

New Catalysts for the Asymmetric Hydrosilylation of Ketones Discovered by Mass Spectrometry Screening

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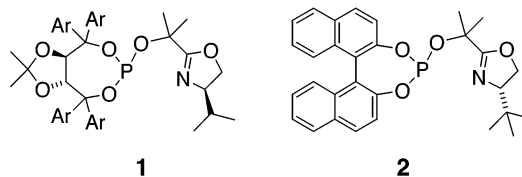
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A method for determining enantiomeric excess by mass spectrometry was employed to screen a family of chiral phosphite P,N-ligands for activity in the rhodium-catalyzed asymmetric hydrosilylation of ketones. The identification of an effective set of ligands was followed by preliminary studies of the reaction scope and mechanism. Asymmetric induction of 84–88% ee for larger-scale reactions was observed, which is close to the level of the best alternative catalysts previously discovered. The screening method was shown to be applicable to a variety of substrates without the need for special optimization.

The asymmetric reduction of prochiral ketones is a powerful approach to the synthesis of chiral alcohols.¹ Hydrosilylation provides for reaction conditions that are exceedingly mild, the process being driven by the formation of a strong Si–O bond. Asymmetric variants of this reaction have been studied for many years.^{2,3} A convenient, albeit relatively undemanding, standard for comparison is acetophenone—the one substrate common to the testing of almost all reported catalysts. By this measure, the state of the art is 94–97% ee, reached by several systems. Bis(oxazolidine)–pyridine (Pybox) complexes of rhodium give up to 94% ee,⁴ while three ferrocenyl-based systems provide levels of enantioselectivity in the range of 95–97% ee.^{5–10} We were attracted to this reaction as a suitable test of our recently developed mass spectrometry enantiomeric excess determination (MSEED) analytical method^{11,12} in the context of a combinatorial-style search for new catalysts. An attractive feature was the prevalent application of P,N-ligands

to Rh- and Ru-catalyzed hydrosilylation.^{13–16} Particularly appropriate for prospects of modular, and therefore combinatorial, synthesis were chiral phosphite and phosphonate ligands reported by the groups of Seebach (such as **1**),^{17,18} Scharf,¹⁹ Pastor,²⁰ and Pfaltz (**2**, used for asymmetric Pd-catalyzed allylation).²¹ Also intriguing was the report of dramatic temperature and solvent effects in the asymmetric hydrosilylation reaction,¹⁹ making methods of efficient reaction optimization of interest for the practical development of effective conditions for particular substrates.



A set of 21 phosphite P,N-ligands related to **1** and **2**, containing chiral diol and amino alcohol components **3**

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SCHEME 1

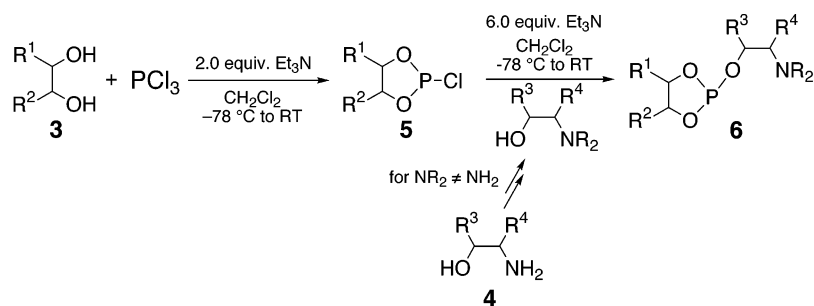
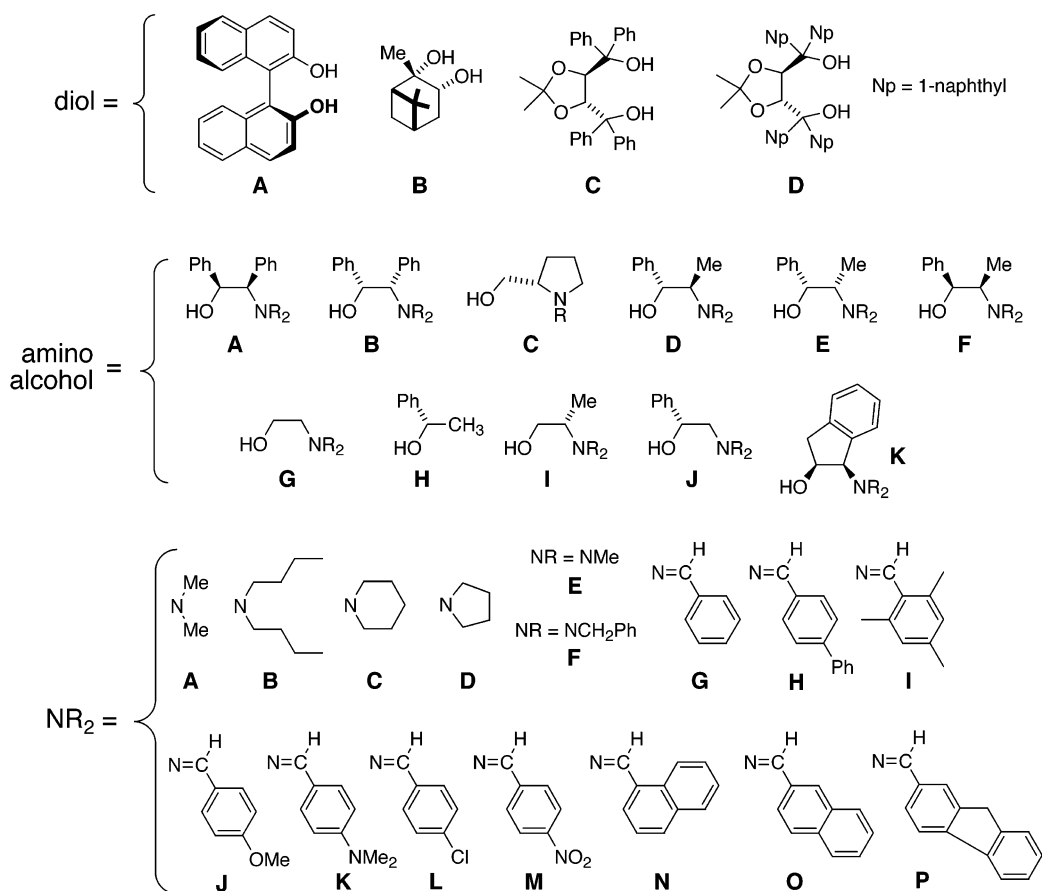


CHART 1



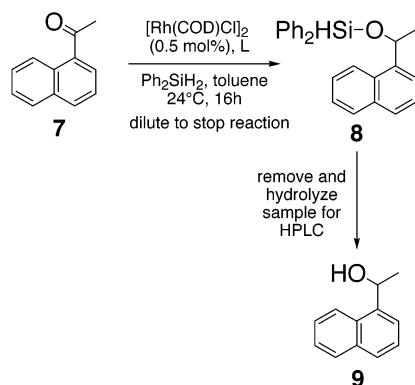
and **4**, was initially assembled by the general method shown in Scheme 1. Stepwise attachment of diol and amino alcohol fragments to phosphorus was accomplished for each ligand in one pot to give phosphites **6**. The structures of the components employed are shown in Chart 1. Amino alcohol components were either used as purchased (i.e., most of the dimethylamino-containing compounds) or capped at nitrogen prior to reaction with the intermediate chlorophosphinite **5**. All ligands were obtained in high yields and high purity after flash chromatography using degassed solvent, and were characterized initially by ^1H and ^{31}P NMR. The identities and purities of the candidates selected for further investigation (see below) were further substantiated by ^{13}C NMR, IR, and combustion analysis.

Complexes of the assembled ligands with rhodium(I) were made by mixing with $[\text{Rh}(\text{COD})\text{Cl}]_2$ and tested for asymmetric catalytic activity toward the hydrosilylation of 1-naphthyl methyl ketone (**7**) as shown in Scheme 2.

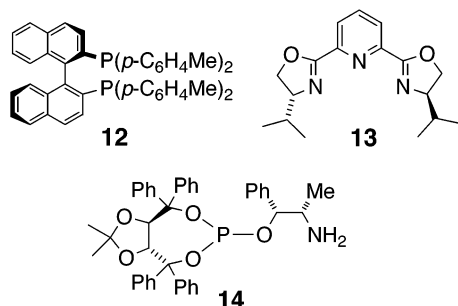
This screen was performed to provide preliminary evaluation of the candidates and to validate the MSEED method^{11,12} in a catalysis trial. The reactions were performed on a 50 μmol scale in substrate to provide samples for ee determination by chiral HPLC as well as MSEED. Thus, silyl ether **8** was hydrolyzed to the alcohol **9** for evaluation by HPLC, and an aliquot of the silyl ether was converted to a mixture of diastereomeric esters **11** by the one-pot combination of fluoride deprotection and carbodiimide-mediated coupling shown. This procedure is necessary to avoid the incorporation of water into aliquots analyzed by acylation with **10a** + **10b**. While the use of an excess of these mass-tagged acids allows a small amount of water to be tolerated, too much water poisons the acylation reaction and leads to poor analytical results. The use of *N*-acylproline reagents **10a,b** has been previously described.¹¹

The results of the preliminary assay are shown in Figure 1 for two sets of reactions, differing only in the

SCHEME 2



ratio of ligand to rhodium. (*R*)-*p*-Tolyl-BINAP (**12**) and (*S*)-Pybox (**13**)^{3,4,22,23} were included for comparison. In the



first set of reactions, employing a ligand:metal ratio of 2.0, all of the reactions showed a fair to good degree of completion as measured by a comparison of the HPLC peaks for the starting ketone and product **9**, corrected for their relative molar absorptivities. The values for enantiomeric excess of the product as measured by HPLC and MSEED were quite similar in most cases and within $\pm 10\%$ ee for all reactions showing substantial enantioselectivity. With the exception of diminished reactivities for four ligands (**ABG**, **BBG**, **AAG**, and **13**), the results for a ligand:Rh ratio of 4:1 are comparable to those of the 2:1 set.

Ligand **CEA**, derived from (+)-TADDOL and (1*S*,2*R*)-(+)-*N*-methylephedrine, immediately emerged as superior among the P,*N*-systems tested, with results slightly better than those of *p*-tolyl-BINAP ligand **12**. Also noteworthy among the results are the following observations: (a) Epimeric ligands **CDA** and **CEA** gave dramatically different results, showing that the configuration of the α -amino carbon center is important. (b) Asymmetric induction dropped upon changing the *N*-methyl substituents of **CEA** to *N*-butyl groups (**CEB**), showing that some steric congestion apparently exists at or near the amine center. (c) None of the imine-containing ligands

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(23) As shown in Figure 1, Pybox ligand **13** performs poorly under our conditions, in contrast to its reported effectiveness when used in a 7:1 ligand:Rh ratio (ref 4). Differences between the reaction conditions include the much shorter time used here for “aging” of the ligand + metal mixture (1 h vs 24 h), the lack of silver salt in our system, and the ligand-to-metal ratio.

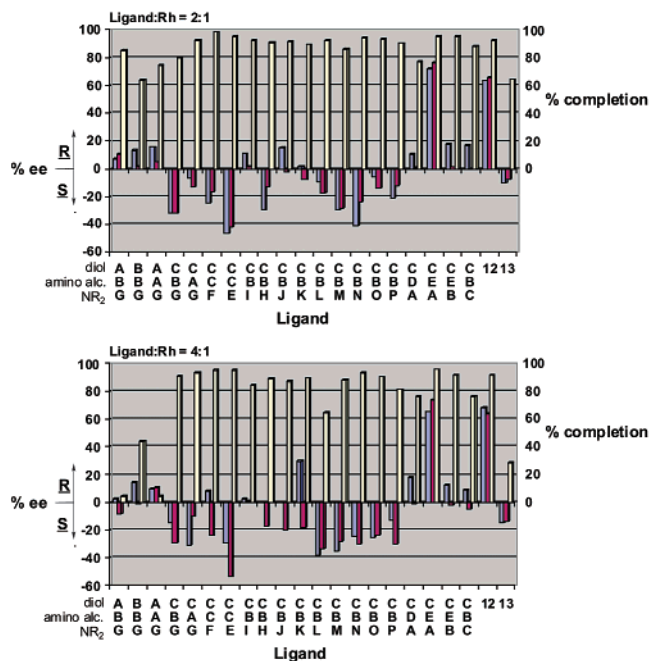
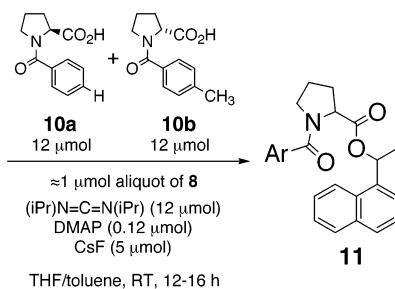
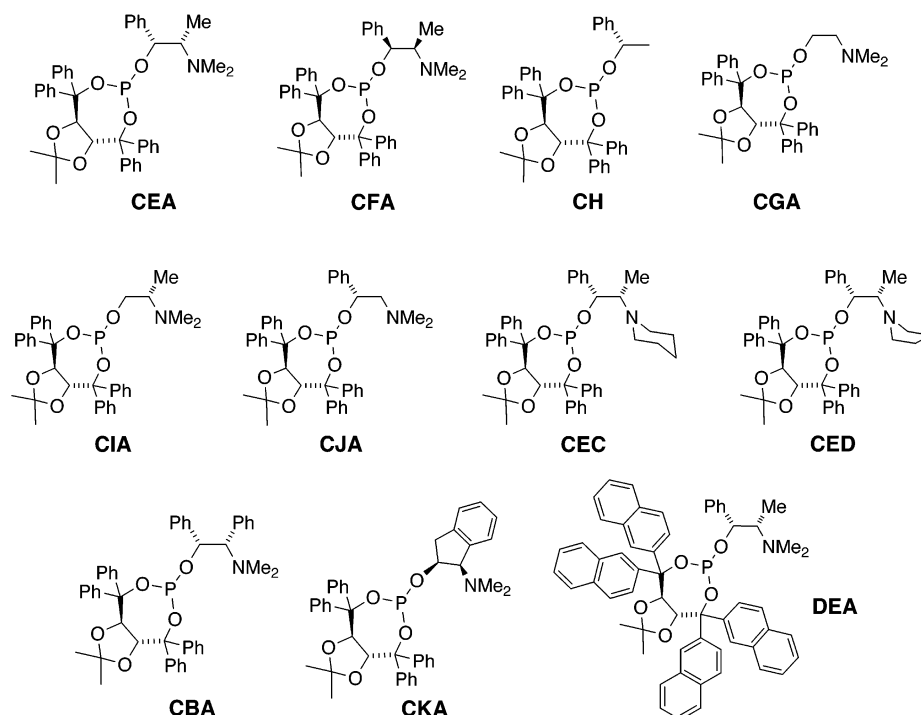


FIGURE 1. Results of hydrosilylation of 1-acetonaphthone with a selection of chiral ligands. Key: yellow, percent completion as measured by HPLC; blue, % ee as measured by the kinetic resolution/mass spectrometry (MSEED) method; red, % ee as measured by chiral HPLC (Chiralcel OD).

(incorporating NR_2 components **G–P**) were effective, despite the common use of such ligating moieties in the chemistry of Rh(I) and other electron-rich transition-metal centers. Unfortunately, imine-containing ligands incorporating the effective TADDOL–norephedrine backbone (such as **CEG**) were found to be unstable toward hydrolysis during purification.

The modified set of ligands shown in Chart 2 was synthesized and tested as above to gain further insight into structure–activity relationships. The results for 1-acetonaphthone and diphenylsilane, determined by chiral HPLC, are summarized in Table 1. The “matched” nature of the diol and amino alcohol in ligand **CEA** is apparent in the poor performance of the catalyst containing the “mismatched” *N*-methylephedrine in **CFA** (entry 2 vs 3). Omitting either the amine substituent (**CH**, entry

CHART 2



4) or chiral substitution on the amino alcohol unit (**CGA**, entry 5) gave poor enantioselectivity. Both the phenyl and methyl substituents on the ephedrine backbone are necessary, as shown by entries 6 and 7 (**CEA** vs **CIA** and **CJA**). The poor result with the *N,N*-dibutyl derivative **CEB** (Figure 1) prompted us to explore the steric environment about the amine center with ligands **CEC** and **CED**, incorporating piperidine and pyrrolidine rings, respectively. Both of these ligands also gave very poor catalysts (entries 8 and 9), as did the replacement of the backbone methyl group with a phenyl moiety in ligand **CBA** (entry 10). These results suggest that the steric environment about the 1-position of the ephedrine component is hindered, and/or that there is a strong dependence of catalyst performance on the conformation about the central ephedrine C–C bond. An attempt to restrict that conformation with ligand **CKA** did not provide good asymmetric induction, although catalytic activity was high (entry 11). Last, replacement of the TADDOL phenyl groups with naphthyls (**DEA**, entry 12) produced an effective catalyst, although slightly less enantioselective than the “parent” **CEA** structure.

The performance of a subset of the above catalysts with a selection of seven ketones (**7**, **15–20**) was measured using the MSEED technique implemented in the chip-

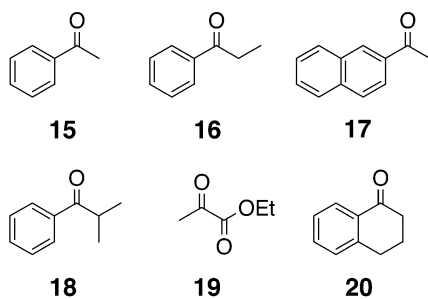


TABLE 1. Results for Hydrosilylation of 1-Acetonaphthone (7) at Room Temperature under Standard Conditions (0.5% [Rh(cod)Cl]₂, 2% Ligand, Ph₂SiH₂, Toluene), Determined by Chiral HPLC

entry	ligand	% ee (config)	% conv	entry	ligand	% ee (config)	% conv
1	none	0	59	7	CJA	47 (<i>R</i>)	94
2	CEA	78 (<i>R</i>)	95	8	CEC	2 (<i>R</i>)	62
3	CFA	0.9	92	9	CED	4 (<i>R</i>)	29
4	CH	14 (<i>S</i>)	97	10	CBA	8 (<i>S</i>)	38
5	CGA	30 (<i>S</i>)	76	11	CKA	18 (<i>R</i>)	95
6	CIA	31 (<i>S</i>)	93	12	DEA	66 (<i>R</i>)	91

based DIOS (desorption/ionization on silicon) mass spectrometry method.^{24–27} In this variation, the hydrosilylation and subsequent mass-tagged derivatization reactions were performed as before (Scheme 2), but the resulting samples were analyzed by depositing 0.1–0.5 μ L aliquots on a porous silicon plate (100 samples per plate) followed by DIOS-MS analysis, instead of injection into an electrospray ionization mass spectrometer. The data collection rate is thereby reduced from 5 min to approximately 10 s per sample.²⁴ The results are shown in Table 2. Note that runs giving higher values of % ee were checked by chiral HPLC, showing the DIOS-MSEED method to be a reliable and convenient screening method for asymmetric induction.

The results show that ligands **CEA** and **CJA** afford the most consistently selective reductions, with enantioselectivities in the 70–94% ee range for five of the seven

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TABLE 2. Screening of Asymmetric Hydrosilylation of a Selection of Ketones (Columns) Using the Indicated Ligands (Rows) in a 2:1 Ligand:Rh Molar Ratio under Standard Conditions^a

	7	15	16	17	18	19	20
CDA	13	−4	16	26	−17	29	−20
CEA	80 (81.9)	84 (80.4)	36	102 (93.9)	15	98 (89.1)	99 (93.6)
DEA	29	48	19	23	6	99 (92.5)	39
CED	46	43	36	75 (78.2)	13	18	35
CJA	58.7 (54.6)	63.0 (64.9)	59	60.4 (62.5)	11	48	80.9 (70.0)
CBG	21	20	34	45	3	17	60 (63.9)
12	67 (62.3)	48	58	60 (53.4)	16	−30	41
13	33	26	51	50	3	31	1

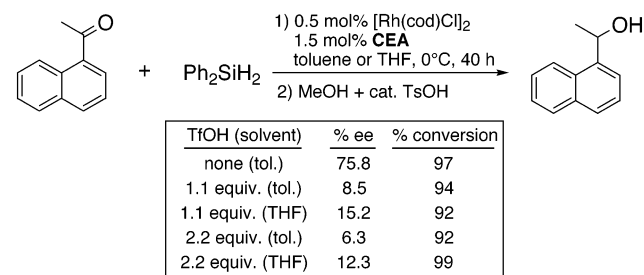
^a The values given are % ee measured by the DIOS-MSEED method; all reactions proceeded to significant levels of completion (> 50%), as determined by relative mass spectral peak intensities. Values in parentheses were obtained by separate analysis on chiral HPLC (Chiralcel OD); negative numbers denote that the *S*-enantiomer is present in excess. The most selective reactions for each ketone are marked with values in bold type.

substrates. Ethyl ketone **16** is accommodated best by ligand **CJA**, but the maximum enantioselectivity (ca. 59%) is only fair. Isopropyl ketone **18** is resistant to asymmetric hydrosilylation by this set of complexes. Interestingly, ethyl pyruvate (**19**) is quite efficiently handled by Rh complexes of **CEA** or **DEA**. Ketones **17** and **20** were subjected to reduction on a 1 mmol scale with ligand **CEA** to obtain the corresponding (*R*)-alcohols in 86.1% ee (54% isolated yield) and 84.0% ee (67% isolated yield), respectively. Ketone **19** was reduced on a 1 mmol scale using ligand **DEA** in 88.0% ee (50% yield). The values obtained in these preparative runs differ from the screening results due to necessary changes in concentration and starting temperature, and presumably can be further optimized.²⁸

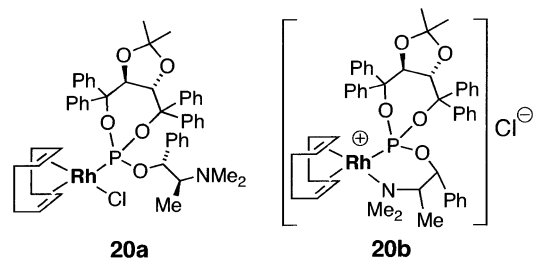
Several additional parameters were checked for a subset of effective ligands. The addition of silver salts to rhodium and ruthenium halide catalysts has been reported to give improved activity and enantioselectivity.^{16,22} However, when screened by normal (i.e., using electrospray ionization MS) MSEED with 2:1 L/Rh catalysts involving ligands **CBG**, **CBN**, **CCE**, **CEA**, **CH**, and **12**, the addition of AgBF₄ in 1–4-fold molar excess with respect to rhodium gave rise to no improvement in asymmetric induction, while AgPF₆ and AgOTf slowed the reaction noticeably without improving enantioselectivity. The use of other silanes (with analysis of ee by chiral HPLC) showed Ph₂SiH₂ and (1-naphthyl)(Ph)SiH₂ to be the best in the reduction of **7**.²⁹

The sensitivity of the process to the presence, size, and stereochemistry of the amino substituent of **CEA** (described above) suggests that coordination of N to Rh may be important in the catalytic cycle. This was supported by the observation that the addition of triflic acid to a 3:1 ligand/Rh catalyst mixture in either toluene or THF poisoned the enantioselectivity of the reaction while retaining catalytic activity (Scheme 3).

Examination of the ³¹P NMR spectrum of the complex formed from a mixture of [Rh(cod)Cl]₂ and **CEA** (ligand: Rh = 1.2:1) in benzene-*d*₆ showed a single dominant

SCHEME 3

species (115.6 ppm, d, ¹J_{P,Rh} = 254 Hz), a minor signal (125.3 ppm, d, ¹J_{P,Rh} = 232 Hz, approximately 1/8 the signal intensity of the major resonance), and a trace signal for the uncomplexed ligand (140.1 ppm, s). The analogous 2.1:1 (ligand/Rh) mixture showed the “major” complex as the only Rh–phosphine species, along with the free ligand signal at equal intensity. These data demonstrate that a complex of 1:1 Rh:**CEA** stoichiometry, presumably a monomer, is formed even in the presence of excess ligand. The ¹H NMR spectra revealed bound cyclooctadiene to be present, so the pre-catalyst can be formulated as [Rh(cod)(**CEA**)]Cl, **20a**, or [Rh(cod)(**CEA**)Cl], **20b**. The difference between them is the occupancy of a coordination site by the pendant amine or chloride, respectively. Monophosphite rhodium complexes have been previously shown to be good catalysts of asymmetric hydrogenation reactions.³⁰



The question of nitrogen coordination in **20** is of interest because known P,N-ligands almost invariably employ sp²-hybridized nitrogen centers, expected to be well matched with the “soft” nature of the Rh(I) center, in contrast to the tertiary amine moiety of **CEA** and related ligands. ¹H–¹⁵N HMQC NMR spectroscopy³¹ was

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(28) Due to heating of the solution upon addition of silane, for the larger-scale reactions the mixture of ketone, catalyst, and solvent was cooled to −10 °C before addition of silane. The reaction mixtures were maintained at 0 °C for 1 h and then allowed to warm to room temperature.

(29) Hydrosilylation of **7** in the presence of 1% Rh and 2% **CEA** (toluene, room temperature) gave the following values of enantiomeric excess (all with the *R*-isomer in excess): Ph₂SiH₂, 77.7%; PhSiH₃, 1.9%; PhMeSiH₂, 5.8%; (1-naphthyl)PhSiH₂, 77.9%; Et₂SiH₂, 34.4%; poly-(methylhydrosiloxane), no reaction.

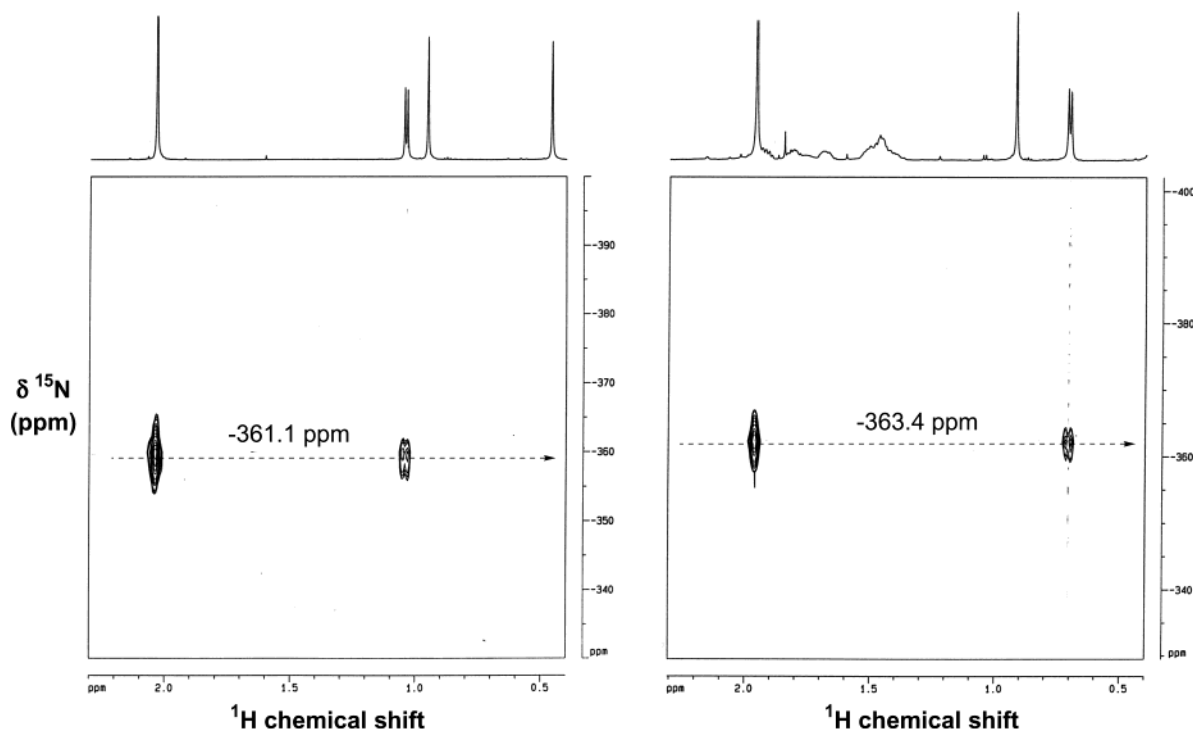


FIGURE 2. ^1H – ^{15}N HMQC NMR spectra of **CEA** (left) and a 1.05:1 (ligand/Rh) mixture of **CEA** and $[\text{Rh}(\text{cod})\text{Cl}]_2$ (right) in C_6D_6 solvent.

used to extract ^{15}N chemical shifts by magnetization transfer from protons coupled to the nitrogen center of interest. The spectra, shown in Figure 2, revealed a scant 2.3 ppm shift in the ^{15}N resonance upon complexation of the ligand to rhodium, suggesting that the nitrogen center is *not* coordinated to the metal. However, one of the NMe_2 methyl groups to which the ^{15}N resonance is coupled shifted upfield by 0.33 ppm, consistent with its occupancy of a position in which it experiences shielding, possibly close to the metal center or an aromatic substituent. Ephedrine-derived P,N-ligand complexes of Rh(I) have been previously described in which the nitrogen center is found to be either bound or free, depending on the ligand-to-metal ratio and the availability of coordination sites.³²

The addition of 10 equiv of **7** did not completely dislodge cyclooctadiene, but did give rise to an additional Rh–monophosphite complex, as evidenced by the appearance of a new signal in the ^{31}P NMR spectrum at 102.4 ppm (d, $^1J_{\text{P,Rh}} = 240$ Hz) in addition to the doublet at 115.6 ppm. A mixture of **CEA**, rhodium, and diphenylsilane (1.2:1.0:12) again showed two major peaks, the normal 115.6 ppm doublet and a new resonance at 128.4 ppm ($^1J_{\text{P,Rh}} = 206$ Hz). These data suggest that the $[\text{Rh}(\text{CEA})]^+$ center is sensitive to weak donor ligands, making it difficult to assign the structure of the active complex. Examination of a reaction mixture (containing excess Ph_2SiH_2 and **7** relative to Rh–**CEA**) after hydrosilylation was complete showed COD to be liberated from the metal and one dominant species by ^{31}P NMR and two species (major and minor) by ^1H – ^{15}N HMQC NMR. The chemical shifts of these signals are very close to those of

the precatalyst, and it would be difficult to detect ^{15}N – ^{103}Rh coupling (expected 8–20 Hz^{33,34}) under these conditions. Amine coordination to rhodium is therefore not proven, but we regard it as likely during the catalytic cycle.

We have described here the implementation of mass spectrometry-based screening methods for the discovery of catalysts for the asymmetric hydrosilylation of a variety of ketones. The MSEED technique, and especially the variant incorporating DIOS mass spectrometry, is a useful tool, particularly when the testing of different substrates would otherwise require the cumbersome optimization of chromatographic techniques for enantiomeric excess determination in each case.

The family of chiral phosphite P,N described here are easy to make and moderately effective in providing an environment for asymmetric induction. High sensitivity to the nature of the silane is also demonstrated. The chiral ligand that emerges as the best candidate, **CEA**, bears diol, amino alcohol, and *N*-alkyl components that each are shown to be important to overall performance. The further optimization of this type of ligand and the application of our methods to other ligands and reactions are subjects of current interest in our laboratory.

Experimental Section

General Methods. Ligand syntheses and catalytic reactions were performed under nitrogen using an inert atmosphere box or standard Schlenk techniques. CH_2Cl_2 was dried over CaH_2 , distilled, and stored over 4 Å molecular sieves.

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Tetrahydrofuran (THF), benzene, and toluene were dried and distilled from sodium–benzophenone. Silica gel (230–400 mesh) was used for flash chromatography. ^1H , ^{31}P , and ^{13}C NMR spectra were recorded at 200, 80.9, and 50.3 MHz, respectively; two-dimensional ^1H – ^{15}N HMQC correlation NMR spectroscopy was performed at 600 MHz for ^1H . Mass spectrometry ee determination via electrospray ionization and DIOS-MS measurements were obtained as previously described.^{25–27} Chiral HPLC analysis was performed using a Chiralpak OD column (hexanes/2-propanol eluent mixtures, flow rate ≤ 0.5 mL/min). Elemental analyses were performed at Midwest Microlabs (Indianapolis, IN). All chiral diol and amino alcohol components were obtained from commercial sources and were used as received. The method for assembly of ligand components was adapted from those reported for structures **1** and **2**.^{17,18,21}

Representative Procedure for Ligand Syntheses (Ligand CEA). To a flame-dried Schlenk tube containing PCl_3 (2.0 mmol, 174 μL) in CH_2Cl_2 (2.0 mL) was added Et_3N (580 μL , 4.1 mmol) at -40 °C under nitrogen. After the mixture was stirred for 5 min, a solution of (–)-TADDOL (2.0 mmol, 93.3 mg) in CH_2Cl_2 (8 mL) was added by syringe over 10 min. The reaction mixture was stirred at -40 to -10 °C for 1 h and then at room temperature for 2 h. To the resulting solution was added Et_3N (1.5 mL, 10 mmol), followed by a solution of (1*R*,2*S*)-(–)-*N*-methylephedrine in CH_2Cl_2 (4 mL) at -40 °C. The reaction mixture was allowed to warm to room temperature slowly and was then stirred for 2 days. Filtration, evaporation of solvents, and flash chromatography purification using 25–40% EtOAc in hexanes (degassed by N_2 purging) afforded the ligand **CEA** as a white power (925 mg, 69%). Mp: 165–167 °C. ^1H NMR: δ 0.42 (s, 3H), 1.09 (d, $J = 7.1$ Hz, 3H), 1.10 (s, 3H), 2.26 (s, 6H), 2.74–2.80 (m, 1H), 4.99–5.09 (m, 2H), 5.58 (dd, $J = 4.8, 9.4$ Hz, 1H), 7.02–7.62 (m, 25H). ^{31}P NMR (CDCl_3): δ 140.31 (s). ^{13}C NMR (CDCl_3): δ 9.41, 26.80, 27.96, 42.07, 66.20, 78.07, 81.83, 83.23, 83.42, 86.55, 113.69, 127.77, 127.81, 127.83, 128.02, 128.10, 128.16, 128.38, 128.4, 128.54, 128.70, 128.77, 129.01, 129.78, 130.19, 130.23, 142.98, 143.51, 146.94, 147.51. Anal. Calcd for $\text{C}_{42}\text{H}_{44}\text{NO}_5\text{P}$: C, 74.87; H, 6.58; N, 2.08. Found: C, 74.85; H, 6.60; N, 2.11. Characterization data for other ligands appears in the Supporting Information.

Procedure for Survey-Scale Catalytic Reactions (Scheme 2). In the drybox a 2 mL vial was charged with 25 μL (0.0025 mmol) of a $[\text{Rh}(\text{COD})\text{Cl}]_2$ stock solution (1.479 g, 3.0 mmol, in 30 mL of benzene) and 25 μL (0.01 mmol) of a ligand stock solution (0.40 mmol in 1.0 mL of benzene). The mixture was stirred for 1 h at room temperature, followed by the addition of 25 μL (0.05 mmol) of ketone (substrate) stock solution (7.0 mmol in 3.5 mL of benzene). The resulting solution was allowed to stand at room temperature for 10 min

and then was chilled to -30 °C for 20 min. The catalytic reaction was initiated by the addition of 25 μL (0.08 mmol) of silane solution. The reaction mixture was agitated with a rotary shaker in the drybox at room temperature overnight and then stopped by dilution with 900 μL of benzene.

MSEED Analysis (Scheme 2). A 25 μL aliquot (containing ≤ 1.0 μmol of product) of the diluted hydrosilylation reaction mixture was removed to a new vial and treated sequentially with 25 μL (≤ 5 μmol) of a CsF suspension (2.25 g, 15.0 mmol, in 15.0 mL of THF), 120 μL (24 μmol) of a stock solution containing an equimolar mixture of mass-tagged acids **10a** and **10b** (15.0 mmol each in 150 mL of CH_2Cl_2), and 100 μL of a stock solution containing DMAP (0.12 mmol) and DIC (12.0 mmol) in 60 mL of CH_2Cl_2 . The resulting reaction was kept at room temperature for about 15 h. The solvent was then allowed to evaporate, the residue was resuspended in 500 μL of methanol, and the solid material was allowed to settle. A 0.5 μL aliquot of the supernatant was used directly for DIOS-MS analysis, whereas an aliquot of 8 μL was diluted with methanol to 1.0 mL for electrospray ionization MS analysis.

Procedure for 1-mmol-Scale Catalytic Reactions. To a flame-dried Schlenk flask containing $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.01 mmol, 4.93 mg) in 1 mL of anhydrous toluene was added a solution of ligand (0.03 mmol) in anhydrous toluene (1 mL) under nitrogen. The mixture was stirred at room temperature for 90 min, after which ketone (2.0 mmol) in 1 mL of anhydrous toluene was added dropwise. After being stirred at room temperature for 10 min, the mixture was cooled to -10 °C, followed by addition of a solution of Ph_2SiH_2 (2.4 mmol, 445 μL) in 2 mL of anhydrous toluene over 15 min. The stirred reaction solution was maintained at 0 °C for 1 h and then was allowed to stir at room temperature for 9 h. A solution of 0.6 mL of MeOH containing 1% TsOH was added dropwise, and the reaction mixture was stirred until it appeared clear. Evaporation of solvents and flash chromatography (20–25% EtOAc in hexanes) afforded the product.

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Supporting Information Available: Characterization data for the ligands and details of experiments involving additives. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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