Asymmetric Hydrosilylation of Aryl Ketones Catalyzed by Copper Hydride Complexed by Nonracemic Biphenyl Bis-phosphine Ligands

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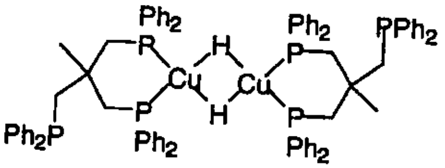
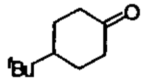
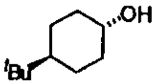
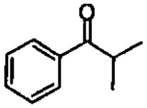
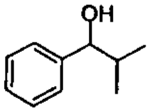
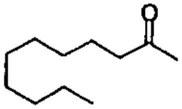
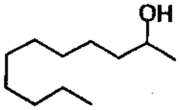
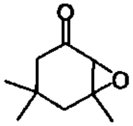
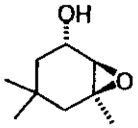
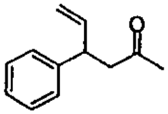
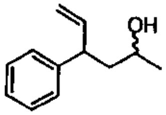
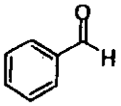
Abstract: When complexed by selected ligands in either the BIPHEP or the SEGPHOS series, CuH is an extremely reactive catalyst capable of effecting asymmetric hydrosilylations of aromatic ketones at temperatures between −50 and −78 °C. Inexpensive silanes serve as stoichiometric sources of hydride. Substrate-to-ligand ratios exceeding 100,000:1 have been documented. The level of induction is usually in the >90% ee category. The nature of the reagent has been investigated using spectroscopic and chemical means, although its composition remains unclear.

2



- REDUCTIONS CLEAN AND NEARLY QUANTITATIVE
- SLOW RATES (ESP FOR STERICALLY HINDERED CARBONYLS)
- PREFERENCE FOR CONJUGATE REDUCTION OF α,β-UNSATURATED KETONES

Table 1. Catalytic reduction of ketones and aldehydes using $[(\eta^2\text{-tripod})CuH]_2$ and H_2

Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b]	Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b]
 **1** **2**	A B	7 24	 92 (8 : 1)[c] 98 (4 : 1)[c]	 **5** **6**	E F	24 48	 91 90
 **3**	C	36	 90	 **7**	D	30	 95 (11 : 1)[c]
 **4**	D	60	 94 (~3 : 2)[d]	 **8** **9**	C G	20 25	 + $PhCO_2CH_2Ph$ 84 (1 : 1)[e] 100 (19 : 1)[e]

[a] Reduction conditions: A, 2.5 mol% $[(tripod)CuH]_2$, 2 equiv. tripod/Cu, THF, 0.1 M in substrate, 50–60 psi H_2, RT; B, as A, except 0.8 mol% $[(Ph_3P)CuH]_6$, 3 equiv. tripod/Cu, 0.2 M; C, as A, except 0.2 M; D, as A, except 0.05 M; E, as C, except 5 mol% catalyst; F, as B, except 0.1 M; G, as B, except 500 psi H_2.

[b] All yields refer to isolated purified products, assignments by comparison to known compounds or authentic materials. All reactions were set up under N_2; quenched by exposure to air and addition of sat. aq NH_4Cl. Products were purified by flash chromatography.

[c] Minor isomer is epimeric at the hydroxy center.

[d] Stereoisomer unassigned.

[e] Conversions and product ratios determined by ^1H NMR spectroscopy.

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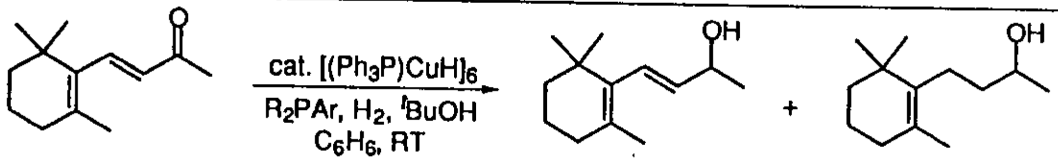
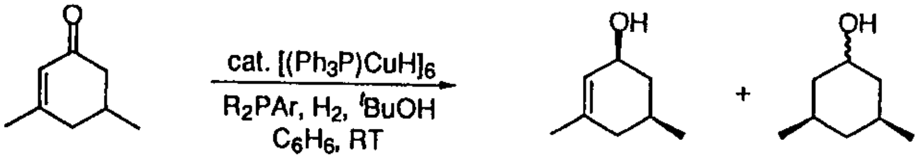
Table 2. Hydrogenation of α,β-unsaturated ketones using phosphine-stabilized copper(I) hydride catalysts and hydrogen (conditions: 0.83 mol% $[(Ph_3P)CuH]_6$, 6 equiv. R_2PAr/Cu, 40 equiv. $^tBuOH/Cu$, C_6H_6, 500 psi H_2, RT. Details in the Experimental section)

Entry	Phosphine	Reaction time	Regioselectivity[a]	Yield (%)[b]
				
1	$^nBu_3P$	18	4:1	[c]
2[1b]	$PhPMe_2$	26	49:1	97
3	PhP(Me)Et	21	>50:1	95
4	$PhP(CH_2)_4$[d]	21	19:1	84
5	PhP(Me)Cy	24	20:1	87
				
6	$^nBu_3P$	18	1 (3:1)[e]:5 (1:1)	85
7[1b]	$PhPMe_2$	30	2.7 (12:1):1[f]	90
8[1b]	$PhPMe_2$[g]	25	4.4 (12:1):1[f]	92
9	PhP(Me)Et	20	3 (7.3:1):1[f]	89
10	$PhP(CH_2)_4$[d]	20	1[f]:2[f]	[c]
11	PhP(Me)Cy	24	3 (4.9:1):1[f]	88

[a] Products identified by comparison to authentic materials prepared by unambiguous synthesis. See Experimental section.
[b] Isolated yield after purification by chromatography.
[c] Complete conversion; isolated yield not determined.
[d] Phenylphospholane.
[e] Major allylic alcohol stereoisomer as indicated; minor isomer epimeric at hydroxyl center.
[f] Stereochemical ratio not determined.
[g] Catalyst derived from CuCl (5 mol%) and NaO^tBu (5 mol%) in the presence of Me_2PPh (6 equiv./Cu).

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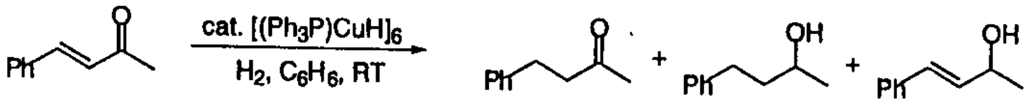

(1)	No added phosphine, 10h 2.7 mol% **1**, 1000 psi H_2	91	:	9	:	0	89%[8]
(2)	Ph_3P (12 equiv/Cu), 24h 2.7 mol% **1**, 1700 psi H_2	0	:	92	:	8	95%[8]
(3)	Me_2PPh (6 equiv/Cu), 18h 0.83 mol% **1**, 500 psi H_2	0	:	8	:	92	91%

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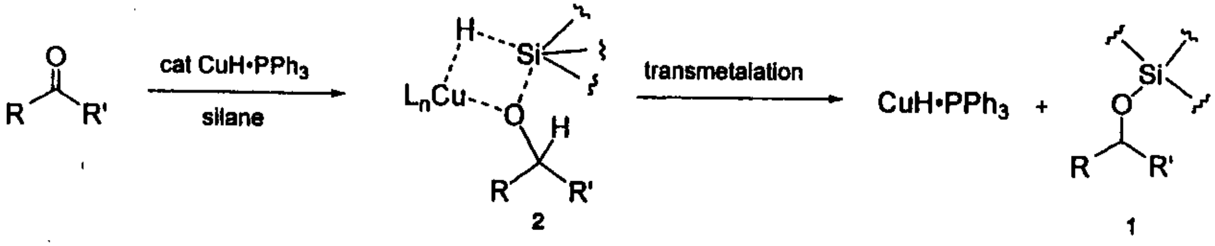
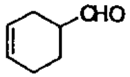
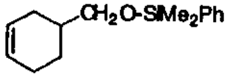
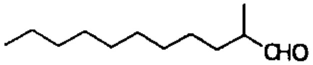
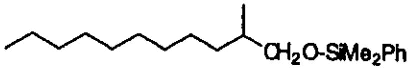
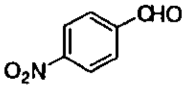
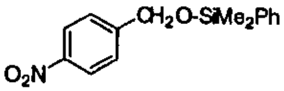
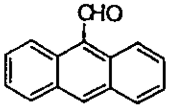
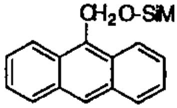
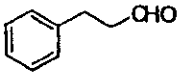
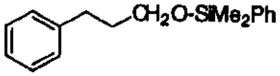
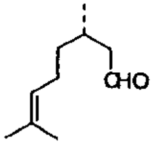
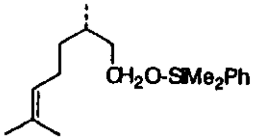
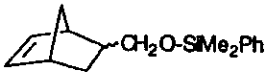
CONCLUSION: PROPERTIES OF PHOSPHINES WILL INFLUENCE REACTIVITY.



Scheme 1. Regeneration of $CuH\cdot PPh_3$ via transmetalation.

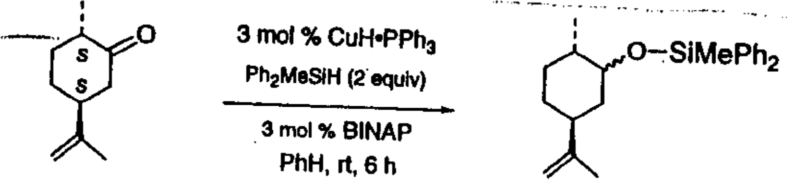
Table 1
Hydrosilylations of aldehydes with cat $CuH\cdot PPh_3/PhMe_2SiH$ [a]

Aldehyde	Product[b]	Yield(%)[c]
		95
		92
		89
		96
		90
		93
		98
		95

3 mol % $CuH\cdot PPh_3$
1.3 equiv $PhMe_2SiH$
TOLUENE/rt/2h.

- ALDEHYDES SELECTIVELY REDUCED IN PRESENCE OF KETONES.

yield of 94%. Interestingly, the presence of bidentate phosphine ligands, such as DPPF and racemic BINAP, in amounts equal to that of CuH·PPh$_3$, had a dramatic effect on accelerating the rates of these hydrosilylations, an observation which is now being pursued further.



9

10 (94%; 2 : 1 ratio, α : β)

(3)

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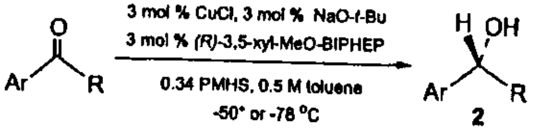
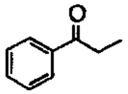
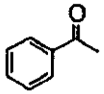
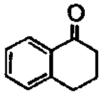
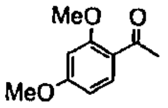
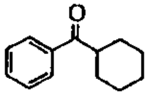
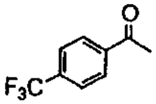
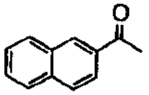
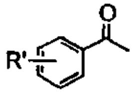
Table 1. Asymmetric Hydrosilylations Using Catalytic CuH and Roche BIPHEP Ligand **1**



Entry	Aryl ketone	Time (h)	Yield (%)^{a}	ee (%)^{b}
1		7.5	95	95^{e}
		48	87	97^{c}
2		5	98	94^{c}
3		6.5	99	92^{e}
4		50	89	94^{d}
5		10	94	88^{e}
6		1	85	95^{e}
7		48	95	95^{c}
8		1.5	98	$67^{e,f}$
		5	99	$93^{c,g}$
		5.5	97	$78^{c,h}$

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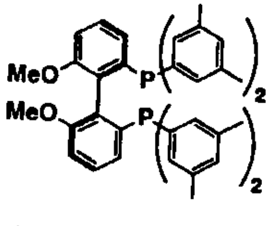
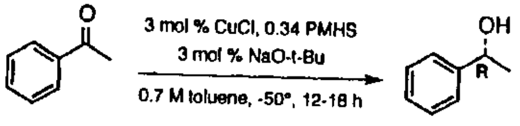
[a] Isolated. See ref 5d. [b] ee values were determined by conversion of each product to its acetate and analysis by chiral capillary GC. [c] Reaction was run at -78 °C. [d] Reaction was given 10 h at −50 °C and then warmed to room temperature. [e] Reaction was run at −50 °C. [f] R′ = *o*-Br. [g] R′ = *m*-Br. [h] R′ = *o*-Cl.



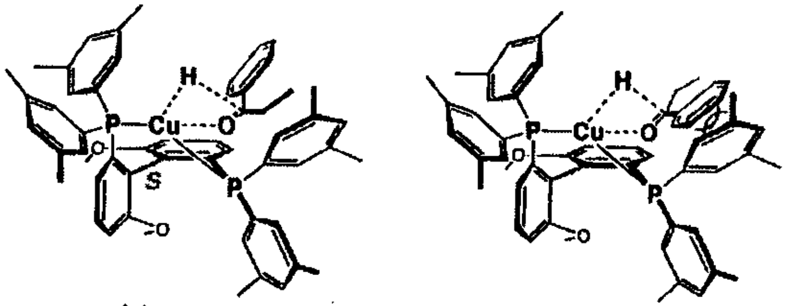
1, *R*-3,5-xyl-MeO-BIPHEP

Table 2. Level of Roche Ligand **1** that Effects CuH-Catalyzed Hydrosilylations



92% ee

mol % (R)-3,5-xyl-MeO-BIPHEP	ratio of substrate / ligand	ratio of copper(I) / ligand
3.00	33	1
0.50	200	6
0.05	2000	60
0.02	5000	150
0.005	**20,000**	600



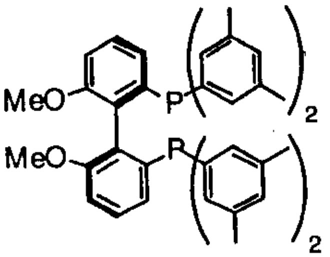
3 (favored)

4 (disfavored)

Figure 1. Rationale for induction observed in CuH·3,5-xyl-MeO-BIPHEP-catalyzed hydrosilylations.

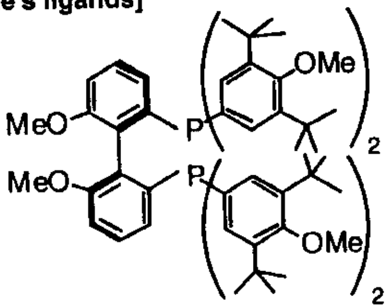
Chart 1. Structures for the BIPHEP and SEGPHOS Ligands Used in This Study

[Roche's ligands]



4A

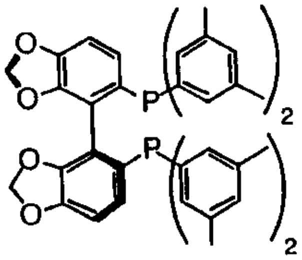
R-3,5-xyl-MeO-BIPHEP



4B

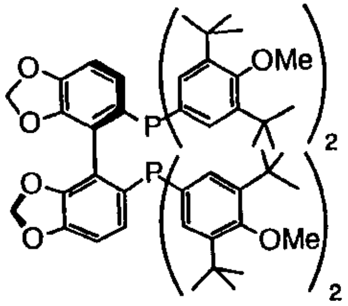
R-4-MeO-3,5-DTBM-MeO-BIPHEP

[Takasago's ligands]



14A

S-(-)-DM-SEGPHOS

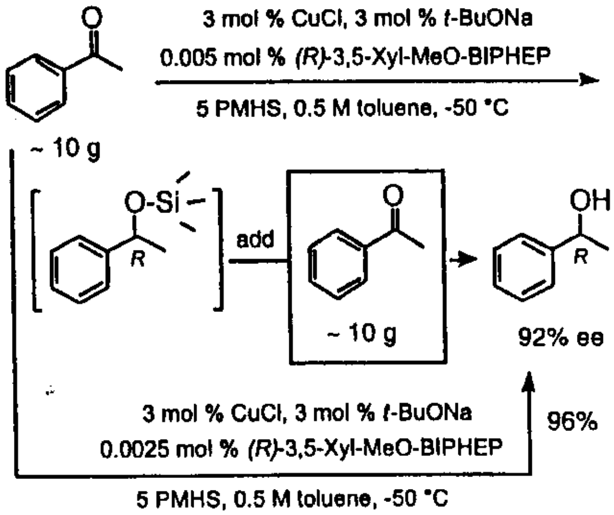


14B

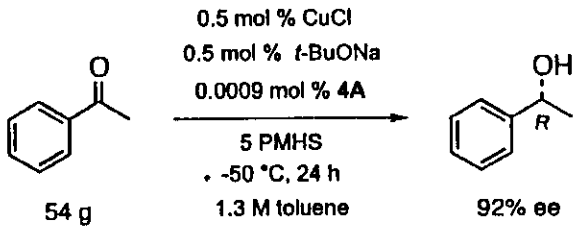
R-(-)-DTBM-SEGPHOS

Scheme 1. Asymmetric Hydrosilylations of Aryl Ketones Using Ligand **4**

Scheme 2. Consecutive Reductions at 20 000:1 S/L and Direct Hydrosilylation at 40 000:1 S/L



Scheme 3. Reduction of Acetophenone Using ≥100 000:1 S/L



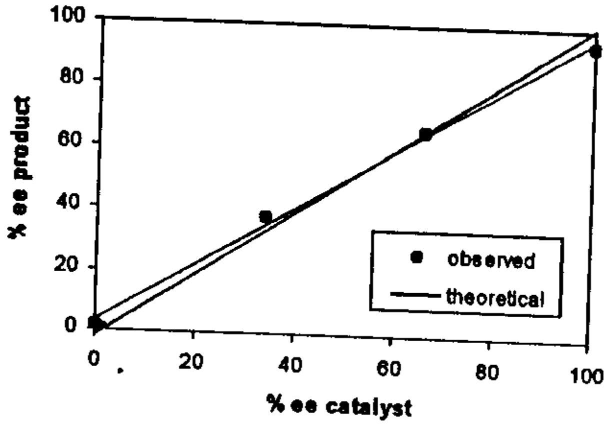


Figure 4. Plot of observed ee of product alcohol as a function of optical purity of 5.

ACETOPHENONE (0.5 M)

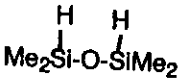
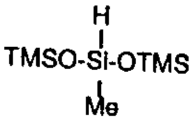
3% $(Ph_3P)CuH$

3% 4A

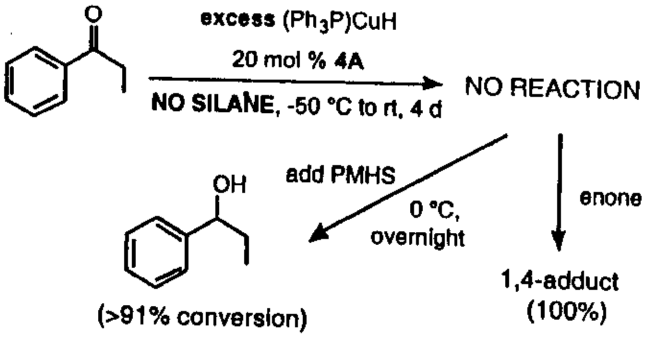
PMHS

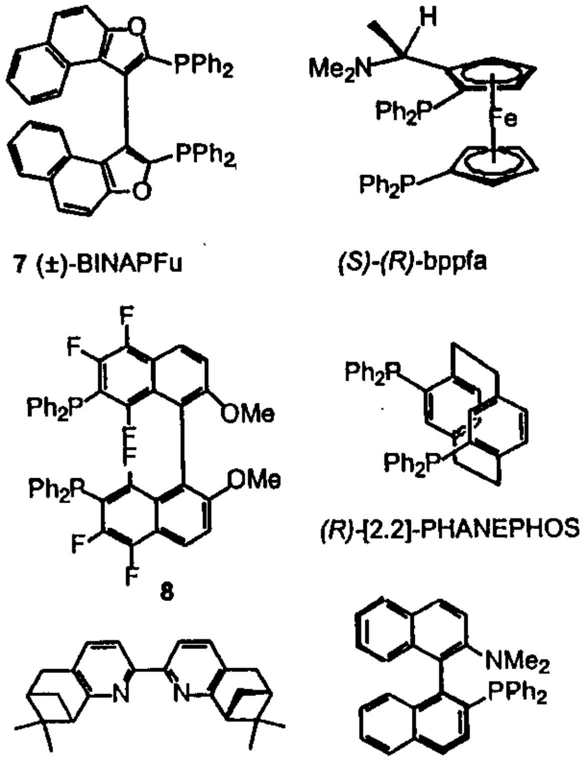
- 50° C

Table 1. Study of Monomeric Silanes as Alternatives to PMHS

silane	**comments**
Ph_2MeSiH	**takes longer than PMHS (12 h);** **leads to silyl ether product in** **95% ee at -78°; 90% yield**
 $Me_2\overset{H}{Si}\text{-O-}\overset{H}{Si}Me_2$ (TMDS)	**takes longer than PMHS (11 h);** **leads to silyl ether product in** **94% ee at -78°; 98% yield**
 $TMSO\text{-}\underset{Me}{\overset{H}{Si}}\text{-OTMS}$ (HMTS)	inactive; no hydrosilylation at -78 °C after 5 h
$Et_3Si\text{-}H$	at 0°, get at most 3% product in the presence of 5 equiv of this silane.
$PhSiH_3$	inactive (toward propiophenone); no hydrosilylation at -78 to 0 °C

Scheme 7. Impact of the Silane on an Aryl Ketone Reduction with CuH





7 (±)-BINAPFu

(S)-*(R)*-bppfa

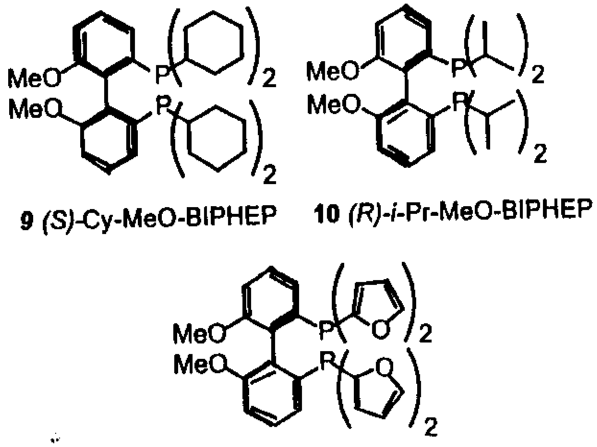
8

(R)-[2.2]-PHANEPHOS

(+)-PINDY

(S)-MAP

Figure 5. Biaryl ligands which showed no activity in the presence of CuH.

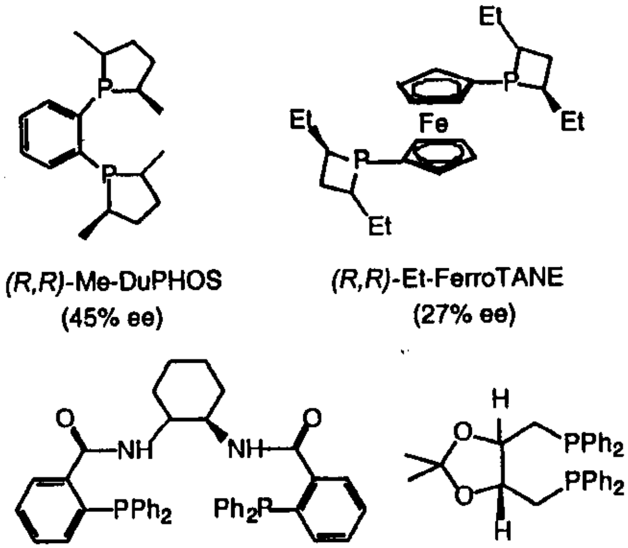


9 *(S)*-Cy-MeO-BIPHEP

10 *(R)*-*i*-Pr-MeO-BIPHEP

11 *(R)*-(2-Furyl)-MeO-BIPHEP

Figure 6. BIPHEP ligands which led to no reaction in the presence of CuH.



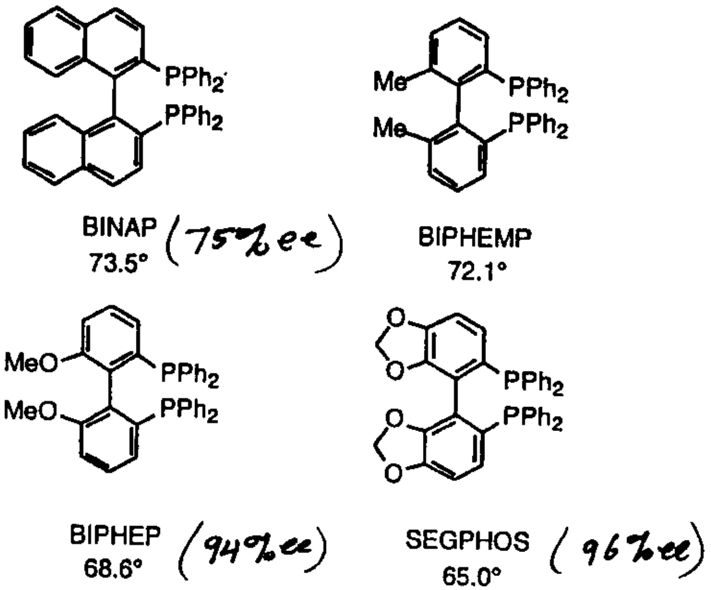
(R,R)-Me-DuPHOS
(45% ee)

(R,R)-Et-FerroTANE
(27% ee)

(R,R)-Trost ligand
(21% ee)

(R,R) - DIOP
(0% ee)

Figure 7. Representative biaryl ligands screened for effectiveness.



BINAP 73.5° (75%ee)

BIPHEMP 72.1°

BIPHEP 68.6° (94%ee)

SEGPHOS 65.0° (96%ee)

Figure 11. Dihedral angles for Ru complexes of various bis-phosphine ligands (CAChe MM2).

CONCLUSIONS:

- CU RATHER THAN RU OR Rh
- CATALYTIC
- CATALYST PREPARED IN SITU (CuCl + LIGAND)
- INEXPENSIVE SILANES USED AS STOICHIOMETRIC REDUCTANT.

FUTURE DIRECTIONS:

- IDENTIFY ACTIVE CATALYST
- EXPAND BEYOND ARYL KETONES AS SUBSTRATES