JOC Article

Synthesis and Application of a New Bisphosphite Ligand Collection for Asymmetric Hydroformylation of Allyl Cyanide

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A series of mono- and bidentate phosphites was prepared with (*S*)-5,5′,6,6′-tetramethyl-3,3′-di-*tert*-butyl-1,1′-biphenyl-2,2′-dioxy [(*S*)-BIPHEN] as a chiral auxiliary and screened in the asymmetric hydroformylation of allyl cyanide. These hydroformylation results were compared with those of two existing chiral ligands, Chiraphite and BINAPHOS, whose utility in asymmetric hydroformylation has been previously demonstrated. Bisphosphite **11** with a 2,2′-biphenol bridge was found to be the best overall ligand for asymmetric hydroformylation of allyl cyanide with up to 80% ee and regioselectivities (branch-to-linear ratio, b/l) of 20 with turnover frequency of 625 [h^{-1}] at 35 °C. BINAPHOS gave enantioselectivities up to 77% ee when the reaction was conducted in either acetone or neat but with poor regioselectivity (b/l 2.8) and activities 7 times lower than that of **11**. The product of allyl cyanide hydroformylation using (*R*,*R*)-**11** was subsequently transformed into (*R*)-2-methyl-4-aminobutanol, a useful chiral building block. Single-crystal X-ray structures of (*S*,*S*)-**11** and its rhodium complex **19** were determined.

Introduction

Asymmetric chemocatalysis is one of the most powerful synthetic methodologies for producing high value added chiral compounds. Its success and potential are due to the achievable combination of high selectivity, high activity, and reduced environmental impact.[1] This has been best demonstrated in the field of asymmetric hydrogenation, which can be regarded as the most highly developed asymmetric chemocatalytic technology to date.[2] Conversely, while hydroformylation is the largest volume homogeneous transition-metal-catalyzed reaction used today, its asymmetric version is relatively underdeveloped. Asymmetric hydroformylation enantioselectively introduces a highly versatile aldehyde functional group that is amenable to a number of synthetic transformations.[3] It is therefore surprising that the development of such a route for the production of highly functionalized chiral building blocks has not been utilized industrially.

To date, most efforts in this field have concentrated on a relatively narrow substrate range, notably the asymmetric hydroformylation of vinylarenes to access enantiomerically enriched 2-aryl propionic acids (the profen class of nonsteroidal antiinflammatory drugs).[4] An important breakthrough in this area was made during the early 1990s with the introduction by Union Carbide of a rhodium-catalyzed system involving chiral bisphosphites, such as (*R*,*R*)-Chiraphite (**1**). Enantioselectivities of up to 90%, along with high branched regioselectivity, were obtained for several prochiral vinylarenes.[5] Van Leeuwen *et al*. reported detailed studies of the effects of

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(2) (a) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley-Interscience: New York: 1994; Chapter 2, p 16. (b) Brown, J. M.; Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, Berlin: 1999; Vol. 1, Chapters 5 and 6, pp 101 and 199. (c) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York: 2000; Chapter 1, p 1.

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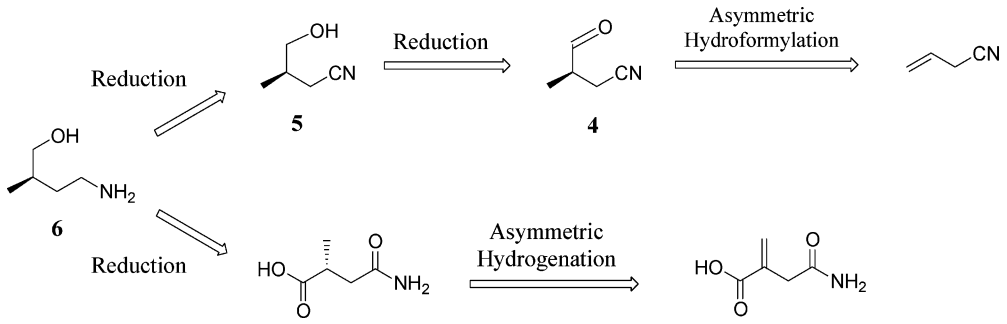
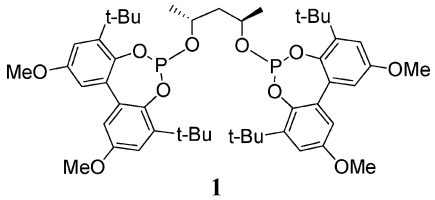
SCHEME 1. Proposed Routes to (*R*)-2-Methyl-4-aminobutanol



structural changes in this ligand class and found that product selectivity was influenced by the bridge length, biphenol substituents and relative configuration of chiral centers in these bisphosphites.[6] Considerable success was also made by Takaya *et al*. using (*R*,*S*)-BINAPHOS (**2**),[7] with enantioselectivities as high as 96% reported for the hydroformylation of styrene, although the regioselectivity with BINAPHOS was substantially lower than that for Chiraphite.



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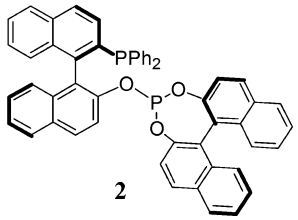

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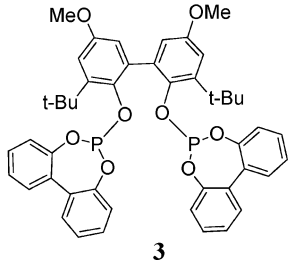

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Herein, we report the extension of the bisphosphites originally developed at Union Carbide to optically active ligands that are bridged by achiral diolate groups. Such a ligand design has the combined advantages of a modular nature and an ease of synthesis, which allows for the introduction of a wide variety of stereoelectronic properties.

The application of these ligands for asymmetric hydroformylation of allyl cyanide is also described (Scheme 1).[8,9] The chiral, branched aldehyde product is converted to 4-hydroxy-3-methylbutyronitrile (**5**) and 2-methyl-4-aminobutanol (**6**), both being important chiral building blocks found in several molecules of biological interest.[10] For example, (*S*)-4-hydroxy-3-methylbutyronitrile has been used by Merck in the synthesis of a potent nonpeptide gonadotropin releasing hormone antagonist (**7**),[10c] whereas (*R*)-2-methyl-4-aminobutanol has been in the preparation of a novel tachykinin NK_1 receptor antagonist (**8**) by Takeda.[10a,b] We have previously demonstrated a highly efficient and selective route to a precursor of **6** via asymmetric hydrogenation,[11] albeit hindered by the downstream chemistry which required a stoichiometric hydride reduction to obtain the final amino alcohol. This alternative approach via asymmetric hydroformylation uses an entirely catalytic approach that circumvents this problem.

Results and Discussion

Ligand Design and Synthesis. Phosphites are highly effective ligands for olefin hydroformylation. Bisphosphite ligands, in particular, allow dramatic control of hydroformylation regioselectivity through structural manipulation. For biphenol-based bisphosphites, the nature and position of substituents can lead to a predominance of either the linear or the branched aldehyde regioisomer. For example, the biphenol-based bisphosphite (**3**), which is bridged by a biphenol unit with 3,3′-*tert*-butyl substituents, is highly selective for the production of linear aldehydes from hydroformylation of terminal olefins.[12] Chiraphite, which has *tert*-butyl substituents on the cyclic dibenzo[*d*,*f*][1,3,2]dioxaphosphepin moiety, leads to a preference for branched aldehyde from terminal olefins.

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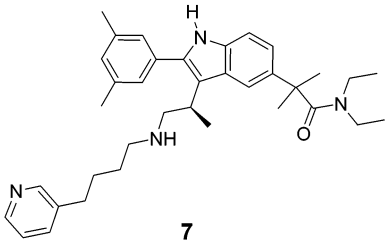

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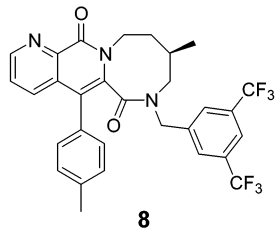

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Indeed for Chiraphite, the nature of the substituents at the 3,3′-positions is critical for obtaining both high regioselectivity and enantioselectivity with vinylarenes. Van Leeuwen has found that trimethylsilyl substituents also lead to highly enantioselective ligands.[6b] In addition, for optically active bisphosphites, the nature of the bridging diolate moiety plays a crucial role. This chiral auxiliary effectively transfers stereochemical information to the *tert*-butyl-substituted biphenol rings, which form a chiral environment around the Rh catalytic center, leading to chiral cooperativity. The bridging diolate also controls the chelate bite angle, a structural feature that has been proposed to influence hydroformylation regioselectivity.[4] For Chiraphite, the (2*R*,4*R*)-pentanediolate moiety, in combination with 3,3′-di-*tert*-butylbiphenol units, leads to high regioselectivity and enantioselectivity for hydroformylation of vinylarenes.

Unfortunately, as with most asymmetric catalysts, no single ligand structure is generally useful for all types of substrates. Therefore, the development of asymmetric hydroformylation into a synthetic method of broad utility requires access to a structurally diverse family of ligands. Such diversity is quite difficult with phosphine ligands, whose syntheses can often require multiple steps. Phosphites, however, can be assembled in a much easier way by reacting an alcohol or diol with a phosphorus halide. Bisphosphites can be prepared by reaction of a phosphorochloridite, $(RO)_2PCl$, with a diol. This diol bridges the two phosphite moieties and controls the bite angle of the resulting ligand. For ligands such as Chiraphite, however, the requirement for this bridging diol to be optically active limits the diversity of readily accessible structures. For this reason we sought to develop a related class of bisphosphite ligands based on achiral diols. By utilizing the commercially available (*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-biphenyl-2,2′-diol (BIPHEN-H_2), as the chiral auxiliary, achiral diols could be used to prepare a much more diverse collection of bisphosphite ligands. Using this strategy we have prepared a library of bisphosphite ligands for evaluation in asymmetric hydroformylation of a variety of olefinic substrates. In this paper, we describe the synthesis and characterization of a subset of this bisphosphite library, along with related monodentate phosphites for comparison.

Phosphite ligands were prepared by the reaction of (*S*)-(BIPHEN)PX (X = Br (**9**), I (**10**)) with the corresponding alcohol or diol (Scheme 2). Reactions were performed in the presence of NEt_3 (1.1 equiv/OH) at ambient temperature in toluene in an N_2-filled glovebox. Use of the phosphorobromidite or phosphoroiodite reagents avoided the need for elevated reaction temperatures often used with analogous phosphorochloridite reagents. Bisphosphites were obtained as white powders after filtration, evaporation of toluene from the filtrate, and trituration of the resulting solid with MeCN. Products were characterized by ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR, HRMS, and elemental analysis.

Monodentate phosphites (**15**−**17**)[13] each exhibit a singlet in the $^{31}P\{^1H\}$ NMR spectrum at approximately 135 ppm. The ^1H and $^{13}C\{^1H\}$ NMR spectra are consistent with C_1 symmetry of these ligands as they show the presence of two and four nonequivalent *t*-Bu and Me groups, respectively. Bisphosphites **11**, **12**, and **14** each exhibit a single resonance in the $^{31}P\{^1H\}$ NMR spectrum, as well as two *t*-Bu and four Me resonances in the ^1H and $^{13}C\{^1H\}$ NMR spectra, which is consistent with the C_2 symmetry of these ligands. Biaryl-bridged bisphosphites **11**−**13** can contain an additional element of chirality and potentially exist in two diastereomeric forms, depending upon the configuration of the bridging biaryl moiety. Bisphosphites **11** and **12**, however, exhibit a single resonance in the $^{31}P\{^1H\}$ NMR spectra, consistent with either formation of a single diastereoisomer or two diastereoisomers undergoing rapid interconversion. The ^1H NMR spectra of **11** and **12** also contained only resonances assignable to a single species. Previous NMR and chiral HPLC studies have found that rotation about the central biphenol axis is slow in related biphenol-bridged bisphosphites.[14] The biphenylmethyl-bridged bisphosphite **13**, however, exhibits two singlets of equal intensity in the $^{31}P\{^1H\}$ NMR spectrum. In addition, four resonances for the methylene groups were observed in the ^1H NMR spectrum of **13**. These results are consistent with formation of a 1:1 mixture of the (*S*,*S*,*S*) and (*S*,*R*,*S*) diastereomers of **13**, which differ by the configuration of the biphenylmethyl moiety. No evidence for interconversion of these two diastereomers was obtained from NOESY experiments at room temperature, suggesting the rotational barrier about the central biaryl bond of **13** is greater than 19 kcal/mol.

Hydroformylation Screening Study. Asymmetric hydroformylation studies were performed in an 8-cell parallel stirred reactor system. Catalysts were generated in situ from the reaction of the appropriate ligand with $Rh(CO)_2(acac)$ in toluene at 150 psi syn gas (H_2:CO 1:1). Under these conditions the active catalyst precursor Rh(bisphosphite)$(CO)_2H$ is formed.[4] Hydroformylation reactions were performed for 3 h in toluene with substrate-to-catalyst ratios of 300 and 500 to 1 for runs at 35 and 70 °C, respectively. These parameters were chosen in order to ensure significant conversions and relatively rapid throughput were obtained. Reaction mixtures were analyzed by chiral stationary phase GC using a Chiraldex A-TA column. This analytical method allowed determination of conversion, regioselectivity (branched/linear) and enantioselectivity, as well as the extent of olefin

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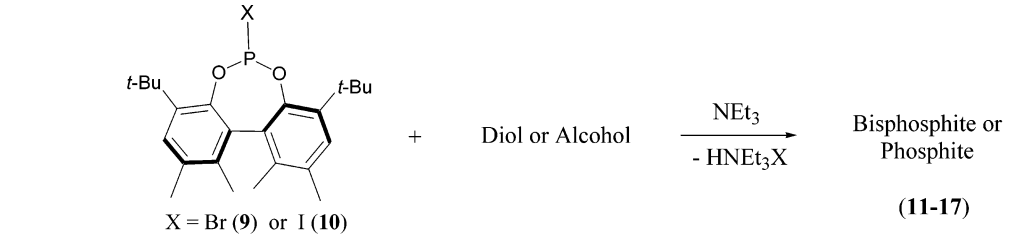
SCHEME 2. Synthesis of Novel Phosphites



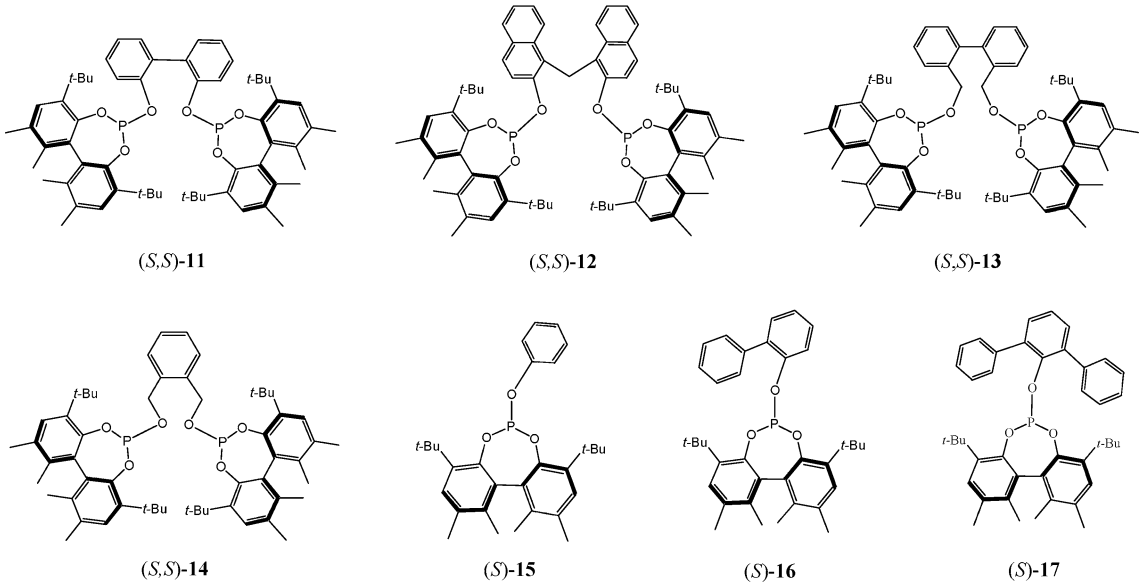


TABLE 1. Asymmetric Hydroformylation of Allyl Cyanide with Ligands 1, 2, and 11−17[a]

entry	ligand	*T* (°C)	conv (%)[b]	regioselectivity (b/l)[c]	% ee (configuration)
1	**1**	35	21.9	7.3	15.3 (*R*)
		70	100	6.1	15.0 (*R*)
2	**2**	35	65.0	2.9	51.5 (*S*)
		70	100	2.3	52.6 (*S*)
3	**2**[d]	35	47.8	**2.7**	**75.6** (*S*)
4	**11**	35	84.8	**15.5**	**78.1** (*S*)
		70	100	11.2	68.3 (*S*)
5	**11**[d]	35	100	15.1	74.5 (*S*)
6	**12**	35	100	12.4	12.1 (*S*)
		70	100	9.3	17.9 (*S*)
7	**13**	35	8.7	7.1	9.2 (*R*)
		70	100	5.2	2.3 (*R*)
8	**14**	35	73.3	8.5	0.7 (*S*)
		70	100	6.7	5.5 (*S*)
9	**15**	35	11.3	6.3	43.7 (*R*)
		70	100	4.3	32.7 (*R*)
10	**16**	35	65.0	5.2	39.1 (*R*)
		70	100	3.8	28.5 (*R*)
11	**17**	35	30.5	5.0	14.1 (*R*)
		70	100	3.9	6.7 (*R*)

[a] Pressure 150 psi. Ligand:Rh = 1.2:1 for bidentate and 2.2:1 for monodentate phosphites. Solvent = toluene (2.5 mL). Molar allyl cyanide:Rh = 300:1 at 35 °C and 500:1 at 70 °C. [b] Percentage conversion of allyl cyanide after 3 h. [c] b/l = branched-to-linear ratio. [d] Runs performed in acetone.

hydrogenation to butyronitrile and olefin isomerization to crotonitrile.

Results of allyl cyanide hydroformylation are given in Table 1. BINAPHOS and Chiraphite were included in the study for comparison. Asymmetric hydroformylation of allyl cyanide using Rh-BINAPHOS was recently reported to occur with 66% ee and b/l of 2.6.[8] Under our conditions, BINAPHOS gave similar results (51.5% ee, b/l 2.9) (entry 2). Slightly lower ee values might be due to differences in the Rh/BINAPHOS ratio used. Chiraphite, which is very effective for asymmetric hydroformylation of vinylarenes, gave low enantioselectivity for allyl cyanide hydroformylation. The regioselectivity for allyl cyanide hydroformylation with Chiraphite, however, was significantly higher (b/l 7.3) than that observed with BINAPHOS (entry 1). The results reported in Table 1 show that the best combination of enantio- and regioselectivity was obtained by employing (*S*)-BIPHEN units in combination with 2,2′-biphenol (ligand **11**), which gave 78.1% ee and b/l of 15.5 at 35 °C (entry 4). The remaining bisphosphites gave very poor enantioselectivities with moderate regioselectivity ranging from 2.4 to 7.1. Interestingly, monodentate phosphites **15** and **16** gave higher enantioselectivities (39.1−43.7% ee) than bisphosphites **12**−**14** but with lower regioselectivity. The fastest hydroformylation rate was observed for ligand **12** with complete conversion attained in 2 h, based on gas consumption curves. As expected, runs conducted at higher temperature (70 °C) led to significantly faster conversions at the cost of lower regio- and enantioselectivities. A brief examination of alternative solvents revealed that when the reaction is conducted in acetone, product enantioselectivity using BINAPHOS is surprisingly increased from 51.5% to 75.6% ee (entries 2 and 3), whereas no major change in performance is observed in the case of **11** (entries 4 and 5). No significant changes in enantioselectivities were observed for phosphites **12**−**17** in acetone. To compare bisphosphite **11** and BINA-

SCHEME 3. Synthesis of 2-Methyl-4-aminobutanol via a Catalytic Asymmetric Hydroformylation−Hydrogenation Sequence

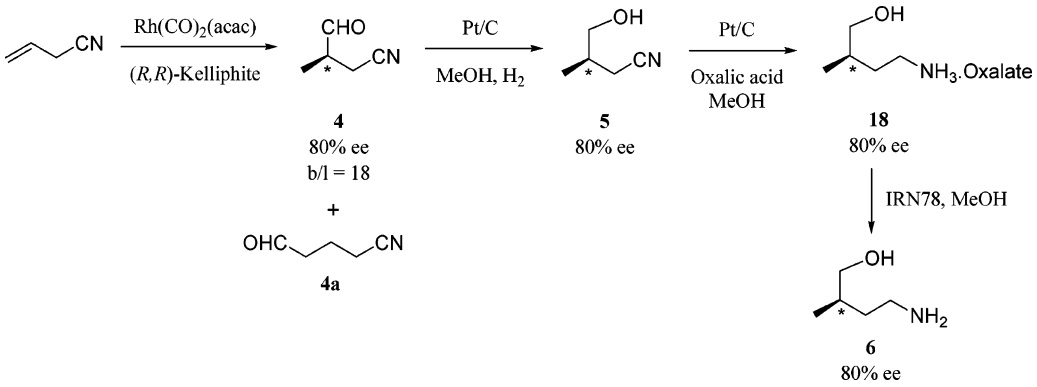


TABLE 2. Comparison between BINAPHOS (2) and Kelliphite (11) in Asymmetric Hydroformylation of Allyl Cyanide at Low Catalyst Loadings[a]

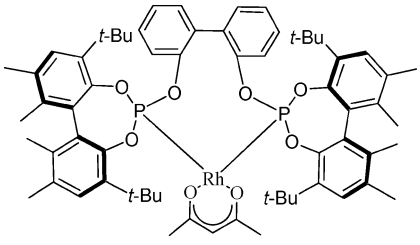
entry	ligand	AC/Rh[b]	conv (%)[c]	regio-selectivity (b/l)[d]	% ee (config-uration)	time for complete conversion[e]
1	**2**	2,000	64.0	2.8	74.7 (*S*)	
		4,000	37.1	2.9	75.1 (*S*)	
		10,000	14.8	2.7	77.2 (*S*)	
2	**11**	2,000	100	17.8	77.8 (*S*)	6 h
		4,000	100	17.3	78.8 (*S*)	8 h
		10,000	100	18.5	78.8 (*S*)	16 h

[a] Pressure 150 psi. Ligand:Rh = 1.2:1. Temp = 35 °C; 3.5 mL of allyl cyanide. [b] Molar AC (allyl cyanide)/Rh ratio. [c] Percent conversion of allyl cyanide after 17 h. [d] b/l = branched-to-linear ratio. [e] Estimated based on gas consumption profiles.

PHOS more extensively, a series of hydroformylation reactions of allyl cyanide was conducted at low catalyst loading (allyl cyanide:Rh of 2,000−10,000:1) in neat olefin as we observed that reaction rates were highest when the reaction was conducted without solvent. As shown in Table 2, the catalyst prepared from **11** is about 7 times more active than BINAPHOS at 10,000:1 allyl cyanide:Rh catalyst loadings. Under these conditions allyl cyanide hydroformylation was complete with ligand **11** within 16 h, which translates into an average turnover frequency of 625 turnovers per hour. Unexpectedly, the regioselectivity with **11** increased from 15.5 (Table 1, entry 4) to 18.5 (Table 2, entry 2) at the lowest catalyst loadings. This appears to be a result of performing these reactions without solvent.[15] Under the same conditions, the regioselectivity with BINAPHOS was not affected. On the other hand, the hydroformylation enantioselectivity with **11** remained unchanged, whereas that with BINAPHOS increased by 25% ee to a maximum value of 77.2% ee at the lowest catalyst loading. This increase in enantioselectivity with BINAPHOS seems to correlate with solution polarity, as higher values were obtained in either acetone or neat allyl cyanide than in toluene solution. A preliminary study to examine the consequences of varying the CO and H_2 partial pressures gave no improvement over the results obtained with a 1:1 CO:H_2 syn gas mixture. In all cases, levels of substrate hydrogenation or isomerization were found to be negligible (<0.5%). These results demonstrate that **11**, which we will now refer to as Kelliphite, is by far the best overall ligand for asymmetric hydroformylation of allyl cyanide.

To demonstrate the feasibility of performing asymmetric hydroformylation on a larger scale, allyl cyanide (75 mL) was hydroformylated in a 300 mL pressure vessel using (*R,R*)-Kelliphite (**11**). Running the reaction at substrate to catalyst (S:C) molar ratio of 1,500:1, 30 °C, and 145 psi syn gas (1:1) gave complete conversion in 5 h with 80% ee and b/l ratio of 20. Synthesis of the aforementioned chiral building block, 2-methyl-4-aminobutanol, was demonstrated, as shown in Scheme 3. Stepwise reduction of the aldehyde and nitrile functionalities was performed using 10% Pt on carbon catalyst. Reduction of the aldehyde group of **4** with Pt/C gave the nitrile alcohol **5** without racemization. The nitrile alcohol **5** was subsequently reduced with Pt/C and oxalic acid to yield **18**, the oxalate salt of the desired amino alcohol, again with no loss of enantioselectivity. Alternatively, both reactions could be performed in one pot by the addition of oxalic acid after reduction of the aldehyde functionality was complete. Treatment of salt **18** with basic resin IRN78 afforded the amino alcohol free base **6** in 80% ee. A limited crystallization screen of several chiral and achiral acids identified (−)-camphanic acid as being suitable for upgrading the enantioselectivity to 96% ee and removing the linear adducts albeit with a low recovery (10% isolated yield); this study is currently ongoing.

Synthesis of [(*S,R,S*)-Kelliphite]Rh(acac) (19). To investigate the coordination mode of ligand Kelliphite **11**, the synthesis of a representative Rh complex was undertaken. Bisphosphite **11** was reacted with 1 equiv of (COD)Rh(acac) in toluene solution, which led to quantitative formation of [(*S,R,S*)-Kelliphite]Rh(acac), **19**. Complex **19** was characterized by multinuclear and multidimensional NMR spectroscopy, HRMS, and X-ray single-crystal analysis (see below). The complex exhibits C_2



19

(15) A small amount of toluene was present in these runs as a result of addition of toluene stock solutions of catalyst and ligand.

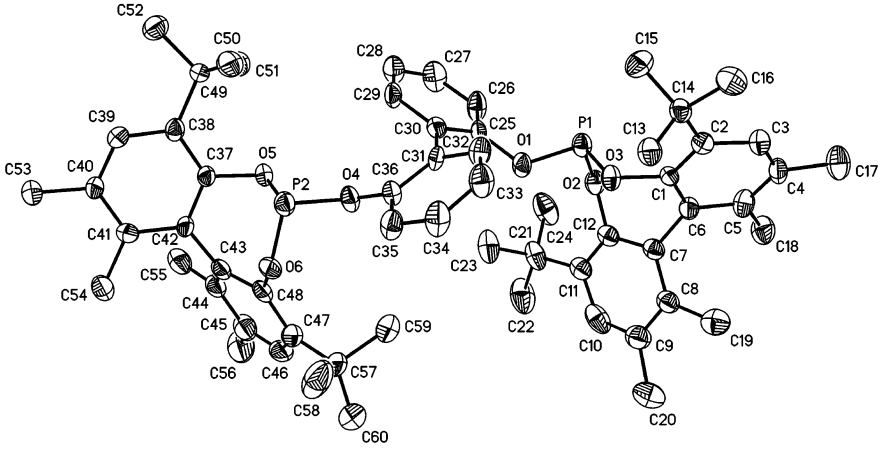


FIGURE 1. Molecular structure and labeling scheme for (*S*,*R*,*S*)-Kelliphite ligand (**11**) with 40% probability of thermal ellipsoids. Hydrogen atoms were removed for clarity.

TABLE 3. Selected Bond Lengths (Å) and Angles (deg) for Ligand 11 and Complex 19

bond/angle	**11**	**19**[19]
P1−O1	1.628(1)	1.601(5), 1.614(5)
P1−O2	1.617(2)	1.610(4), 1.625(4)
P1−O3	1.639(2)	1.636(5), 1.622(5)
P2−O4	1.644(2)	1.608(5), 1.611(5)
P2−O5	1.631(2)	1.631(4), 1.611(5)
P2−O6	1.607(2)	1.619(4), 1.615(5)
O1−P1−O2	102.92(8)	100.3(2), 100.4(2)
O1−P1−O3	92.11(8)	96.5(2), 98.0(2)
O2−P1−O3	101.96(8)	103.2(2), 103.2(2)
O4−P2−O5	91.80(8)	98.1(2), 97.1(2)
O4−P2−O6	103.12(8)	99.9(2), 101.2(3)
O5−P2−O6	102.14(7)	103.0(2), 102.2(2)
Rh−O7		2.077(5), 2.084(5)
Rh−O8		2.085(5), 2.053(4)
P1−P2	7.704	3.234, 3.234
Rh−P1		2.149(2), 2.140(2)
Rh−P2		2.145(2), 2.147(2)
P2−Rh−P1		97.74(8), 97.94(7)
P1−Rh−O8		88.6(2), 85.5(2)
P2−Rh−O7		85.0(2), 87.2(2)
O7−Rh−O8		88.9(2), 88.9(2)

symmetry in solution based on NMR spectroscopy. The ^{1}H NMR spectrum of **19** exhibited only one set of BIPHEN resonances (two *t*-Bu and four Me signals) and four aromatic signals for the bridging 2,2′-biphenyldiol. The ^{31}P{^{1}H} NMR spectrum of **19** shows a doublet at δ 130.57 ($^1J_{Rh-P}$ = 317.3 Hz).

Crystal Structure Analysis of (*S*,*R*,*S*)-Kelliphite (11) Ligand. Crystals of **11** were obtained from acetonitrile solution at −35 °C. A thermal ellipsoid drawing of **11** is shown in Figure 1. Selected bond distances and angles are included in Table 3. Bisphosphite **11** crystallizes in the monoclinic, noncentrosymmetric space group $P2_1$ together with two acetonitrile solvent molecules in the asymmetric unit. In the solid state the ligand has molecular C_2 symmetry with a 2-fold axis positioned at the center of the C30−C31 bond. The dihedral angles between the aryl rings of the dibenzo[*d*,*f*][1,3,2]dioxaphosphepin rings are 62.2° and 62.4°. This torsion angle is very similar to that in the only other known phosphite structure containing a 3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-2,2′-bisphenoxy (BIPHEN) unit (63.5°).[16] The magnitude of this dihedral angle strongly depends on the O−X−O (X = heteroatom) bond angle of the BIPHEN

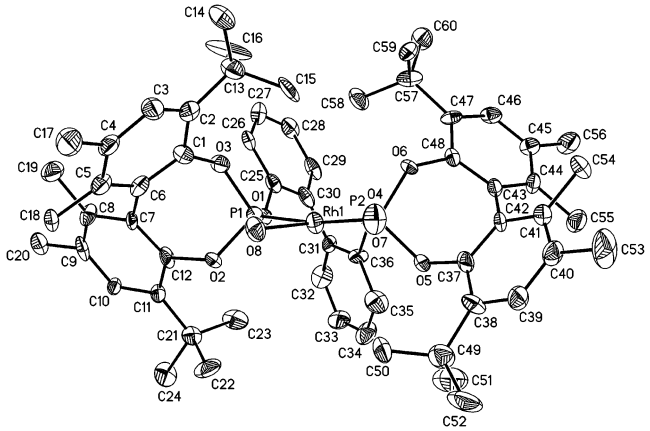


FIGURE 2. Molecular structure and labeling scheme for [(*S*,*R*,*S*)-Kelliphite]Rh(acac) complex (**19**) with 40% probability of thermal ellipsoids. Carbon atoms of acac fragment and all hydrogen atoms were removed for clarity.

fragment. For example, this dihedral angle is much larger (102.2°) in a molybdenum carbene complex[17] containing BIPHEN unit, which is a direct consequence of a larger O−Mo−O bond angle (127.0°) as compared to the endocyclic O−P−O in **11** (102.0°). The dihedral angle between aryl rings in analogous 3,3′,5,5′-tetra-*tert*-butyl-2,2′-bisphenoxyphosphite ligands is significantly smaller (48−55°)[18] suggesting that steric repulsions between the two methyl groups in the 6,6′-position of BIPHEN contribute to widening of this angle in **11**. The stereochemistry around the central 2,2′-biphenoxy unit is of (*R*) configuration and is the same as that found in rhodium complex **19** (vide infra). The dihedral angle between aryl rings in the 2,2′-biphenoxy fragment is 123.9°. The two phosphorus atoms are separated by 7.7 Å. The sum of

(16) Suárez, A.; Méndez-Rojas, M. A.; Pizzano, A. *Organometallics* **2002**, *21*, 4611.

(17) Alexander, J. B.; Schrock R. R.; Davis, W. D.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometalllics* **2000**, *19*, 3700.

(18) (a) Pastor, S. D.; Shum, S. P.; Rodebaugh, R. K.; Delellis, A. D.; Clarke, F. H. *Helv. Chem. Acta* **1993**, *76*, 900. (b) Pastor, S. D.; Shum, S. P.; DeBellis, A. D.; Burke, L. P.; Rodebaugh, R. K.; Clarke, F. H.; Rihs, G. *Inorg. Chem*. **1996**, *35*, 949. (c) DeBellis, A. D.; Pastor, S. D.; Rihs, G.; Rodebaugh, R. K.; Smith, A. R. *Inorg. Chem*. **2001**, *40*, 2156. (d) Shum, Sai P.; Pastor, S. D.; Rihs, G. *Inorg. Chem*. **2002**, *41*, 127.

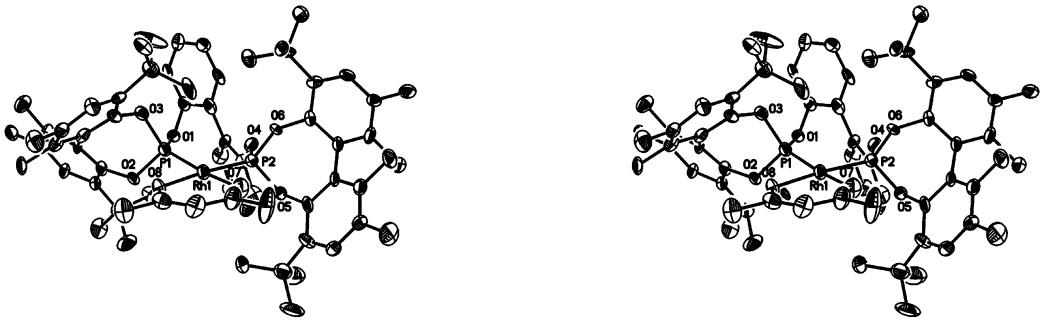


FIGURE 3. Stereoview of [(*S*,*R*,*S*)-Kelliphite]Rh(acac) complex (**19**).

bond angles around phosphorus atoms is 297.0°, which is very similar to the values observed in other phosphites of this type.[18]

Crystal Structure Analysis of [(*S*,*R*,*S*)-Kelliphite]-Rh(acac) (19). Crystals of **19** were obtained at room temperature by slow evaporation of an acetonitile solution that contained a small amount of toluene. Thermal ellipsoid drawing and stereoview of **19** are shown in Figures 2 and 3, respectively. Selected bond distances and angles are included in Table 3. The complex crystallizes in the orthorhombic, noncentrosymmetric space group $C222_1$. Two crystallographically independent molecules of complex **19** are present in the asymmetric unit together with two molecules of acetonitrile and one-half molecule of toluene. The geometry around the rhodium atom is close to idealized square planar with mean deviation from planarity of 0.03 Å. The chelate bond angle P1−Rh−P2 (97.74(8)°, 97.94(7)°)[19] is larger than found in analogous complexes containing monodentate phosphites[20] (e.g., *cis*-$[P(OPh)_3]_2$Rh(acac), 93.8°)[20b] but is similar to related complexes containing bidentate[21] phosphite ligands coordinated to the Rh(acac) fragment, which fall in the range of 96.7−99.9°. This increase in the P1−Rh−P2 bite angle is a consequence of steric congestion between the two very bulky phosphite groups. In the solid state the complex has molecular C_2 symmetry with 2-fold axis positioned at the center of the C30−C31 bond. Because of the substantial size and C_2 symmetry of the bisphosphite, fragments of the ligand extend into the rhodium coordination sphere (see Figure 3). Two methyl carbons of *t*-Bu groups that are related by C_2 symmetry (C15 and C50) are positioned only 3.3−3.7 Å above and below the Rh−O8 and Rh−O7 bond vectors, indicating close proximity of these *t*-Bu groups to the coordination environment of rhodium. Presumably, this sterically restricted C_2 symmetric environment is responsible for the high enantioselectivity observed with ligand **11**. The dihedral angles between aryl rings of the dibenzo[*d*,*f*]-[1,3,2]-dioxaphosphepin rings are 63.1° (62.3°) and 62.8° (58.4°) and are very similar to those found in free ligand **11** (vide supra). The central 2,2′-biphenoxy unit has (*R*) absolute configuration with a biaryl dihedral angle of 60.5° (59.8°). Unlike in the case of **11** where it is not clearly apparent why there is a preference for (*R*) configuration in the middle biphenoxy unit in the solid state,[22] the metal complex of **19** with (*S*,*S*,*S*) configuration would certainly be disfavored as a result of steric repulsions between BIPHEN *tert*-butyl groups and the bridging 2,2′-biphenoxy fragment. In metal complexes containing the sterically less crowded tris(2,2′-biphenyl)-bisphosphite ligand, both (*S*,*S*,*S*)/(*R*,*R*,*R*) and (*S*,*R*,*S*)/(*R*,*S*,*R*) configurations are encountered.[22] The distance between the two phosphorus atoms in **19** equals 3.234 Å. The sum of bond angles around phosphorus atoms in **19** is also very similar to that in **11** (297.0°) and equals 300.0° (301.6°) and 301.0° (300.5°) for P1 and P2, respectively.

Conclusion

Novel mono- and bidentate phosphites were prepared from commercially available (*S*)-5,5′-6,6′-tetramethyl-3,3′-di-*tert*-butyl-1,1′-biphenyl-2,2′-diol [(*S*)-BIPHEN-H_2] and phenols in high yields. All new ligands were investigated in asymmetric hydroformylation of allyl cyanide as the product of this reaction can be transformed into enantiomerically enriched 2-methyl-4-aminobutanol, a useful chiral building block. The C_2 symmetric bisphosphite **11** (Kelliphite) with 2,2′-biphenoxy bridge was found to be the best ligand for asymmetric hydroformylation of allyl cyanide with up to 80% ee and regioselectivities (branch-to-linear ratio, b/l) of 20 with turnover frequency of 625 [h^{-1}] at 35 °C. It was also found that enantioselectivities induced by BINAPHOS increased from 51% ee, when reaction was performed in toluene, to 77% ee when the reaction was conducted in either acetone or neat. In all cases, however, the regioselectivity (b/l 2.8) and catalytic activity was substantially lower than that of **11**. The product of allyl cyanide hydroformylation was further converted to (*R*)-2-methyl-4-aminobutanol via two reduction steps without any loss of enantioselectivity.

Experimental Section

The 6,6′-(((1*R*,3*R*)-1,3-dimethyl-1,3-propanediyl)bis(oxy))bis-(4,8-bis(1,1-dimethylethyl)-2,10-dimethoxy-dibenzo(*d*,*f*)(1,3,2)-

(19) Because there are two independent molecules in the asymmetric unit, two values for each bond distance and angle are provided.

(20) (a) Lamprecht, G. J.; Leipoldt, J. G.; Van Zyl, G. J. *Inorg. Chem. Acta* **1985**, *97*, 31. (b) Leipoldt, J. G.; Lamprecht, G. J.; Van Zyl, G. J. *Inorg. Chem. Acta* **1985**, *96*, L31. (c) Van Zyl, G. J.; Lamprecht, G. J.; Leipoldt, J. G. *Inorg. Chem. Acta* **1985**, *102*, L1. (d) Heaton, B. T.; Jacob, C.; Markopoulos, J.; Markopoulou, O.; Nahring, J.; Skylaris, C. K.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1996**, 1701.

(21) (a) Van den Beuken, E. K.; de Lange, W. G. J.; Van Leeuwen, P. W. N. M.; Veldman, N.; Spek, A. L.; Feringa, B. L. *J. Chem. Soc., Dalton Trans.* **1996**, 3561. (b) Meetsma. A.; Jongsma, T.; Challa, G.; Van Leeuwen, P. W. N. M. *Acta Crystallogr.* **1993**, *C49*, 1160. (c) Jiang, Y.; Xue, S.; Yu, K.; Li, Z.; Deng, J.; Mi A.; Chan, A. S. C. *J. Organomet. Chem.* **1999**, *586*, 159. (d) Van Rooy, A.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J.; Veldman, N.; Spek, A. L. *Organometallics* **1996**, *15*, 835.

(22) Interestingly the stereochemistry of tris(2,2′-biphenyl)bisphosphite ligand is (*R*, *R*, *R*)/(*S*, *S*, *S*). Baker, M. J.; Harrison, K. N.; Orpen, A. G.; Pringle, P. G.; Shaw, G. *Chem. Commun.* **1991**, 803.

dioxaphosphepin[5] (Chiraphite) and (*R,S*)-2-(diphenylphosphino)-(1,1′-binaphthalen-2′-yl-1,1-binaphthalene-2,2′-diyl)phosphite [(*R,S*)-BINAPHOS)] [7] were prepared according to literature procedures.

Crystal Structures of 11 and 19. Data were collected on diffractometers equipped with graphite monochromatic crystals, Mo Kα radiation sources (λ = 0.71073 Å), and SMART CCD detectors. Cell parameters were refined using 4918 and 8192 reflections for **11** and **19**, respectively. The structures were solved by direct methods in SHELXTL6.1[23] from which the positions of all non-H atoms were obtained. The non-H atoms were refined with anisotropic thermal parameters, and all of the H atoms were calculated in idealized positions, refined riding on their parent atoms. The asymmetric unit of **11** consists of the ligand and two acetonitrile molecules. The asymmetric unit of **19** contains two Rh complexes, two acetonitrile molecules and one-half of a toluene molecule. The solvent molecules in both structures were disordered and could not be modeled properly; thus the program SQUEEZE, a part of the PLATON package[24] of crystallographic software, was used to calculate the solvent disorder area and remove its contribution to the overall intensity data. For **11** a total of 633 parameters were refined in the final cycle using 9856 observed reflections with $I > 2\sigma(I)$ to yield R_1, wR_2 and S (goodness of fit) of 5.45%, 10.65% and 0.853, respectively. For **19** a total of 1427 parameters were refined in the final cycle using 10710 observed reflections with $I > 2\sigma(I)$ to yield R_1, wR_2, and S (goodness of fit) of 4.68%, 9.56% and 0.909, respectively.

Preparation of (*S*)-4,8-Di-*tert*-butyl-6-chloro-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a,c*]cycloheptene. To a 200 mL toluene solution containing (*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-biphenyl-2,2′-diol [(*S*)-BIPHEN-H$_2$] (4.3395 g, 12.2 mmol) was added 1.7146 g (14.49 mmol) of PCl_3 followed by addition of 4.1 mL of NEt_3. During amine addition copious amounts of white precipitate appeared. After stirring overnight the solvent volume was reduced to 80 mL and the solution was filtered. The solid was filtered and washed with 20 mL of cold toluene. Solvent was removed under reduced pressure to give 5.10 g of white solid. Yield 99.5%. ^{1}H NMR (C_6D_6): δ 1.47 (s, 9H, C(CH_3)), 1.53 (s, 9H, C(CH_3)), 1.64 (s, 3H, CH_3) 1.65 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 7.16 (1H), 7.24 (1H). ^{13}C{^{1}H} NMR (C_6D_6): δ 16.46 (*C*H$_3$), 16.73 (*C*H$_3$), 20.38 (*C*H$_3$), 20.42 (*C*H$_3$), 31.29 (d, J_{C-P} = 5.4 Hz, C(*C*H$_3$)$_3$), 32.49 (C(*C*H$_3$)$_3$), 34.81 (*C*(CH$_3$)$_3$), 35.31 (C(*C*H$_3$)$_3$), 128.56 (*C*H), 129.28 (*C*H), 131.91 (d, J_{C-P} = 3.3 Hz, quat), 132.27 (d, J_{C-P} = 6.0 Hz, quat), 133.18 (quat), 134.00 (quat), 135.03 (d, J_{C-P} = 1.4 Hz, quat), 135.85, 137.91 (d, J_{C-P} = 2.0 Hz, quat), 138.72 (d, J_{C-P} = 4.1 Hz, quat), 144.52 (d, J_{C-P} = 6.0 Hz), 146.14 (d, J_{C-P} = 2.0 Hz, quat). ^{31}P{^{1}H} NMR (C_6D_6): δ 166.1.

Preparation of (*S*)-4,8-Di-*tert*-butyl-6-bromo-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a,c*]cycloheptene (9). (*S*)-3,3′-Di-*tert*-butyl-5,5′,6,6′-tetramethyl-biphenyl-2,2′-diol [(*S*)-BIPHEN-H$_2$] (4.06 g, 11.45 mmol) was dissolved in 100 mL of toluene. NEt_3 (3.25 mL, 23.31 mmol) was added. PBr_3 (1.1 mL, 11.6 mmol) was added to the reaction mixture, which was then stirred for 18 h. The suspension was filtered, and the filtrate was evaporated to give the product as a white solid (3.41 g, 7.87 mmol, 69% yield). ^{1}H NMR (C_6D_6): δ 7.18 (s, 1H), 7.08 (s, 1H), 1.93 (s, 3H), 1.92 (s, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.48 (s, 9H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (C_6D_6): δ 16.39 (s, CH$_3$), 16.72 (s, CH$_3$), 20.34 (s, CH$_3$), 20.37 (s, CH$_3$), 31.20 (d, J_{C-P} = 3.7 Hz, C*C*H$_3$), 32.76 (s, C*C*H$_3$), 34.74 (s, *C*CH$_3$), 35.44 (s, *C*CH$_3$), 128.65 (*C*H), 129.55 (s, *C*H), 130.89 (d, J_{C-P} = 3.0 Hz, quat), 132.16 (d, J_{C-P} = 6.0 Hz, quat), 133.27 (quat), 134.10 (quat), 135.08 (quat), 135.89 (quat), 137.65 (d, J_{C-P} = 1.6 Hz, quat), 138.73 (d, J_{C-P} = 3.4 Hz, quat), 145.45 (d, J_{C-P} = 5.3 Hz, quat), 147.00 (d, J_{C-P} = 2.3 Hz, quat). ^{31}P{^{1}H} NMR (C_6D_6): δ 182.4.

Preparation of (*S*)-4,8-Di-*tert*-butyl-6-iodo-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[a,c]cycloheptene (10). (*S*)-4,8-Di-*tert*-butyl-6-chloro-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[a,c]cycloheptene (5.4 g, 12.89 mmol) was dissolved in 50 mL of toluene. To this solution was added TMS-I (3.10 g, 15.5 mmol) dissolved in 5 mL of toluene. After addition of TMS-I the solution assumed a light yellow color. The reaction mixture was stirred overnight. Solvent was removed under reduced pressure to give 6.57 g of product as an off-white powder. Yield 99.9%. ^{1}H NMR (C_6D_6): δ 1.45 (s, 9H, C(CH_3)$_2$), 1.57 (s, 9H, C(CH_3)$_2$), 1.61 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 7.13 (1H), 7.24 (1H). NOESY1D (C_6D_6): irradiation at 7.13 ppm, NOE response at 1.45 and 1.98 ppm; irradiation at 7.24 ppm, NOE response at 1.57 and 1.99 ppm. ^{13}C{^{1}H} NMR (C_6D_6): δ 16.34 (*C*H$_3$), 16.73 (*C*H$_3$), 20.40 (2x*C*H$_3$), 31.02 (d, J_{C-P} = 4.8 Hz, C(*C*H$_3$)$_2$), 33.17 (C(*C*H$_3$)$_2$), 34.61 (*C*(CH$_3$)$_2$), 35.58 (C(*C*H$_3$)$_2$), 128.70 (*C*H), 129.88 (d, J_{C-P} = 1.4 Hz, *C*H), 131.00 (d, J_{C-P} = 3.3 Hz, quat), 131.96 (d, J_{C-P} = 6.0 Hz, quat), 133.32 (quat), 134.12 (quat), 135.15 (quat), 135.93 (quat), 136.99 (d, J_{C-P} = 2.0 Hz, quat), 138.52 (d, J_{C-P} = 3.1 Hz), 147.32 (d, J_{C-P} = 6.6 Hz), 148.48 (d, J_{C-P} = 2.0 Hz). HSQC (C_6D_6): δ 1.45/31.02, 1.57/33.17, 1.61/16.34, 1.63/16.73, 1.98/20.40, 1.99/20.40, 7.13/128.70, 7.24/129.88. ^{31}P{^{1}H} NMR (C_6D_6): δ 209.1. Anal. Calcd for $C_{24}H_{32}IO_2P$: C, 56.48; H, 6.32. Found: C, 56.60; H, 6.59.

Preparation of (*S,S*)-6,6′-((1,1′-Biphenyl)-2,2′-diylbis(oxy))bis(4,8-bis(1,1-dimethylethyl)-1,2,10,11-tetramethyldibenzo(*d,f*)(1,3,2)dioxaphosphepin (11). A solution of 2,2′-biphenol (212 mg, 1.14 mmol) and 300 μL NEt_3 in 15 mL of toluene was added to a solution of (*S*)-4,8-di-*tert*-butyl-6-bromo-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a,c*]cycloheptene (**9**) (983 mg, 2.27 mmol) in 20 mL toluene. The solution was stirred for 18 h at ambient temperature and then filtered. The filtrate was evaporated to a white solid that was triturated with MeCN. The supernatant was decanted, and the solid product was dried under vacuum (737 mg, 68% yield). ^{1}H NMR (C_6D_6): δ 1.38 (s, 18H, C(CH_3)$_3$), 1.42 (s, 18H, C(CH_3)$_3$), 1.70 (s, 6H, CH_3), 1.77 (s, 6H, CH_3), 2.05 (s, 6H, CH_3), 2.12 (s, 6H, CH_3), 6.81 (ddd, 2H, $^3J_{H-H}$ = 7.5 Hz, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 1.2 Hz), 6.98 (ddd, 2H, $^3J_{H-H}$ = 8.1 Hz, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 1.8 Hz), 7.17 (s, 2H), 7.19 (s, 2H), 7.22 (d, 2H, $^3J_{H-H}$ = 8.1 Hz), 7.40 (dd, 2H, $^3J_{H-H}$ = 7.8 Hz, $^4J_{H-H}$ = 1.5 Hz). COSY (C_6D_6): δ 6.81/6.98, 7.40; 6.98/6.81, 7.22; 7.22/6.98; 7.40/6.81, 6.98 (weak). NOESY1D (C_6D_6): irradiation at 2.05 ppm, NOE response at 7.17, 1.70 ppm; irradiation at 2.12 ppm, NOE response at 7.19, 1.77 ppm. ^{13}C{^{1}H} NMR (C_6D_6): δ 16.58 (*C*H$_3$), 16.86 (*C*H$_3$), 20.38 (*C*H$_3$), 20.43 (*C*H$_3$), 31.38 (C(*C*H$_3$)$_3$), 31.58 (C(*C*H$_3$)$_3$), 34.81 (*C*(CH$_3$)), 34.90 (C(*C*H$_3$)$_3$), 121.97 (t, J_{C-P} = 5.4 Hz, *C*H), 123.79 (*C*H) 128.19 (*C*H), 128.51 (*C*H), 128.69 (*C*H), 130.49 (quat), 131.11 (quat), 131.82 (quat), 132.77 (d, J_{C-P} = 2.7 Hz, quat), 132.92 (quat), 133.01 (*C*H), 134.47 (quat), 135.52 (quat), 137.94 (quat), 138.64 (quat) 145.35 (quat), 145.92 (t, J_{C-P} = 3.3 Hz), 149.67 (quat). HSQC (C_6D_6): δ 1.38/31.58, 1.42/31.38, 1.70/16.58, 1.77/16.86, 2.05/20.38, 2.12/20.43, 6.81/123.79, 6.98/128.51, 7.17/128.19, 7.19/128.69, 7.22/121.97, 7.40/133.01. ^{31}P{^{1}H} NMR (C_6D_6): δ 134. Single crystals were grown from acetonitrile solution at −35 °C. HRMS (ESI, (M + Na)$^+$) (*m*/*z*): calcd for $C_{60}H_{72}O_6P_2Na$ 973.470, found 973.469. Anal. Calcd for $C_{60}H_{72}O_6P_2$: C, 75.76; H, 7.63. Found: C, 76.32; H, 8.39.

Preparation of (*S*)-4,8-Bis(1,1-dimethylethyl)-1,2,10,-11-tetramethyl-6-phenoxy-dibenzo(*d,f*)(1,3,2)dioxaphosphepin (15). To 447.7 mg (0.88 mmol) of (*S*)-4,8-di-*tert*-butyl-6-iodo-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a,c*]-cycloheptene (**10**) dissolved in 5 mL of toluene was added 82.6 mg (0.88 mmol) of phenol followed by addition of 1.6 mL (1.14 mmol) of NEt_3. During amine addition, a white solid appeared. After stirring overnight the solution was filtered and solvent was removed under reduced pressure. The residue was redis-

(23) *SHELXTL6.1*; Bruker-AXS: Madison, WI, 2000.

(24) PLATON, written by Professor Anthony L. Spek, Bijvoet Centre for Biomolecular Research, Utrecht University. Current versions of PLATON for Windows are available from Professor Louis J. Farrugia, Department of Chemistry, University of Glasgow at www.chem.gla.ac.uk/~louis/software/.

solved in 4 mL of hexane and filtered, and solvent was removed under reduced pressure to give 410 mg of product as a white solid. Yield 98.0%. ^{1}H NMR (C_6D_6): δ 1.52 (s, 9H, C(CH_3)$_3$), 1.62 (s, 9H, C(CH_3)$_3$), 1.75 (s, 6H, CH_3) 2.07 (s, 6H, CH_3), 6.78 (tm, $^3J_{H-H}$ = 7.5 Hz, 1H), 6.97 (tm, $^3J_{H-H}$ = 8.1 Hz, 2H), 7.14 (dm, $^3J_{H-H}$ = 8.3 Hz, 2H), 7.21 (s, 1H), 7.28 (s, 1H). NOESY1D (C_6D_6): irradiation at 1.52 ppm, NOE response at 7.21 ppm; irradiation at 1.62 ppm, NOE response at 7.28 ppm; irradiation at 2.07 ppm, NOE response at 7.21, 7.28 ppm. ^{13}C{^{1}H} NMR (C_6D_6): δ 17.10 (*C*H$_3$), 17.27 (*C*H$_3$), 20.84 (2x*C*H$_3$), 31.83 (d, J_{C-P} = 5.4 Hz C(*C*H$_3$)$_3$), 32.41 (C(*C*H$_3$)$_3$), 35.26 (*C*(CH$_3$)), 35.59 (C(*C*H$_3$)), 120.76 (d, J_{C-P} = 8.0 Hz, *o*-PhO), 124.10 (*p*-PhO) 128.24 (*C*H), 128.64 (*C*H), 129.91 (*m*-PhO), 131.35 (d, J_{C-P} = 3.4 Hz, quat), 132.28 (quat), 132.28, 132.72 (d, J_{C-P} = 5.4 Hz, quat), 133.01 (quat), 134.84 (quat), 135.58 (quat), 138.50 (d, J_{C-P} = 2.6 Hz), 145.40 (d, J_{C-P} = 6.0 Hz), 152.62 (d, J_{C-P} = 7.4 Hz). HSQC (C_6D_6): δ 1.52/31.83, 1.62/32.41, 1.75/17.10, 17.27, 2.07/20.84, 6.78/124.10, 6.97/129.91, 7.14/120.76, 7.21/128.24, 7.28/128.64. ^{31}P{^{1}H} NMR (C_6D_6): δ 135.60. HRMS (ESI, (M + Na)$^+$) (*m*/*z*): calcd for $C_{30}H_{37}O_3PNa$ 499.2378, found 499.2384. Anal. Calcd for $C_{30}H_{37}O_3P$: C, 75.60; H, 7.83. Found: C, 75.56; H, 7.86.

Preparation of (*S*,*R*,*S*)-(6,6′-(((1,1′-Biphenyl)-2,2′-diyl)-bis(oxy))bis(4,8-bis(1,1-dimethylethyl)-1,2,10,11-tetramethyldibenzo(*d*,*f*)(1,3,2)dioxaphosphepin-kappaP6))-(2,4-pentanedionato-*O*,*O*′)-rhodium [(*S*,*R*,*S*)-Kelliphite Rh(acac)] (19). To a vial was added 150 mg (0.16 mmol) of (*S*,*S*)-6,6′-((1,1′-biphenyl)-2,2′-diylbis(oxy))bis(4,8-bis(1,1-dimethylethyl)-1,2,10,11-tetramethyl-dibenzo(*d*,*f*)(1,3,2)dioxaphosphepin (**11**) and 48.3 mg (0.16 mmol) of [(COD)Rh(acac)]. To this was added 5 mL of toluene, and the yellow solution was stirred overnight. Solvent was removed under reduced pressure, leaving 180 mg of product as a yellow solid. ^{1}H NMR (C_6D_6): δ 1.24 (s, 6H, acac-CH_3), 1.33 (s, 18H, C(CH_3)$_3$), 1.85 (s, 6H, CH_3), 1.92 (s, 18H, C(CH_3)$_3$), 1.97 (s, 6H, CH_3), 2.10 (s, 6H, CH_3), 5.19 (s, 1H, acac-C*H*), 6.77 (ddd, 2H, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 1.5 Hz), 6.84 (ddd, 2H, $^3J_{H-H}$ = 8.3 Hz, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 2.1 Hz), 6.92 (dd, 2H, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 2.1 Hz), 7.11 (s, 2H), 7.26 (s, 2H) 7.81 (dd, 2H, $^3J_{H-H}$ = 8.1 Hz, $^4J_{H-H}$ = 1.2 Hz), one methyl group resonance is overlapping with *t*-Bu peak at 1.92 ppm. ^{13}C{^{1}H} NMR (C_6D_6): δ 16.75 (*C*H$_3$), 17.00 (*C*H$_3$), 20.32 (*C*H$_3$), 20.40 (*C*H$_3$), 27.32 (J_{C-P} = 5.1 Hz, acac-*C*H$_3$), 32.12 (C(*C*H$_3$)), 33.59 (C(*C*H$_3$)), 35.09 (*C*(CH$_3$)), 35.77 (C(*C*H$_3$)), 99.76 (acac-*C*H), 120.14 (*C*H), 124.15 (*C*H), 128.65 (*C*H), 129.34 (*C*H), 129.47 (*C*H), 130.50 (quat), 130.74 (quat) 131.45 (quat) 132.03 (*C*H), 132.25 (quat), 134.77 (quat), 135.05 (quat), 138.14 (quat), 145.52 (t, J_{C-P} = 7.3 Hz, quat), 146.42 (quat), 150.80 (t, J_{C-P} = 6.6 Hz, quat), 184.45 (acac-*C*-O). HSQC (C_6D_6): δ 1.24/27.32, 1.33/32.12, 1.85/16.75, 1.92/33.59, 1.92/17.00, 1.97/20.40, 2.10/20.32, 5.19/99.76, 6.77/124.15, 6.84/128.65, 6.92/132.03, 7.11/129.47, 7.26/129.34, 7.81/120.14. ^{31}P{^{1}H} NMR (C_6D_6): δ 130.57 (d, $^1J_{Rh-P}$ = 317.3 Hz). HRMS (FAB (positive)) (*m*/*z*): calcd for $C_{65}H_{79}O_8P_2Rh$ 1152.4305, found 1152.4377.

Asymmetric Hydroformylation of Allyl Cyanide. Hydroformylation solutions were prepared by addition of ligand and Rh(CO)$_2$(acac) stock solutions to toluene solvent, followed by addition of allyl cyanide solution. Ligand solutions (0.06 M for bidentate ligands and 0.11 M for monodentate ligands) and Rh(CO)$_2$(acac) (0.05 M) were prepared in the drybox by dissolving appropriate amount of compound in toluene at room temperature. The allyl cyanide solution was prepared by mixing 15.3206 g of allyl cyanide, 3.2494 g of decane (as a GC internal standard), and 6.3124 g of toluene (1:0.1:0.3 molar ratio). Hydroformylation reactions were conducted in a reactor system housed in an inert atmosphere glovebox. The reactor system consists of eight parallel, mechanically stirred pressure reactors with individual temperature and pressure controls. Upon charging the catalyst solutions, the reactors were pressurized with 150 psi of syn gas (H_2:CO 1:1) and then heated to the desired temperature (35 or 70 °C). The runs were stopped after 3 h by venting the system and purging with nitrogen. In a typical 70 °C run, 0.153 mL of ligand and 0.153 mL of Rh(CO)$_2$(acac) stock solutions were added to 2.697 mL of toluene followed by addition of 0.5 mL of allyl cyanide solution (Rh:allyl cyanide 1:500). This solution was transferred to the reactor system housed in the inert atmosphere glovebox. The reactors were pressurized with 150 psi of H_2:CO 1:1 and then heated to 70 °C while stirring at 800 rpm. After 3 h reactors were cooled, vented, and purged with nitrogen. Upon opening the reactor 0.1 mL of each reaction mixture was taken out and diluted with 1 mL of toluene, and this solution was analyzed by gas chromatography (Astec Chiraldex A-TA column, temperature program of 90 °C for 7 min, then 5 °C/min to 180 °C. Retention times: 6.44 min for allyl cyanide, 17.42 and 17.77 min for the enantiomers of the aldehyde-nitrile branched regioisomer, and 21.78 for the linear aldehyde-nitrile regioisomer). Reaction mixtures for the runs included in Table 2 were prepared by mixing 3.5 mL of neat allyl cyanide with catalyst and ligand toluene solutions described above.

Scale-Up of Asymmetric Hydroformylation of Allyl Cyanide. A 300 mL mechanically stirred pressure vessel fitted with a glass liner was charged with [Rh(CO)$_2$(acac)] (160 mg, 0.62 mmol) and (*R*,*R*)-Kelliphite (**11**) (65 mg, 0.68 mmol). The vessel was sealed and purged three times with nitrogen (145 psi). Allyl cyanide (75 mL, 0.93 mmol, deoxygenated) was added via the injection port, and the vessel was purged a further three times with nitrogen (145 psi). The reaction mixture was stirred at 1,000 rpm and heated to 30 °C. The vessel was then pressurized with H_2/CO (145 psi, 1:1), and the gas consumption was monitored, recharging the syn gas pressure as required. After 5 h, gas consumption was complete. The vessel was vented, purged once with nitrogen (145 psi), and opened. The crude reaction mixture was obtained with >99% conversion, 80% ee, b/l 20.1 as determined by chiral GC. This crude product was used in subsequent reactions without further purification. NMR spectra were obtained by evaporation of a sample of the reaction mixture to an oil that was redissolved in $CDCl_3$. NMR data for the linear regioisomers (aldehyde product and derivatives) were obtained from products prepared by hydroformylation of allyl cyanide (100 mL allyl cyanide (83.4 g), allyl cyanide:Rh = 2000:1, 147 psi, 30 °C, neat, ligand:Rh 1:1) using Chiraphite (**1**) as ligand (b/l 6.6, 20.1% ee). **3-Methyl-4-oxo-butyronitrile (4):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.43 (dd, 1H, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 7.6 Hz, CH*H*CN), 2.61 (dd, 1H, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 5.2 Hz, C*H*HCN), 2.75 (m, 1H, C*H*), 9.59 (s, 1H, C*H*O); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.3 (*C*H$_3$). 18.0 (*C*H$_2$), 42.7 (*C*H), 118.0 (*C*N), 200.3 (*C*HO). **5-Oxo-pentanenitrile (4a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (m, 2H, CH_2), 2.40 (t, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2CN), 2.63 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2CHO), 9.74 (s, 1H, C*H*O); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.6 (CH$_2$), 18.1 (*C*H$_2$CN), 42.0 (*C*H$_2$CHO), 117.3 (CN), 200.5 (CHO).

Reduction of 3-Methyl-4-oxo-butyronitrile and 5-Oxo-pentanenitrile. A 300 mL pressure vessel fitted with a glass liner was charged with 10% platinum on activated carbon (2.7 g, ~1 mol %), the crude hydroformylation product mixture containing 3-methyl-4-oxo-butyronitrile and 5-oxo-pentanenitrile (11.25 g, 0.116 mol, 80% ee, b/l 20.1) and methanol (50 mL). The vessel was sealed and purged three times with nitrogen (145 psi). The reaction mixture was then stirred at room temperature under nitrogen (87 psi) for 30 min in order to deoxygenate the solvent. After venting, the vessel was purged twice with hydrogen (145 psi), then charged with hydrogen (145 psi), and stirred at room temperature, repressurizing with hydrogen as necessary. Once consumption was complete, the vessel was purged once with nitrogen (145 psi) and opened. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give a dark liquid in 96% yield with 80% ee and b/l 20.1. The compound was derivatized in situ with trifluoroacetic anhydride prior to GC analysis, which was performed on an Astec Chiraldex A-TA column (30 m × 0.25 mm, 0.25 μm, temperature program 125

°C for 15 min, then 15 °C/min to 180 °C. Retention times = 11.63 and 12.20 min for branched enantiomers and 21.0 min for the linear regioisomer). **4-Hydroxy-3-methyl-butyronitrile (5):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, $^3J_{HH}$ = 6.7 Hz, CH_3), 2.06 (m, 1H, C*H*), 2.38 (dd, 1H, $^2J_{HH}$ = 16.5 Hz, $^3J_{HH}$ = 6.3 Hz, C*H*HCN), 2.50 (dd, 1H, $^2J_{HH}$ = 16.5 Hz, $^3J_{HH}$ = 5.6 Hz, C*H*HCN), 3.49 (dd, 1H, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.5 Hz, CH*H*OH), 3.65 (dd, 1H, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.0 Hz, C*H*HOH); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.9 (CH_3), 19.9 (CH_2CN), 31.9 (CH), 64.8 (CH_2OH), 117.7 (CN). NMR data are identical to those reported in the literature.[25] **5-Hydroxypentanenitrile (5a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 4H, CH_2CH_2), 2.41 (t, 2H, $^3J_{HH}$ = 6.3 Hz, CH_2CN), 3.70 (t, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2OH); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_2CH_2CN), 21.0 (CH_2CN), 30.3 (CH_2CH_2OH), 60.6 (CH_2OH), 118.7 (CN).

Formation of 2-Methyl-4-aminobutanol (6). A 300 mL pressure vessel fitted with a glass liner was charged with a mixture of 4-hydroxy-3-methyl-butyronitrile and 5-hydroxypentanenitrile (20.1:1, 5.07 g, 51.2 mmol), oxalic acid dihydrate (6.44 g, 51.2 mmol), 10% platinum on activated carbon (1.03 g), and methanol (100 mL). The vessel was sealed and purged 3 times with nitrogen (145 psi). The vessel was then heated to 60 °C, and the reaction mixture was stirred under nitrogen (145 psi) for 30 min in order to deoxygenate the solvent. After venting, the vessel was purged twice with hydrogen (145 psi), then charged with hydrogen (145 psi) and stirred at 60 °C, repressurizing with hydrogen as necessary. Once consumption was complete, the vessel was cooled to room temperature, purged once with nitrogen, and opened. The reaction mixture was filtered through Celite that had been prewashed with methanol. IRN78 resin (45 g, 4meq/g) was added, and the reaction mixture was stirred at room temperature for 48 h. The resin was filtered off and washed with methanol (50 mL) and water (40 mL). The filtrate was concentrated on a rotary evaporator to give crude 2-methyl-4-aminobutanol as a yellow oil (76% with 80% ee). The compound was derivatized in situ with trifluoroacetic anhydride prior to enantioselectivity determination by chiral GC analysis (Chirasil Dex CB column, 25 m × 0.25 mm × 0.25 μm), indicating no racemization had occurred (temperature program: 100 °C for 15 min then 5 °C/min to 220 °C. Retention times = 20.7 and 20.9 min for branched enantiomers). The linear isomer was not observed. **2-Methyl-4-aminobutanol (6):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, $^3J_{HH}$ = 6.5 Hz, CH_3), 1.77−1.61 (m, 1H, C*H*), 1.53−1.46 (m, 2H, CH_2), 2.65−2.52 (m, 1H, CH*H*NH_2), 2.82−2.69 (m, 1H, C*H*HNH_2), 3.33 (dd, 1H, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.6 Hz, CH*H*OH), 3.45 (dd, 1H, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 4.5 Hz, C*H*HOH), 4.05 (br s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3), 35.3 (CH_2), 35.6 (CH), 47.8 (CH_2NH_2), 68.2 (CH_2OH). NMR and GC data of this sample are identical to those obtained from commercially available sample.

General Method for Crystallization Screen. A scintillation vial was charged with 2-methyl-4-aminobutanol (130 mg, 1.26 mmol), ethanol (2 mL), and the desired acid (1 or 2 equiv). The solution was stirred for 24 h at room temperature. If no precipitation was observed, ethanol was removed in vacuo and replaced with 2-propanol (1.5 mL). If precipitation was still not observed after an additional 24 h, 2-propanol was removed in vacuo and replaced with ethyl acetate (1.5 mL). If no precipitation was obtained after an additional 24 h, ethyl acetate was removed in vacuo and replaced with MTBE (1.5 mL). Any crystalline salts that formed were filtered off. These salts were then cracked with IRN78 resin using the method described above. The resulting free amines were then analyzed for enantiomeric excess by chiral GC.

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Supporting Information Available: Preparation procedures for compounds **12**, **13**, **14**, **16**, and **17**; stereoview of **9**; NMR spectra of compounds **4**, **9**, and **19**; and crystallographic tables for compounds **9** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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