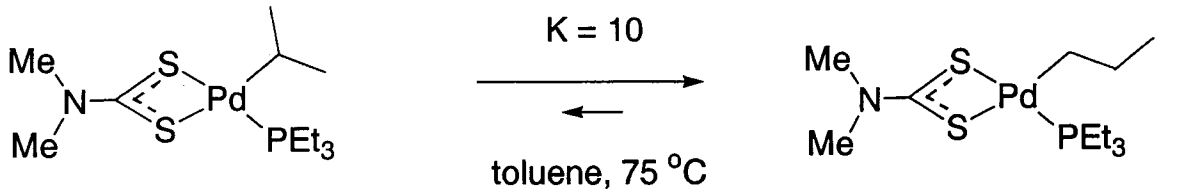


demposition in hexane at 75 °C

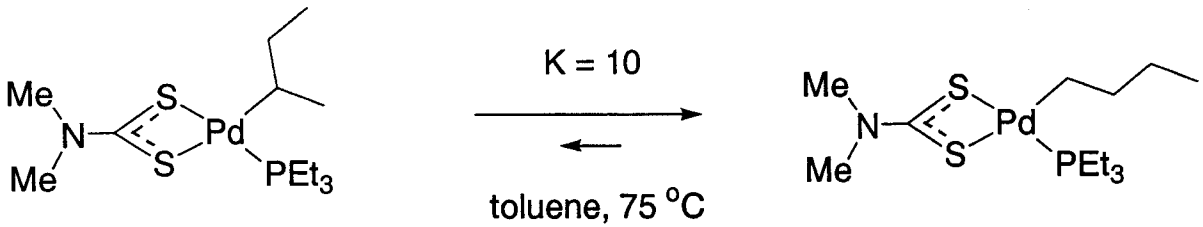


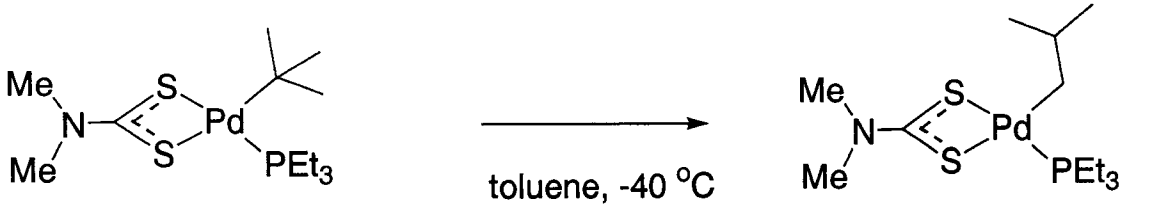
Reger, D. L. et.al. *Organometallics*, **1991**, *10*, 902

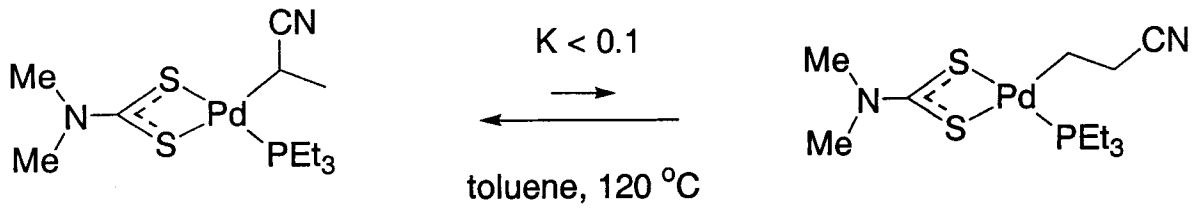
Isomerization of Alkyl Ligands



1.6 kcal/mol free energy difference between 1° and 2° in the absence of steric constrants





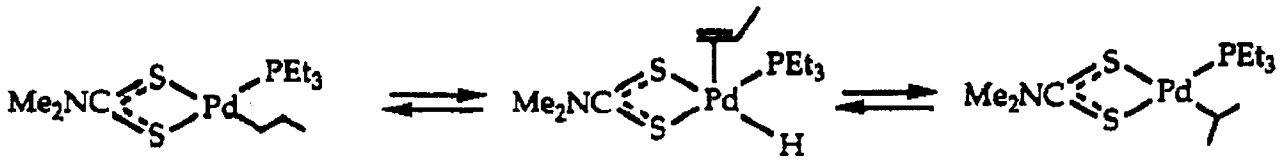


Cyanide substituent has stablizing effect on partial negative charge on carbon

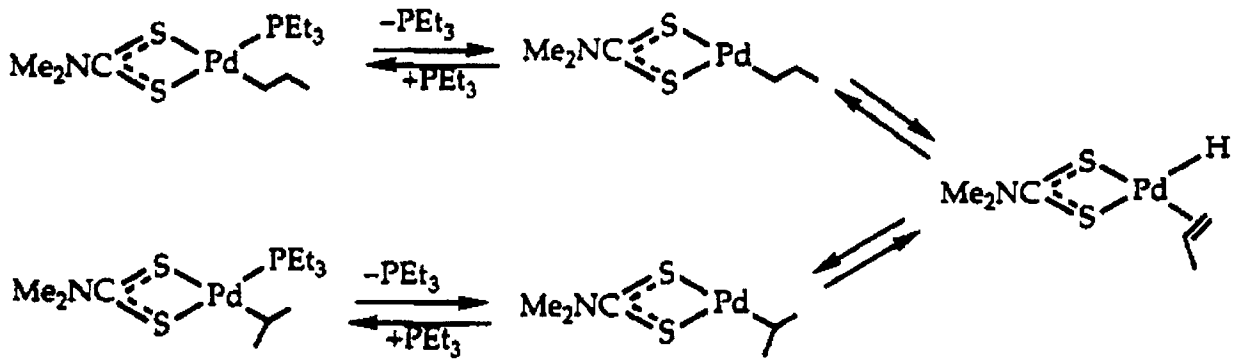
Reger, D. L. et.al. *Organometallics*, **1991**, *10*, 902

Mechanism of Isomerization Reaction

Scheme II

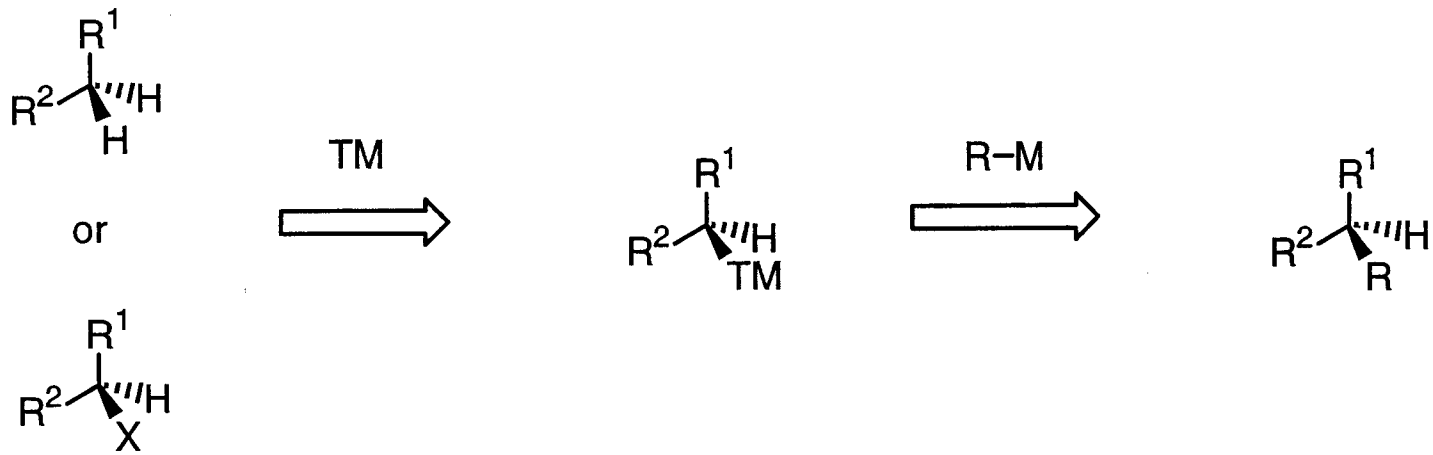


Scheme III



- Inhibition of isomerization reaction by added phosphine
- Inhibition of isomerization reaction observed in donor solvants

Reger, D. L. et.al. *Organometallics*, **1991**, *10*, 902



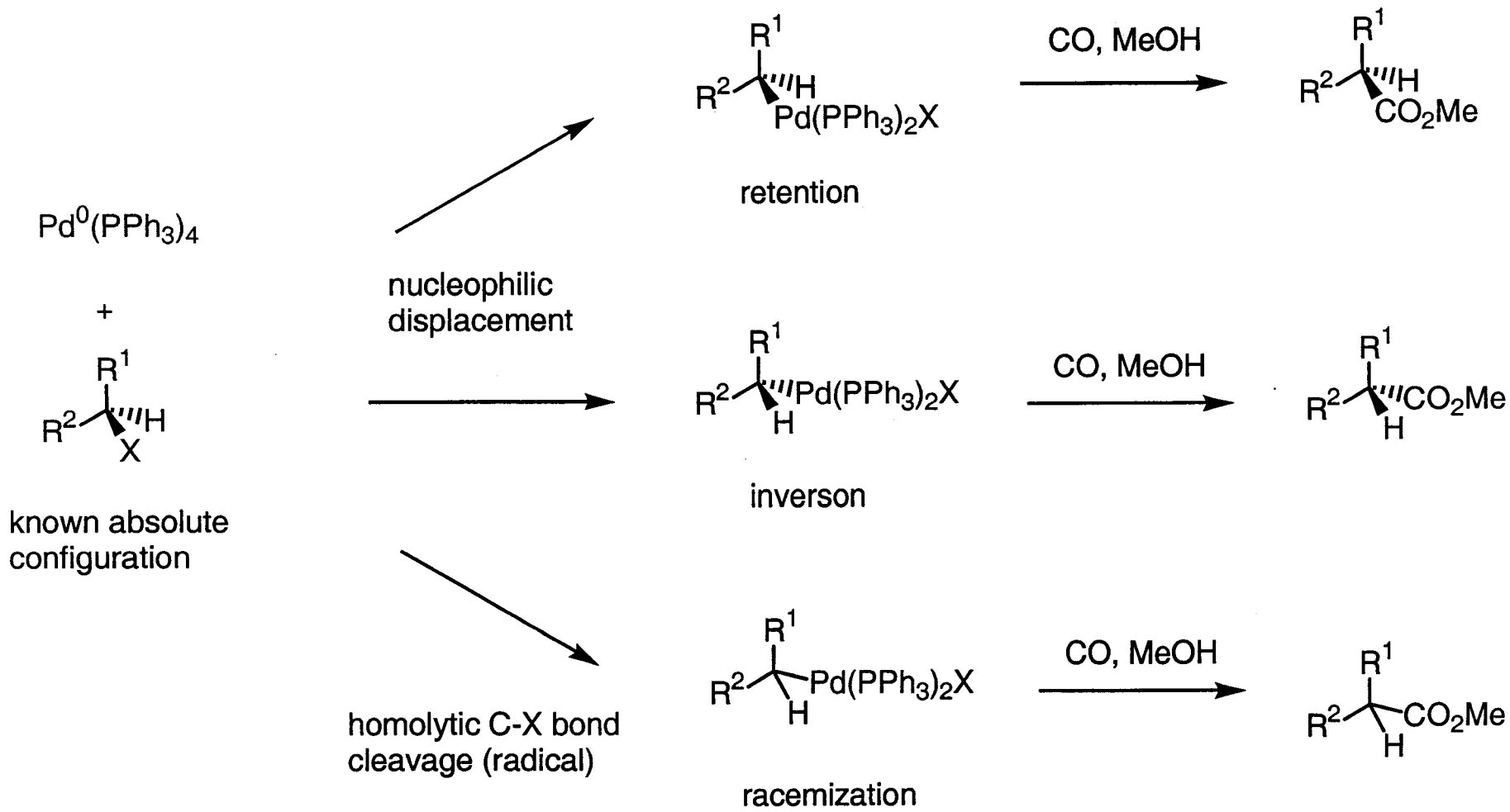
Stability of C*sp^3-TM center

Stereochemical Course of Csp^3-TM Bond Formation

Stereochemical Course Of Csp^3-C Bond Formation

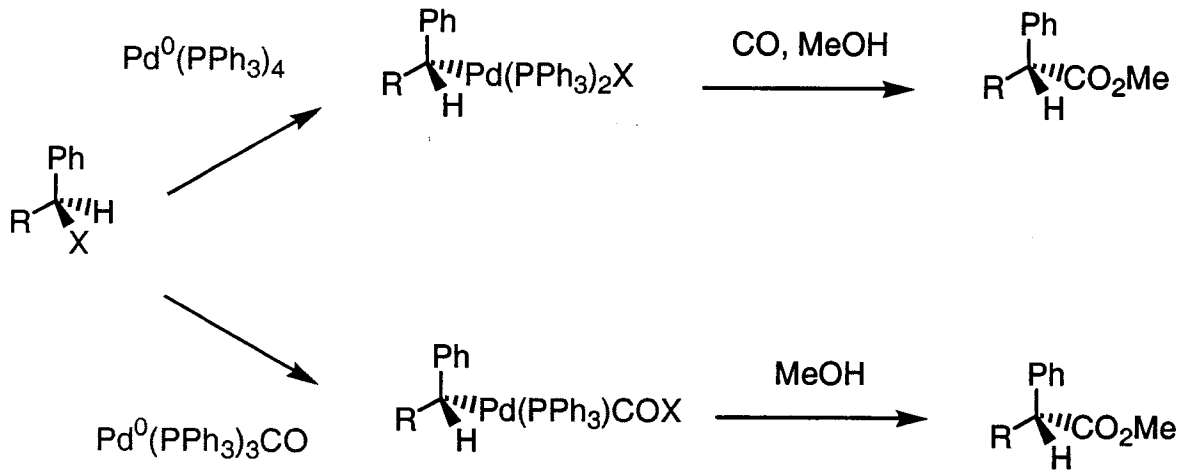
Methodology For Asymmetry Transfer

Stereochemical Course of the C*sp^3-TM Bond Formation: Oxidative Addition of *Organic Halides*



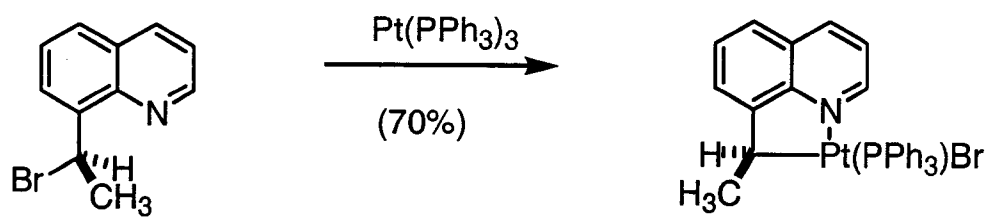
Stille, J. K. et.al. Acc. Chem. Res., **1977**, *10*, 434

Stereochemical Course of the C*sp^3-TM Bond Formation: Oxidative Addition of *Organic Halides*



P(0) complex	R	X	Net inversion
Pd^0(PPh$_3$)$_4$	D	Cl	74
Pd^0(PPh$_3$)$_4$	D	Cl	100
Pd^0(PPh$_3$)$_3$CO	D	Cl	100
Pd^0(PPh$_3$)$_4$	D	Br	69
Pd^0(PPh$_3$)$_4$	Me	Br	90

Stille, J. K. et.al. Acc. Chem. Res., **1977**, *10*, 434



$[\alpha]_D$ +17.3° (CH_2Cl_2)

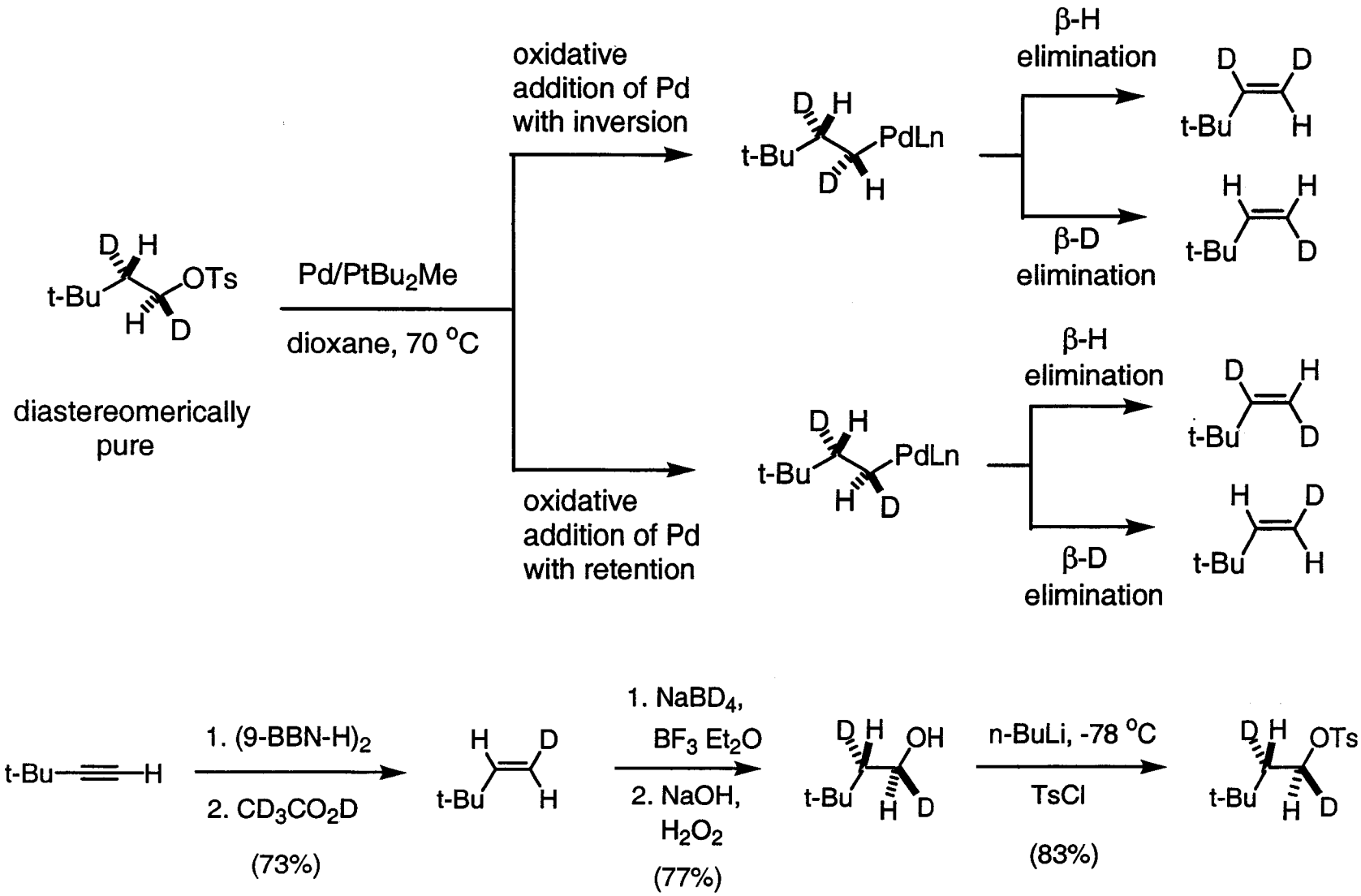
$[M]_D$ +40.8° (CH_2Cl_2)

$[\alpha]_D$ -2.8° (CH_2Cl_2)

$[M]_D$ -19.^{4o} (CH_2Cl_2)

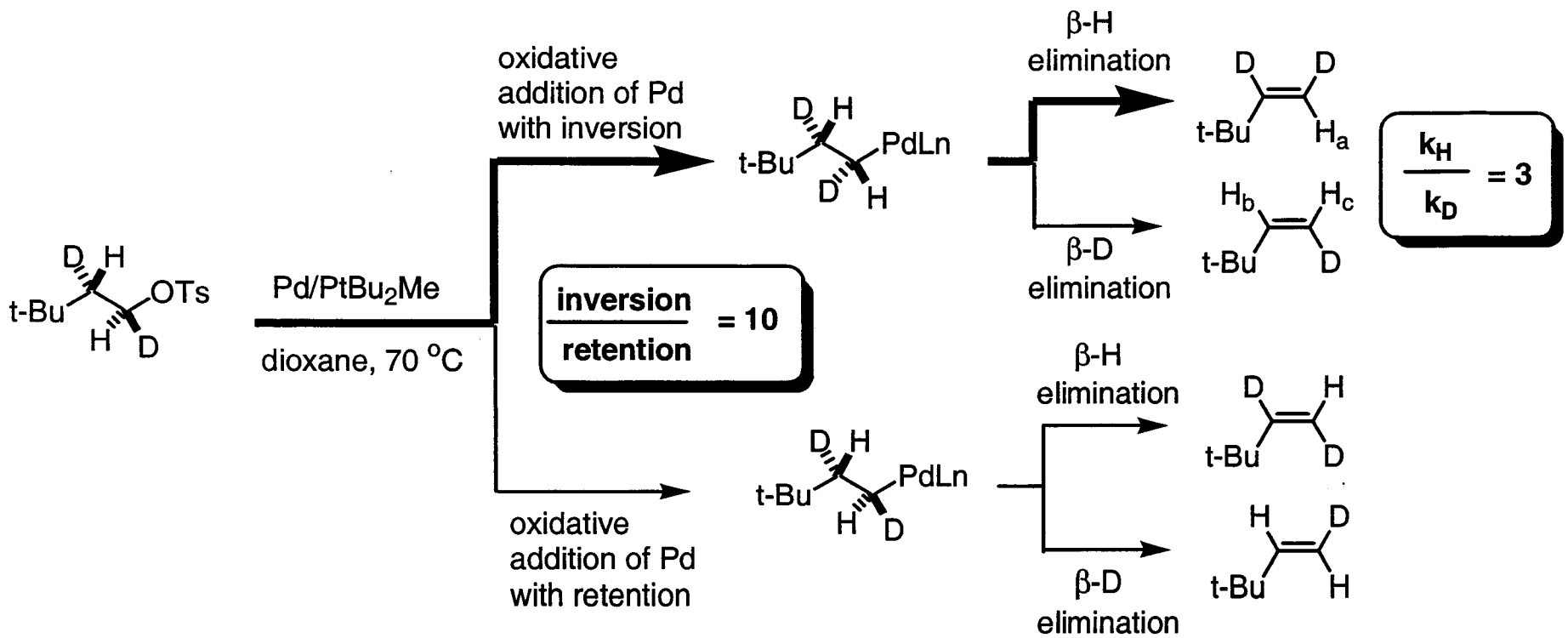
Sokolov, V. I. Inorg. Chim. Acta., **1976**, *18*, L9

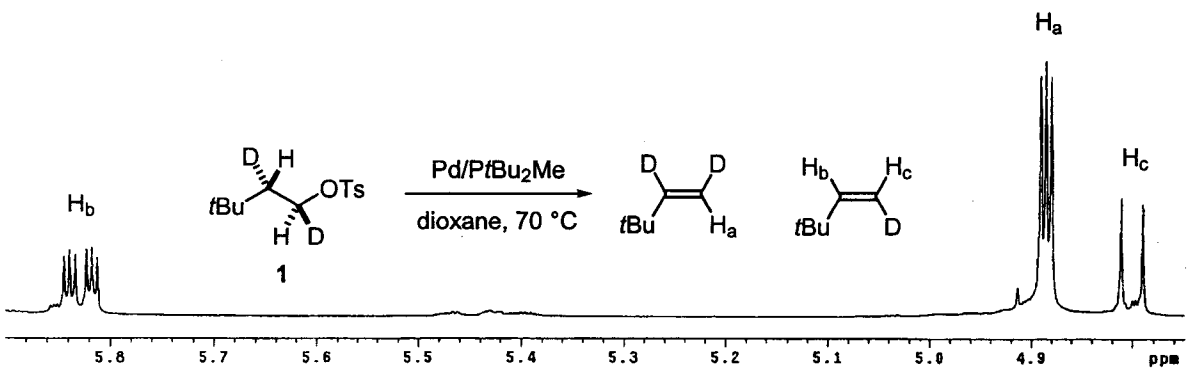
Stereochemical Course of the C*sp^3-TM Bond Formation: Oxidative Addition of *Alkyl Tosylates*



Fu, G. C. et.al. *Angew. Chem. Int. Ed.* **2002**, *41*. 3910

Stereochemical Course of the C*sp^3-TM Bond Formation: Oxidative Addition of *Alkyl Tosylates*

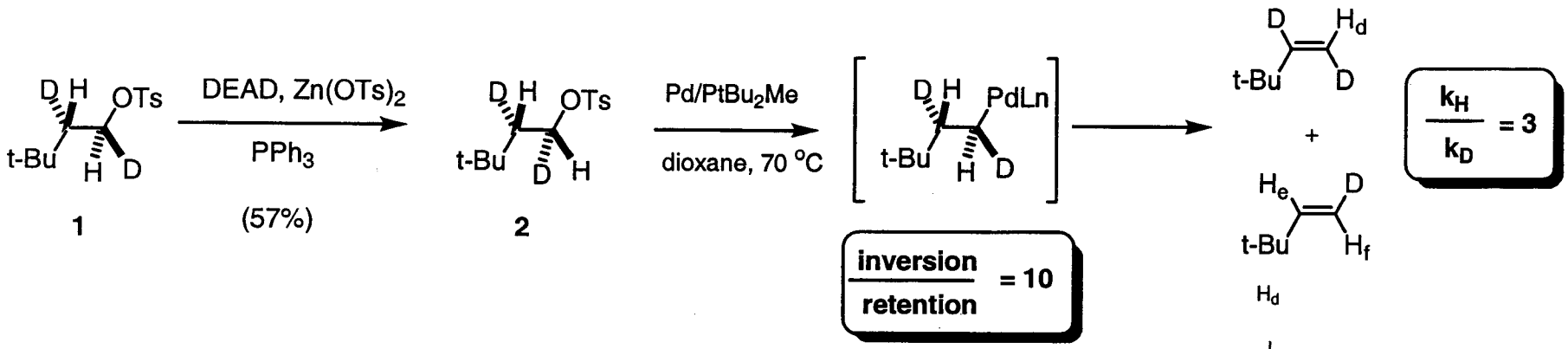


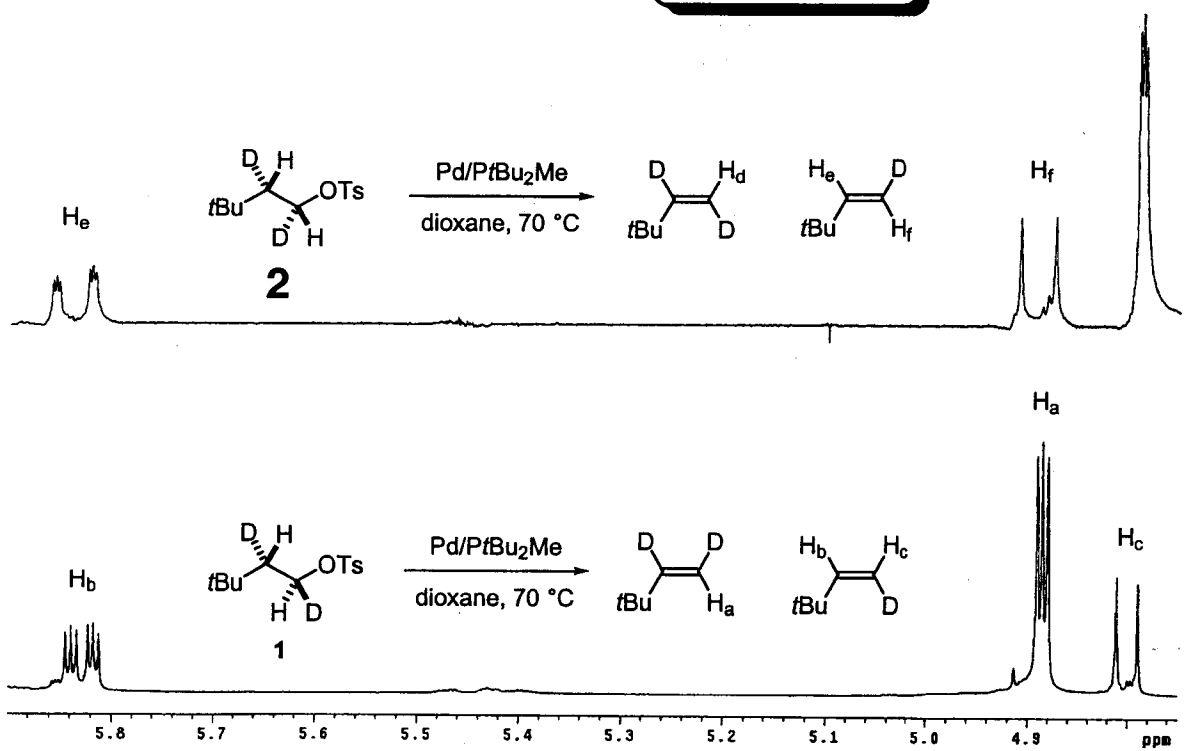


82% of [Pd(Pt-Bu$_2$Me)$_2$H(OTs)] was also isolated from the rxn.

Fu, G. C. et.al. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910

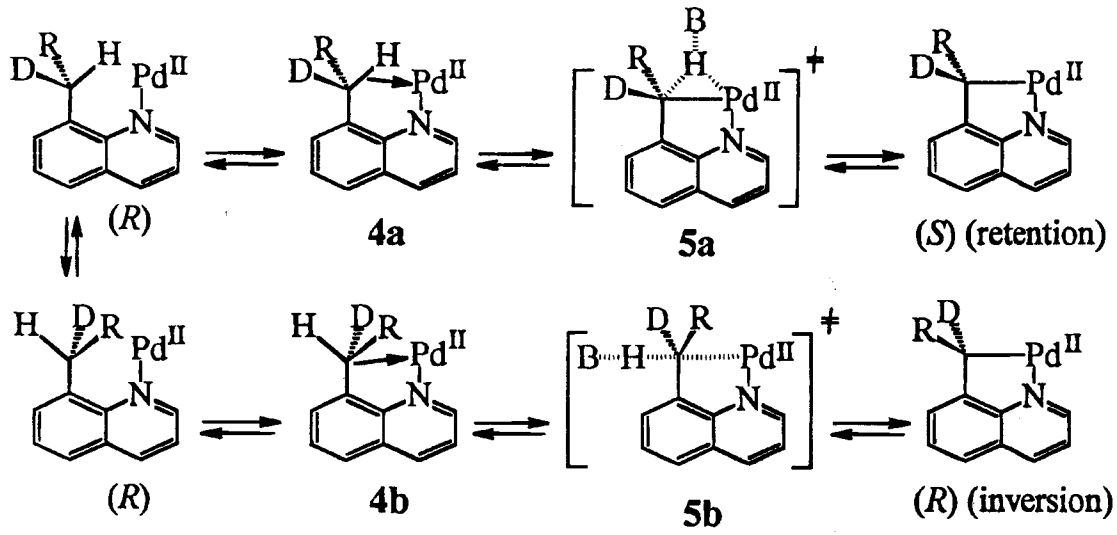
Stereochemical Course of the C*sp^3-TM Bond Formation: Oxidative Addition of *Alkyl Tosylates*

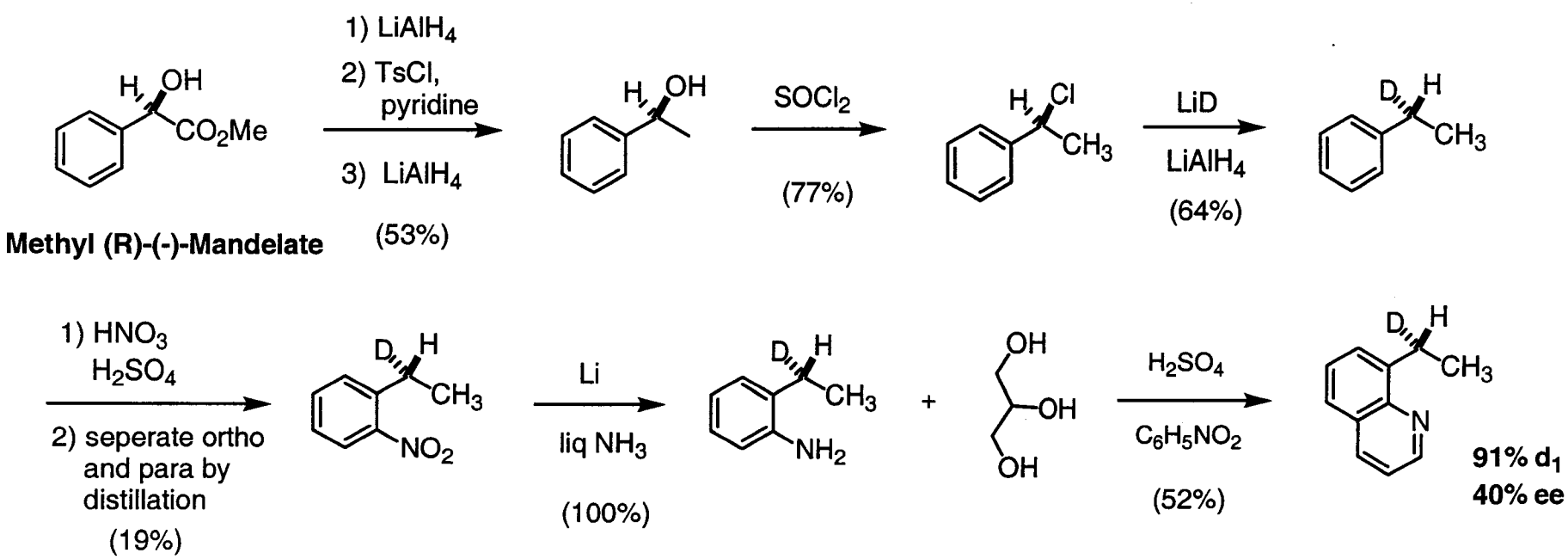




Fu, G. C. et.al. *Angew. Chem. Int. Ed.* **2002**, *41*. 3910

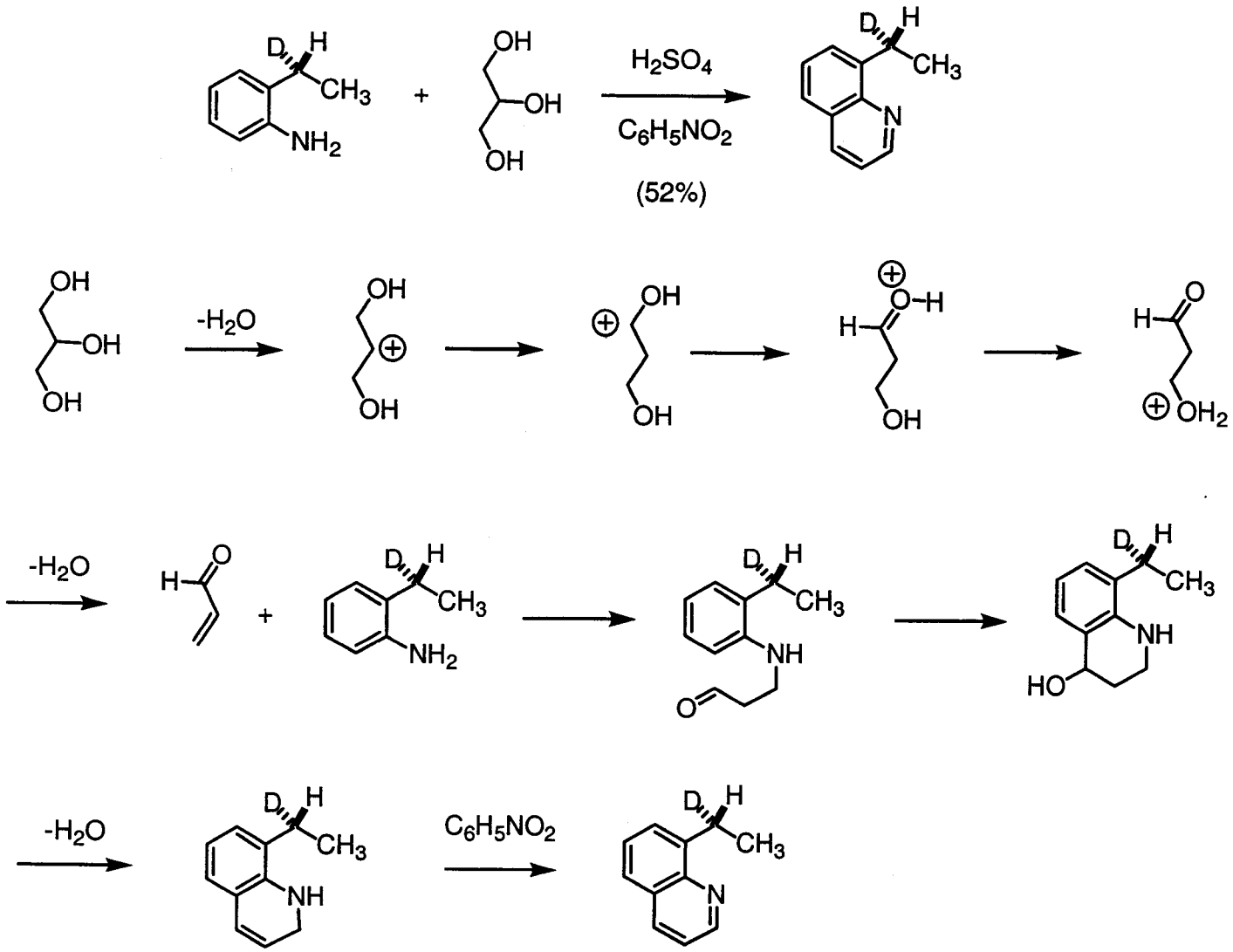
Stereochemical Course of the C*sp^3-TM Bond Formation: *Electrophilic Cyclopallidation*



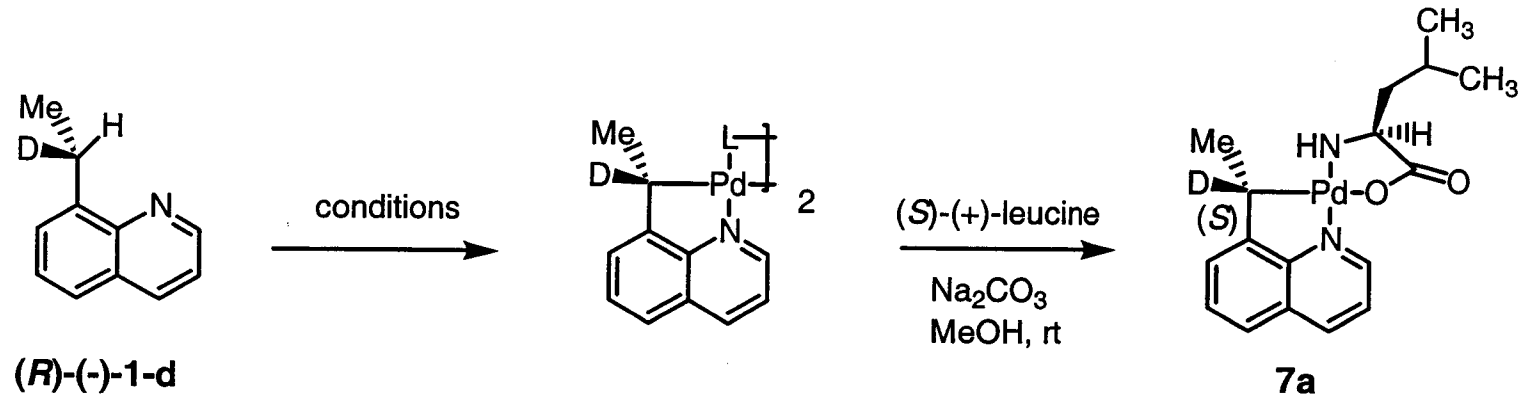


Flood, T. C., et.al. *Organometallics* **1996**, *15*, 4228

Skraup Synthesis



Stereochemical Course of the C*sp^3-TM Bond Formation: Electrophilic Cyclopallidation



(*R*)-(-)-1-d

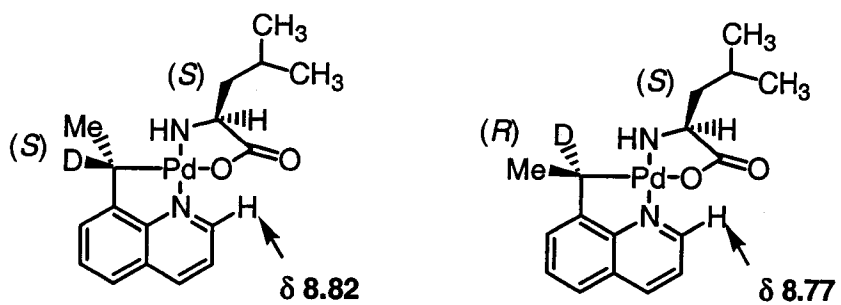
91% d_1, 40% ee

7a

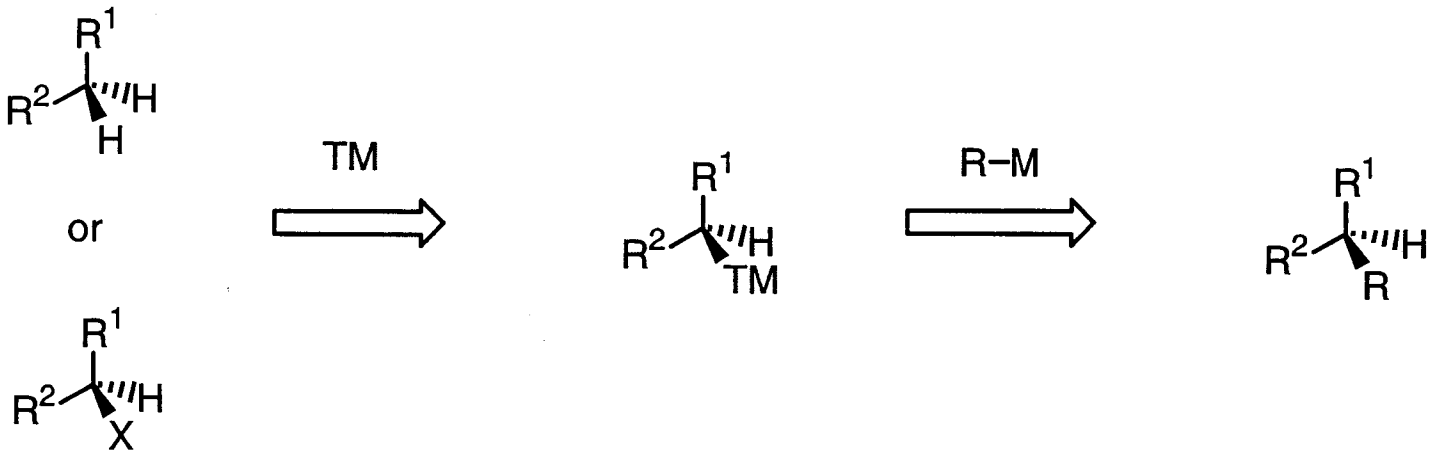
K_H/K_D ~ 11 determined with racemic 1-d

reagent	conditions	% de of **7a**[b]	% net retention
$PdCl_2$	H_2O, MeOH	17	44
K_2PdCl_4	H_2O, MeOH	22	58
$Pd(OAc)_2$	CH_2Cl_2	36	94

[a] (*R*)-**1**-*d* was 91% d_1, and the d_1 portion was of 40% ee. [b] Diastereomer ratio of **7a** corrected for 4.5% each of (*RS*)-d_0 and (*SS*)-d_0 which come from unlabeled (achiral) starting **1**.



Flood, T. C., et.al. *Organometallics* **1996**, *15*, 4228



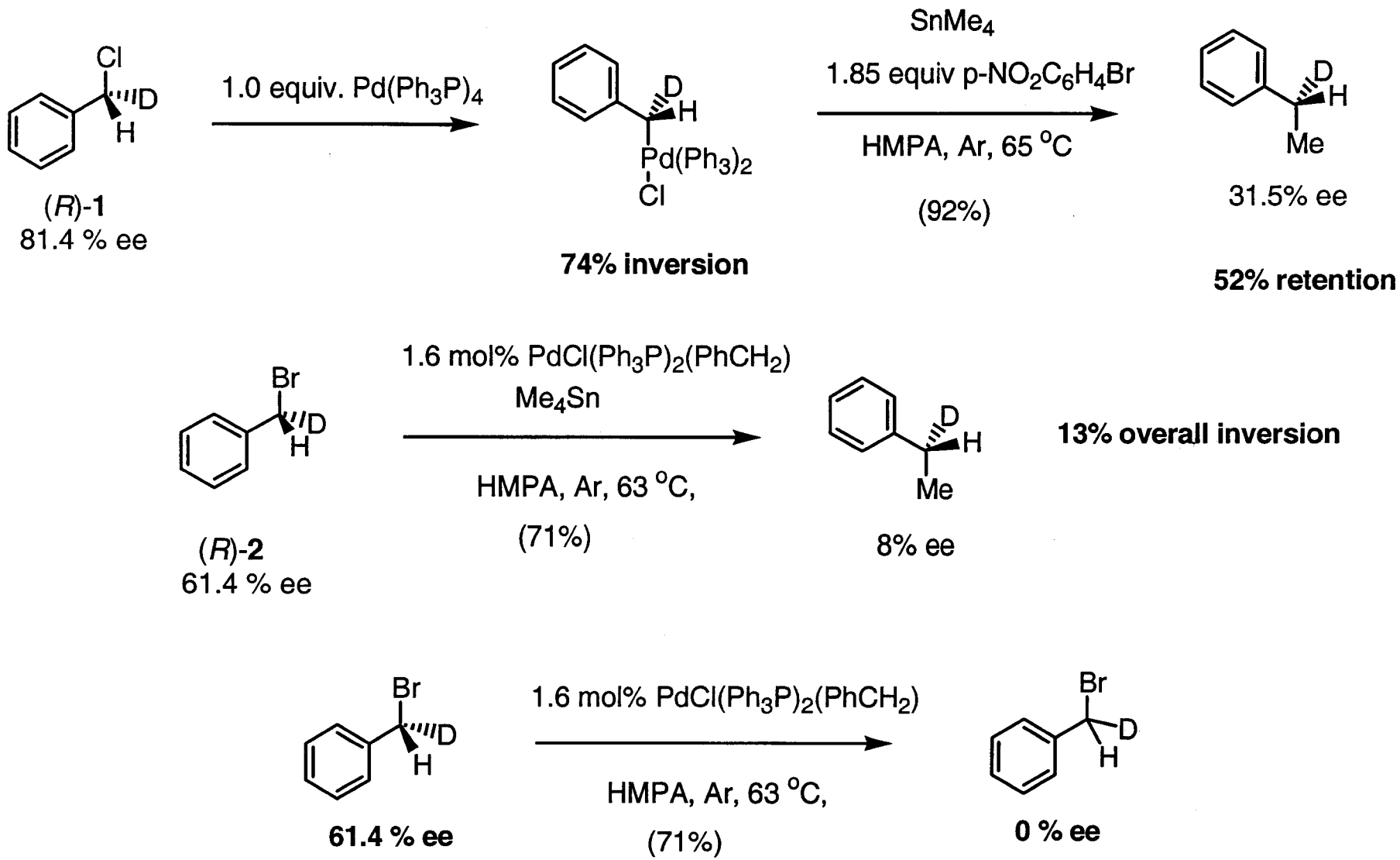
Stability of C*sp^3-TM center

Stereochemical Course of Csp^3-TM Bond Formation

Stereochemical Course Of Csp^3-C Bond Formation

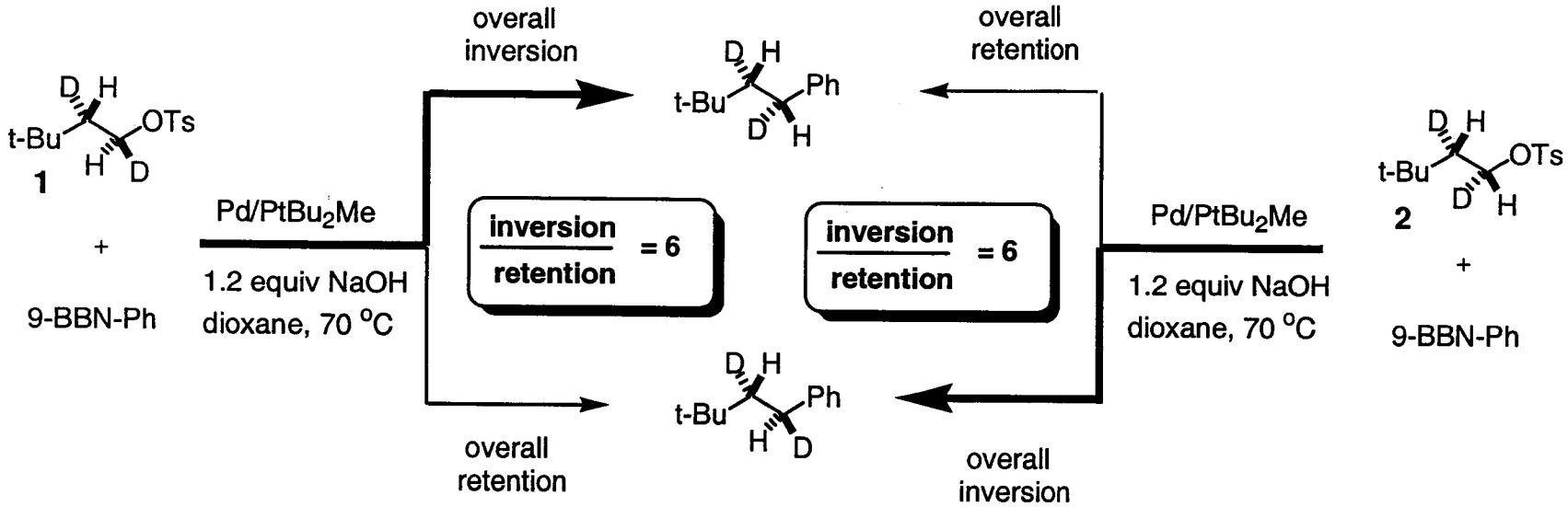
Methodology For Asymmetry Transfer

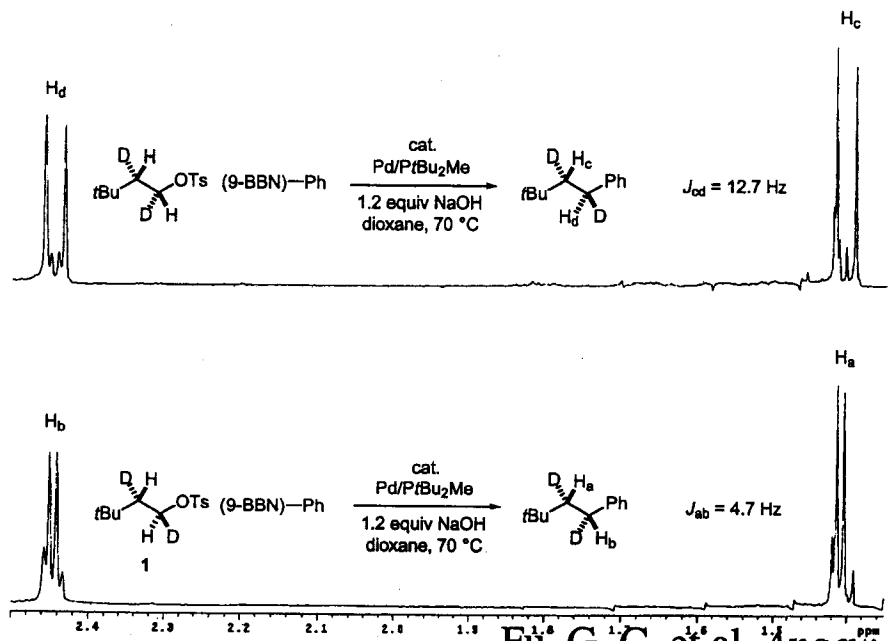
Stereochemical Course of Conversion of a C*sp^3-TM Bond Into a C*sp^3-C Bond



Stille, J. K. et.al. J. Am. Chem. Soc. **1979**, *101*, 4981

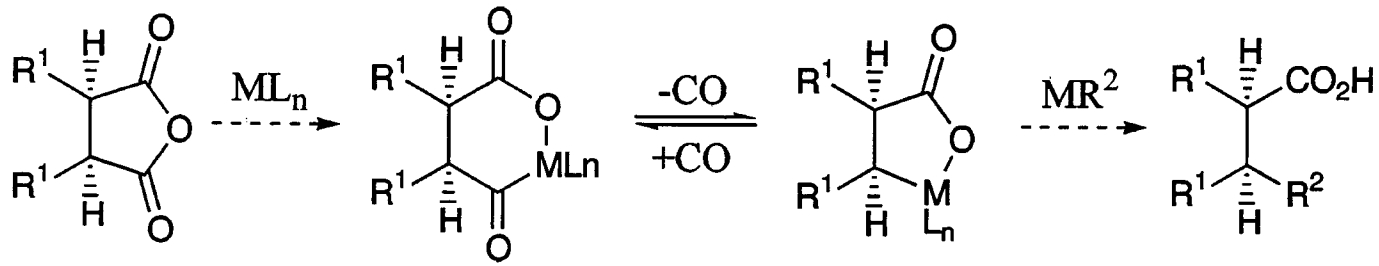
Stereochemical Course of Conversion of a C*sp^3-TM Bond Into a C*sp^3-C Bond

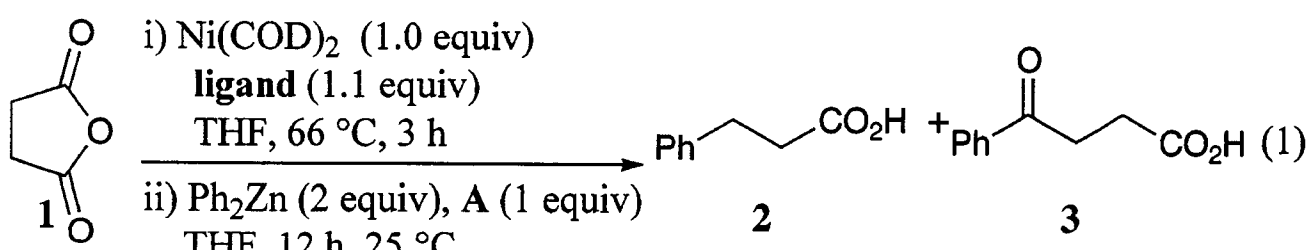




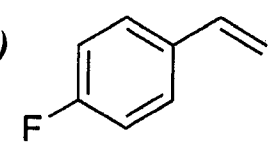
Fu, G. C. et.al. *Angew. Chem. Int. Ed.* **2002**, *41*. 3910

Stereoselective Coupling of a Csp^3-TM to a Sp^2-Hybridized Carbon

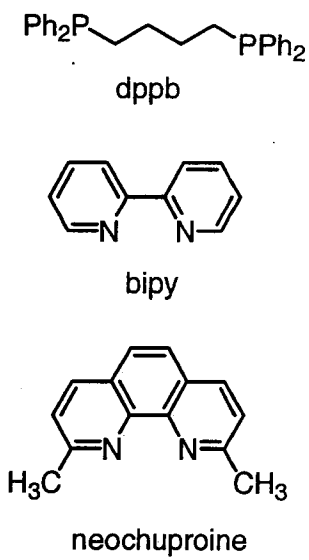




ligand	*2:3*	*Combined Yield (%)*
dppb	<5 :>95	<5
bipy	37 : 63	90
neocuproine	>95:<5	53

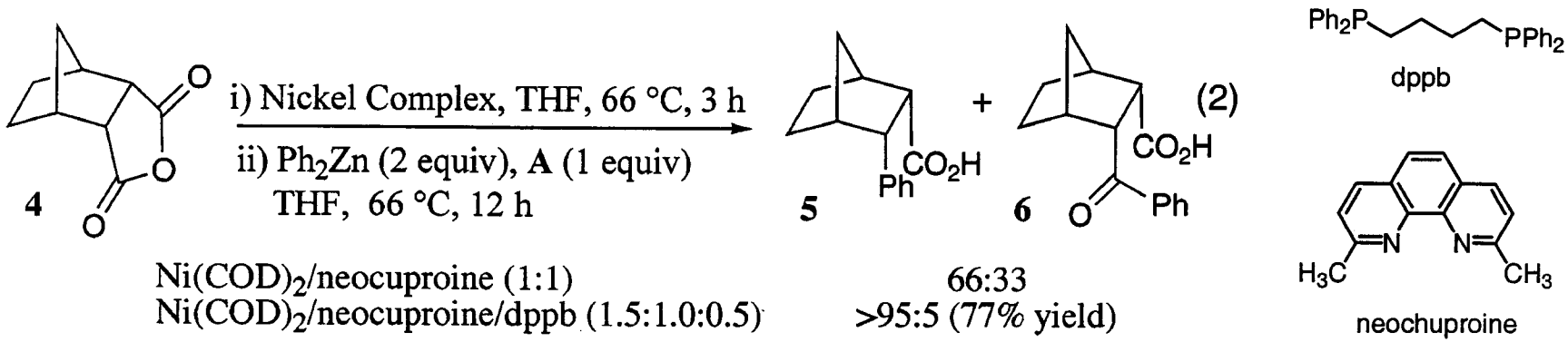


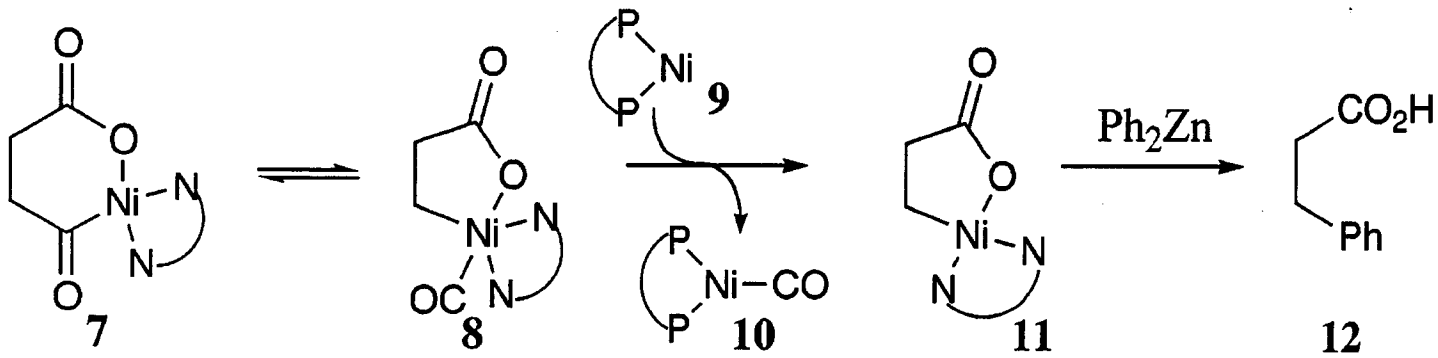
A



Rovis, T., et.al. *J. Am. Chem. Soc.* **2003**, *125*, 10498

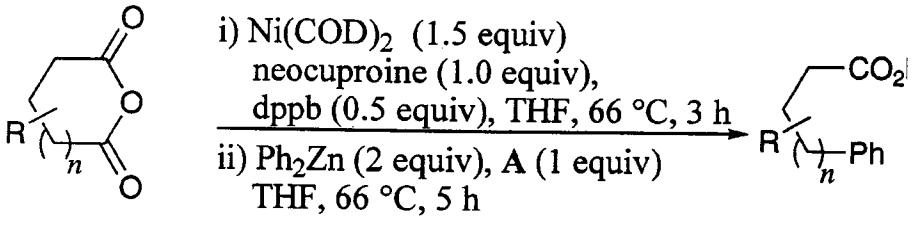
Stereoselective Coupling of a Csp^3-TM to a Sp^2-Hybridized Carbon



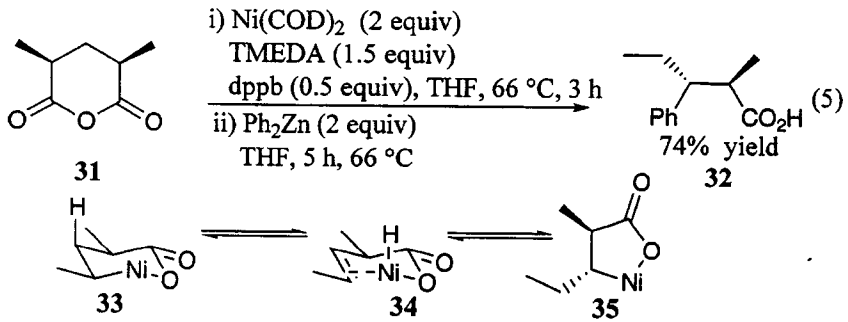


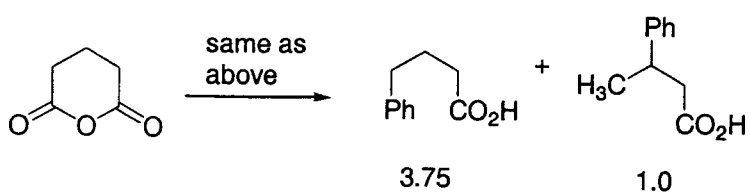
Rovis, T., et.al. *J. Am. Chem. Soc.* **2003**, *125*, 10498

Stereoselective Coupling of a Csp^3-TM to a Sp^2-Hybridized Carbon



In all cases, no diastereomeric acids were observed

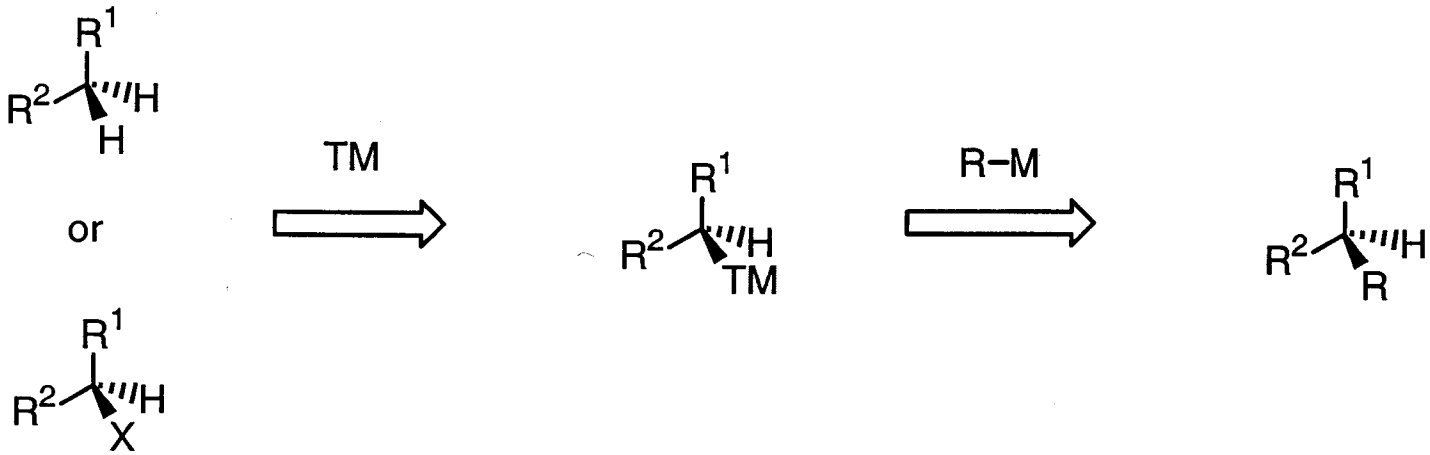




Entry	Anhydride	Product	Yield (%)[a]
1	**13**	**14**	60
2	**15** *exo*- R-R = CH_2CH_2	**16** *exo*- R-R = CH_2CH_2	78
3	**17** *exo*- R-R = CH=CH	**18** *exo*- R-R = CH=CH	56
4	**4** *endo*- R-R = CH_2CH_2	**5** *endo*- R-R = CH_2CH_2	77
5	**19** R-R = CH=CH	**20** R-R = CH=CH	51[b]
6	**21** R-R = CH_2CH_2	**22** R-R = CH_2CH_2	50[b]
7	**23**	**24**	85[c]
8	**25**	**26**	77[d]

[a] Isolated yield of analytically pure material. In every case, direct addition product is not visible by ^1H NMR in the unpurified reaction mixture (<5%). Mass balance typically resides in reduced decarbonylated product. [b] Reaction conducted in dioxane at 80 °C. [c] Reaction conducted using TMEDA (1.5 equiv), $Ni(COD)_2$ (2 equiv). [d] Reaction conducted at 45 °C.

Rovis, T., et.al. *J. Am. Chem. Soc.* **2003**, *125*, 10498



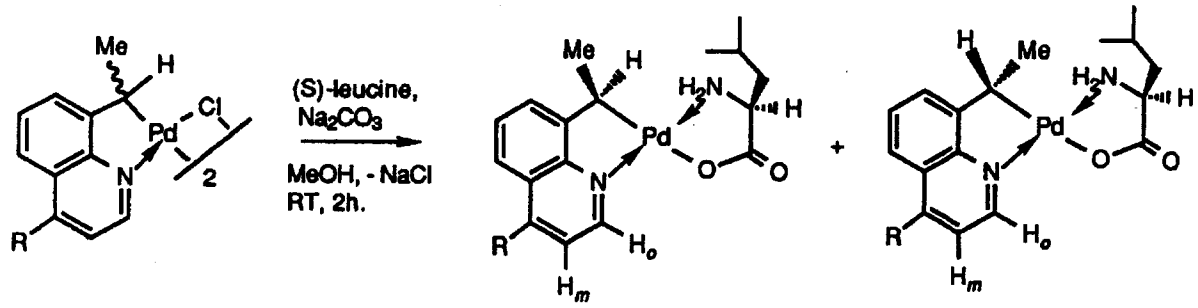
Stability of C*sp^3-TM vcenter

Stereochemical Course of Csp^3-TM Bond Formation

Stereochemical Course Of Csp^3-C Bond Formation

Methodology For Asymmetry Transfer

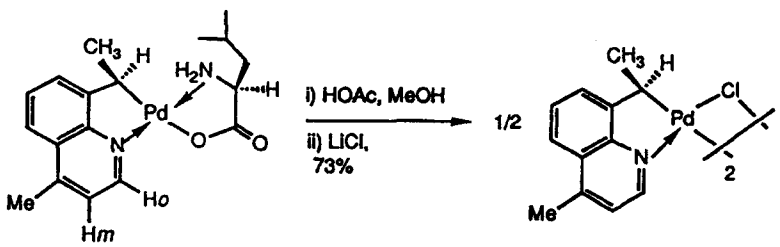
Synthesis of Stable Nonracemic Organometallics with Csp^3-TM Bonds: *Classical Resolution*



1a : R = H
1b : R = Me

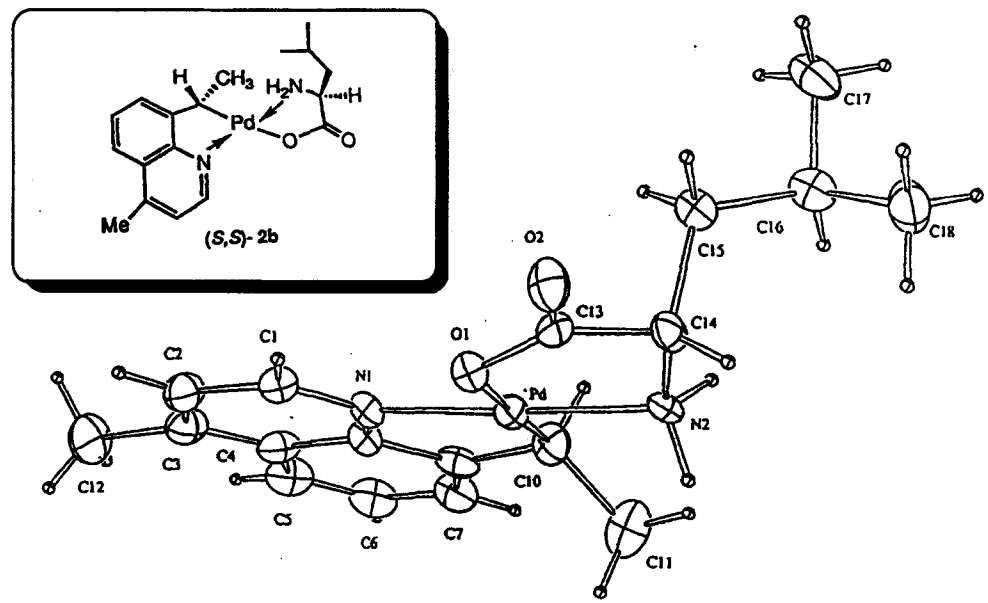
(*R,S*)-**2a**, R = H
(*R,S*)-**2b**, R = Me

(*S,S*)-**2a**, R = H
(*S,S*)-**2b**, R = Me



(*R,S*)-**2b**
d.e. = 33%

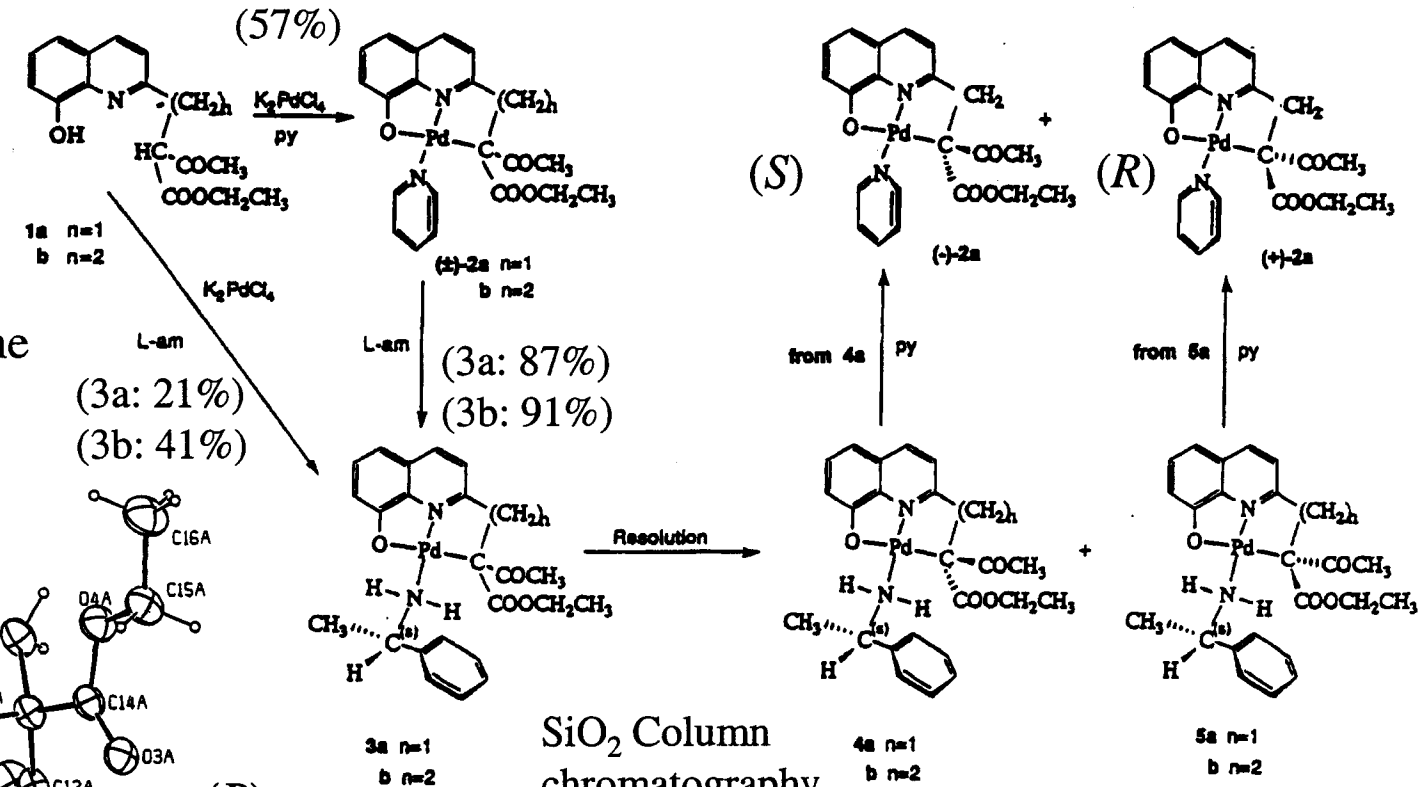
(*R*)-**1b**
e.e. = 28%



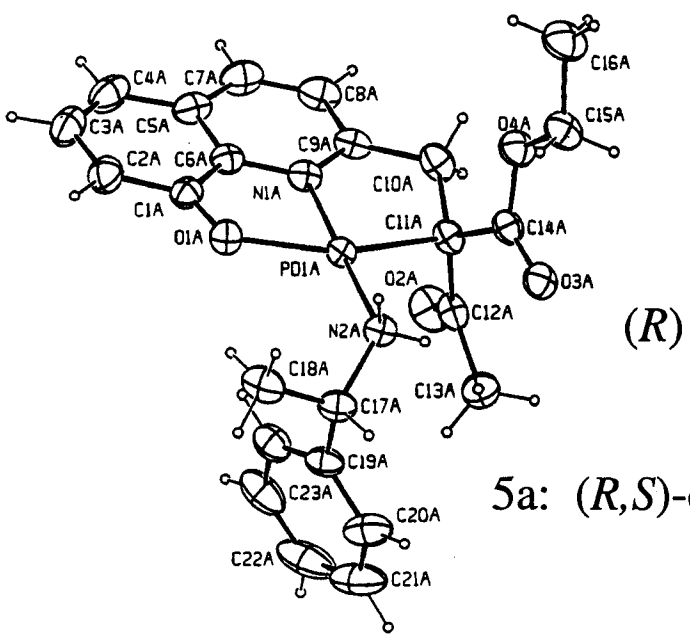
Pfeffer, M., et.al. *Tetraheron: Asymmetry,* **1994**, *6*, 321

Synthesis of Stable Nonracemic Organometallics with Csp^3-TM Bonds: *Classical Resolution*

L-am =
(S)-phenylethylamine



SiO_2 Column chromatography



(R)

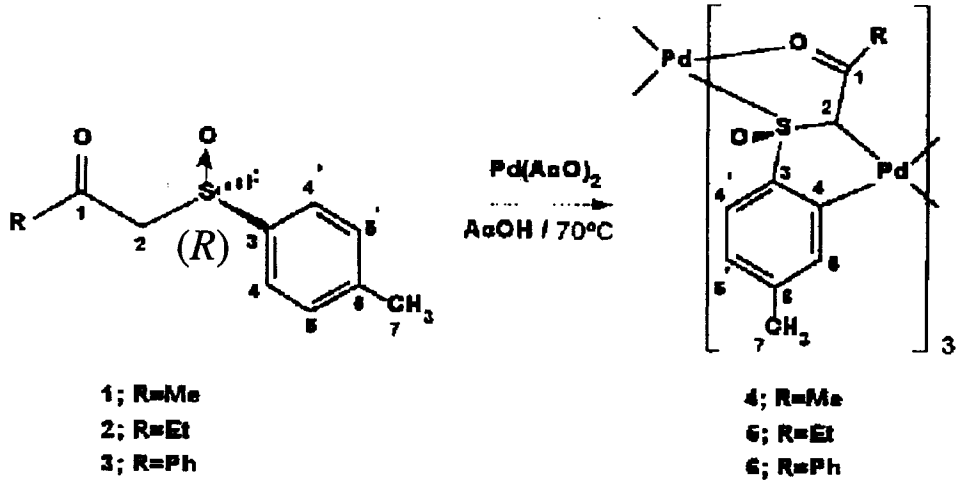
5a: (R,S)-diastereomer

4a: mp = 193 °C
4b: mp = 178 °C

5a: mp = 176 °C
5b: mp = 169 °C

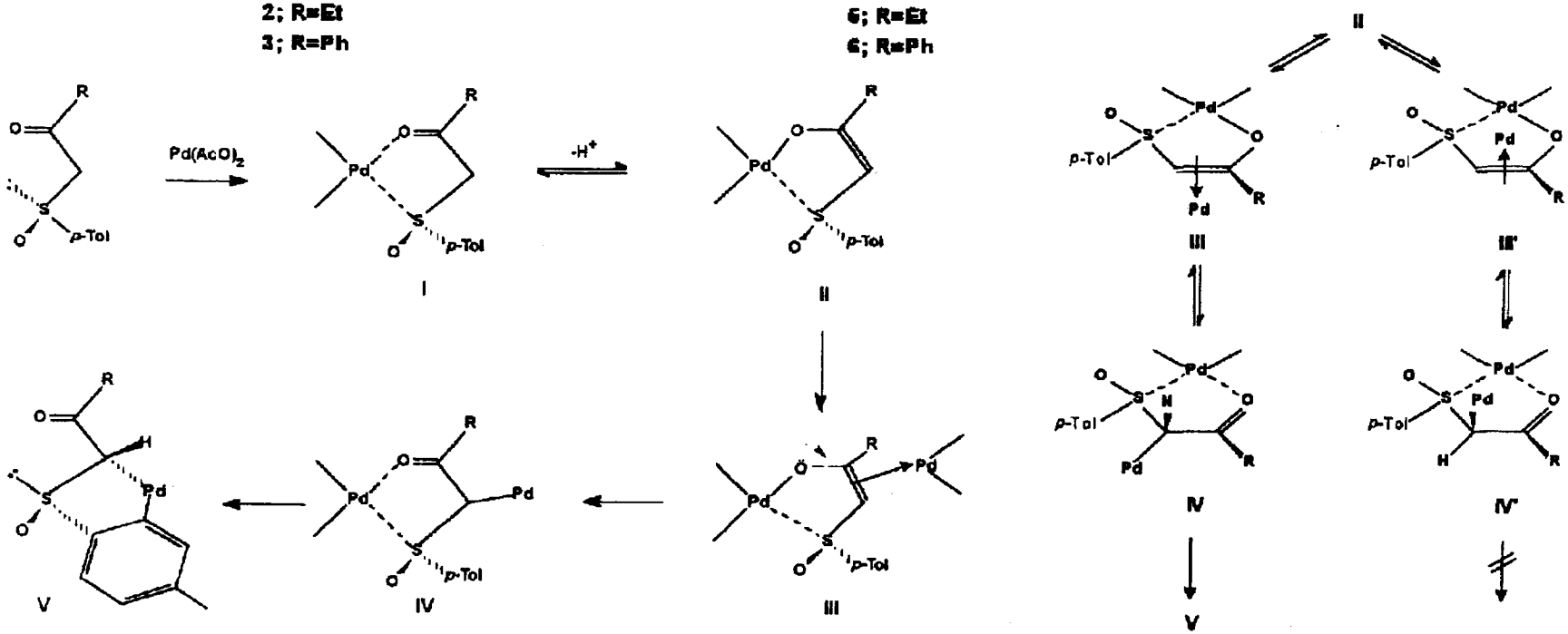
Yoneda, A., et.al. *Organometallics*, **1994**, *13*. 4912

Synthesis of Stable Nonracemic Organometallics with Csp^3-TM Bonds: *Substrate-Directed Asymmetry Transfer*



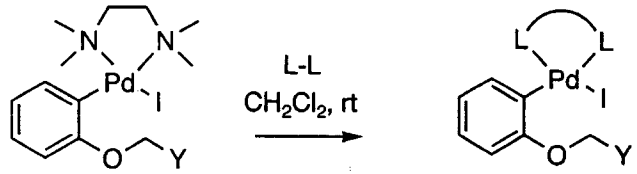
4: 42% yield mp 348 °C
5: 49% yield mp 350 °C
6: 49% yield mp 293 °C

d.e. >98% in all cases



Garcia-Ruano,J. L., et.al. *Tetrahedron: Asymmetry,* **1996**, *7*, 139

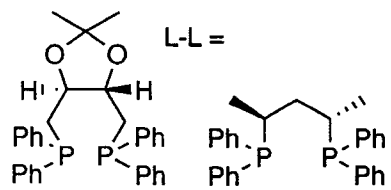
Synthesis of Stable Nonracemic Organometallics with Csp^3-TM Bonds: *Auxiliary Ligand-Controlled Asymmetry Transfer*



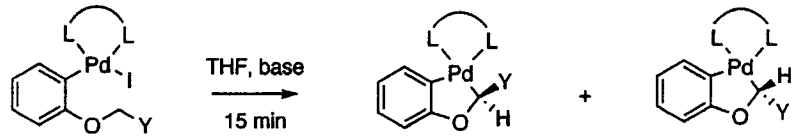
3a: Y = COOEt
3b: Y = $CONEt_2$

4a: Y = COOEt, L-L = (*S,S*)-DIOP;(98%)
4b: Y = $CONEt_2$, L-L = (*S,S*)-DIOP;(98%)
4c: Y = COOEt, L-L = (*S,S*)-BDPP;(98%)

L-L =



(*S,S*)-DIOP (*S,S*)-BDPP

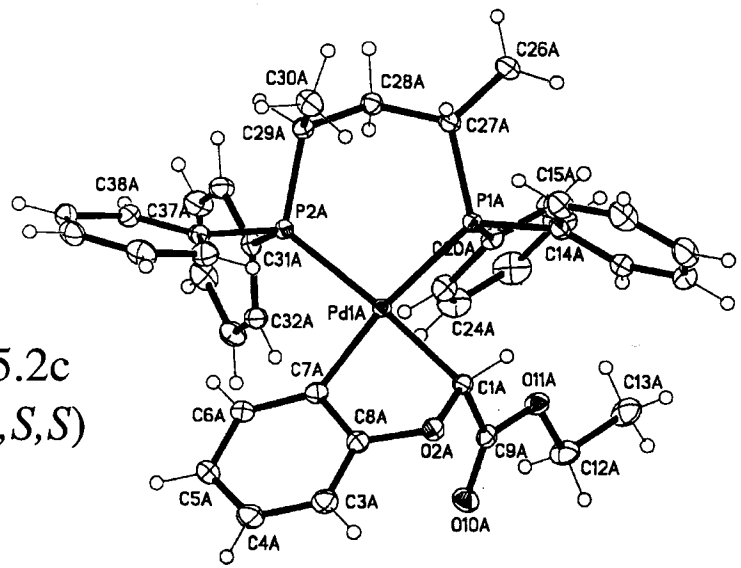


4a-c **5.1a- 5.1c** **5.2a - 5.2c**

a: Y = COOEt, L-L = (*S,S*)-DIOP; **b:** Y = $CONEt_2$, L-L = (*S,S*)-DIOP;
c: Y = COOEt, L-L = (*S,S*)-BDPP

	sub-strate	base	temp (°C)	diastereomeric ratio 5.1a–c (%)	diastereomeric ratio 5.2a–c (%)	de (%)	combined yield (%)
	4a			**5.1a**	**5.2a**		
1		KHMDS[a]	−78	35	65	30	94
2		*t*-BuOK	rt	44	56	12	72
3			−78	69	31	38	88
4		LDA	rt	63	37	26	72
5			−78	86	14	72	89
6		(R*)MeNLi[b]	−78	90	10	80	98
	4b			**5.1b**[c]	**5.2b**[c]		
7		*t*-BuOK	rt	24	76	52	71
8			0	25	75	50	88
9			−78	44	56	12	*d*
10		LDA	rt	54	46	8	82
11			−78	77	23	54	91
	4c			**5.1c**	**5.2c**		
12		*t*-BuOK	rt	64	36	28	99
13			−78	87	13	74	99
14		LDA	rt	42	58	16	94
15			−78	12	88	76	99

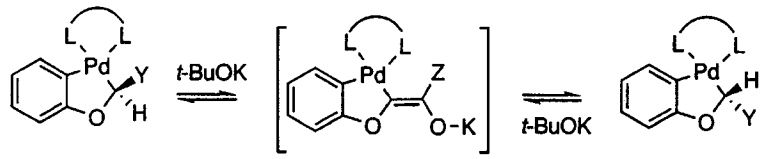
[a] Reaction time was extended to 2 h. [b] R* = PhCH(Me)− with a *R* configuration. [c] The assignment of the absolute configuration is arbitrary. See ref 26. [d] The reaction proceeded with only a partial conversion of the starting material.



5.2c
(*R,S,S*)

Malinakova, H. C., et.al. *Organometallics* **2003**, *22*. 2961

Synthesis of Stable Nonracemic Organometallics with Csp^3-TM Bonds: *Auxiliary Ligand-Controlled Asymmetry Transfer*



5.1a-c **6a-c** **5.2a-c**

a: Y = COOEt, Z = OEt, L-L = (*S,S*)-DIOP;

b: Y = $CONEt_2$, Z = NEt_2, L-L = (*S,S*)-DIOP;

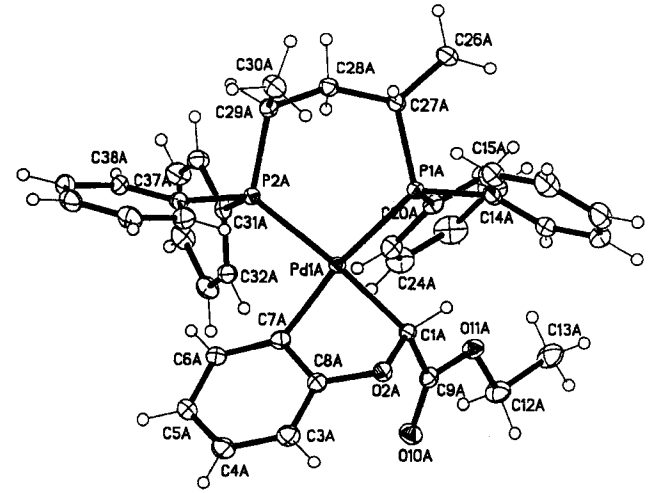
c: Y = COOEt, Z = OEt, L-L = (*S,S*)-BDPP

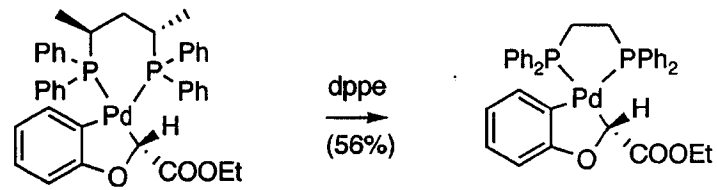
	diastereomeric ratio in substrate		time[a]	diastereomeric ratio in product		product	recovery
	5.1 (%)	**5.2** (%)	(h)	**5.1** (%)	**5.2** (%)	de (%)	(%)
	5a			**5a**			
1	82	18	1	71	29	42	76
2	43	57	1	27	73	46	81
3	43	57	3	38	62	24	69
	5b[b]			**5b**[b]			
4	69	31	1	55	45	10	71
5	27	73	1	18	82	64	76
6	28	72	3	13	87	74	61
	5c			**5c**			
7	87	13	1	36	64	28	93
8	19	81	1	14	86	72	95
9	19	81	3	12	88	76	90

[a] To solutions of the substrates **5a–c** in THF was added 1.1 mol equiv of *t*-BuOK (1 M solutions in THF). Reaction mixtures were stirred for the indicated time period at room temperature. Diastereomeric composition of the recovered palladacycles **5a–c** was determined by ^{1}H NMR. [b] The assignment of the absolute configuration is arbitrary. See ref 26.

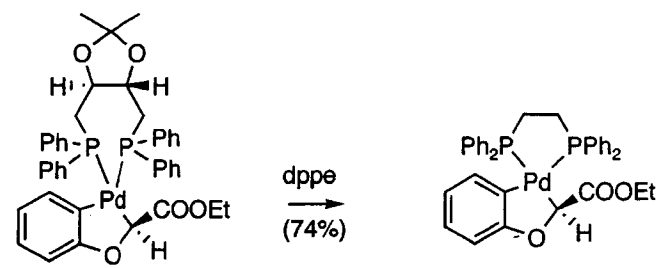
5.1a: 80% de **5.1b**: 54% de **5.1c**: 74% de

5.2a: 46% de **5.2b**: 74% de **5.1c**: 76% de





5.2c (62% *de*, ^{1}H NMR) **(+)-7** (62.1% *ee*, HPLC) $[\alpha]_D$ + 71.7 (c 0.52, CH_2Cl_2)

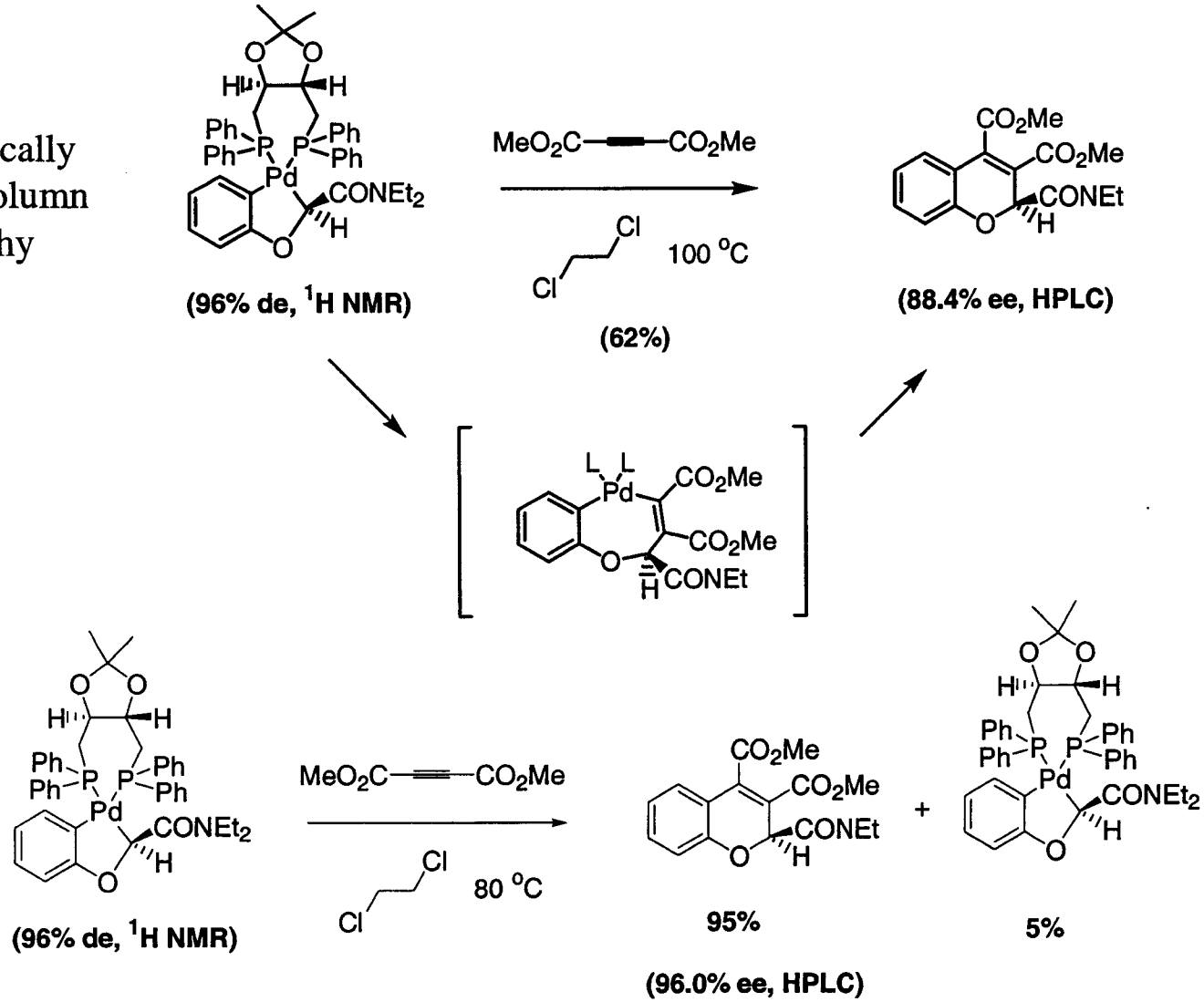


5.1a (66% *de*, ^{1}H NMR) **(-)-7** (68.2% *ee*, HPLC) $[\alpha]_D$ - 78.7 (c 0.40, CH_2Cl_2)

Malinakova, H. C., et.al. *Organometallics* **2003**, *22*, 2961

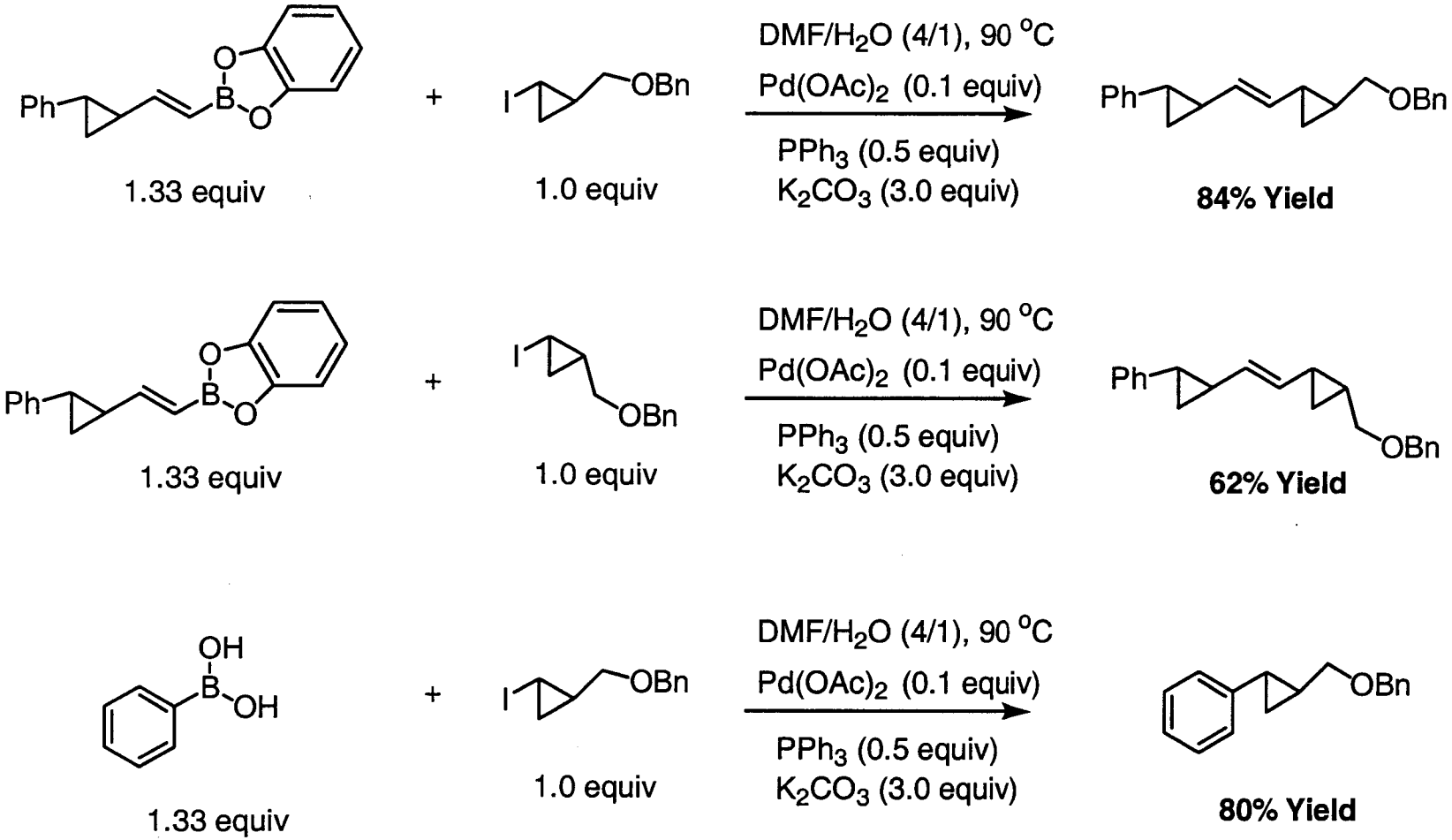
Stereoselective Coupling of a Csp^3-TM to a Sp-Hybridized Carbon

Diastereomerically enriched by column chromatography



Malinakova, H. C., et.al. *Organometallics* **2003**, *22*. 2961

Stereoselective Coupling of Iodocyclopropanes



Charette, A. B., et.al. *Organometallics* **1996**, *61*, 8718