Selective formation of a C_3 -symmetric P-stereogenic tris(phosphine) *via* platinum-catalyzed asymmetric alkylation of a tris(secondary phosphine)

Zhiming Xu,^a Matthew F. Cain,^a Alexander V. Rupert,^a David S. Glueck,^{*a} James A. Golen,^b and Arnold L. Rheingold^b

^a 6128 Burke Laboratory, Department of Chemistry, Dartmouth College, Hanover, New Hampshire, 03755, USA. ^b Department of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093, USA.

*Corresponding author. E-mail: glueck@dartmouth.edu

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

ABSTRACT

Alkylation of $\text{MeC}(\text{CH}_2\text{PPh})_3$ **1** with 2-cyanobenzyl bromide and NaOSiMe_3 using the catalyst precursor $\text{Pt}((R,R)\text{-Me-DuPhos})(\text{Ph})(\text{Cl})$ gave a mixture of tris(phosphines) enriched in C_3 - $\text{MeC}(\text{CH}_2\text{PPh}(\text{CH}_2(o\text{-C}_6\text{H}_4\text{CN}))_3$ **3**; Cu-catalyzed phosphination yielded C_1 -enriched **3**. Oxidation of **3** by sulfur or H_2O_2 formed $\text{MeC}(\text{CH}_2\text{P}(\text{E})\text{Ph}(\text{CH}_2(o\text{-C}_6\text{H}_4\text{CN}))_3$ ($\text{E} = \text{S}$ **4**; $\text{E} = \text{O}$ **5**). Repeated recrystallization gave a low yield of (R,R,R) -**4**, which was crystallographically characterized. Tris(phosphine) **3** was formed with a diastereomeric ratio ($\text{dr} = C_3/C_1$) of 2.1(2) and enantiomeric ratios of 54(10) and 3.8(7) for C_3 -**3** and C_1 -**3** respectively, which showed that the selectivity of the triple alkylation was not the same at each site (substrate control).

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1. Introduction

C_2 -Symmetric bis(phosphines) are valuable ligands for metal-catalyzed asymmetric reactions,¹ but analogous C_3 -symmetric tris(phosphines) are rare and have found little use in catalysis.² P-Stereogenic derivatives (Scheme 1) are especially scarce. Synthesis of the first ligand in this class, Siliphos, required preparative chiral MPLC, thus limiting its applications.³ We recently described the asymmetric synthesis of the analogous (Me, *t*-Bu)-Siliphos (MT-Siliphos) using (–)-sparteine as a stoichiometric chiral auxiliary.⁴ To investigate asymmetric catalysis as a potentially more efficient synthetic route,⁵ we studied tris(secondary phosphine) **1**,⁶ whose deprotonation/alkylation was known to give mixtures of C_3 - and C_1 -symmetric tris(phosphines).⁷ Herein we report the diastereo- and enantioselective formation of C_3 -**2** (Triphos*, Scheme 1) *via* catalytic alkylation of **1** mediated by a chiral platinum complex; repeated recrystallization gave a highly diastereomerically enriched tris(phosphine sulfide) derivative.

The stereoselectivity of the triple alkylation is of interest as a rare example of asymmetric catalysis on a symmetrical trifunctional substrate.⁸ Scheme 2 shows a general process in which functional groups Y are converted into (*R*)- or (*S*)-stereocenters; the same tripod scaffold $\text{MeC}(\text{CH}_2\text{Y})_3$ was investigated in sulfide oxidation ($\text{Y} = \text{SR} \rightarrow (\text{R})\text{- or } (\text{S})\text{-S}(\text{O})\text{R}$)^{8b} and here in phosphine alkylation ($\text{Y} = \text{PPh} \rightarrow (\text{R})\text{- or } (\text{S})\text{-PPh}(\text{CH}_2\text{Ar})$). If the selectivity, defined by the mole fraction x , is the same for each

Scheme 1. Enantiomerically enriched C_3 -symmetric P-stereogenic tris(phosphines) have been prepared via separation (siliphos), asymmetric synthesis (MT-Siliphos), or asymmetric catalysis (triphos*, herein)

transformation (catalyst control), then the product ratios reflect “Horeau amplification,” resulting in a high enantiomeric excess of the major C_3 -symmetric product.^{9,4,8} For example, a relatively modest selectivity for one step ($x = 0.9$, or 80% ee) leads to a 729:1 enantiomeric ratio (er) in the C_3 product (99.7% ee). This enantioselectivity comes at the cost of reduced diastereoselectivity (the C_3/C_1 diastereomeric ratio (dr) is 2.7 in this example), since any “mistakes” made by the catalyst lead to undesired C_1 -symmetric products, although if C_3/C_1 separation is possible, highly enriched C_3 -symmetric product could be obtained.

Scheme 2. Formation of C_3 and C_1 products from triple asymmetric catalysis on a symmetrical trifunctional substrate, such as **1**. In sulfide oxidation,^{8b} $Y = SR$ is converted into (*R*)- or (*S*)- $S(O)R$; herein, $Y = PPh$ is converted into (*R*)- or (*S*)- $PPh(CH_2Ar)$.

catalyst control (same selectivity in each step)

$$dr(C_3/C_1) = \frac{x^3 + (1-x)^3}{3x^2(1-x) + 3x(1-x)^2}$$

$$er(C_3) = \frac{x^3}{(1-x)^3}$$

$$er(C_1) = \frac{x}{1-x}$$

substrate control (different selectivity in each step)

positive cooperativity: increased selectivity
negative cooperativity: decreased selectivity

Scheme 3. Screening benzyl halides in Pt-catalyzed asymmetric alkylation of tris(secondary phosphine) **1**

Alternatively, if the selectivity of each transformation is different (substrate control), the product ratios of the triple functionalization will depend on specific substrate-catalyst interactions. This could result in positive cooperativity (higher *dr* and/or *er* than available from the inherent selectivity of the catalyst), or negative cooperativity, with selectivity lower than that expected for one catalyst-mediated transformations (Scheme 2).⁸

Substrate control is likely in the conformationally restricted $MeC(CH_2Y)_3$ system,¹⁰ where the three arms of the tripod affect each other's positions; indeed this was observed in catalytic asymmetric sulfide oxidations.^{8b} We hypothesized that packing three bulky $CH_2PPh(CH_2Ar)$ groups around the MeC tripodal center would lead to substrate control with positive cooperativity. Therefore, our goals were to determine the stereoselectivity of the triple asymmetric alkylation; to investigate structure-selectivity relationships involving catalyst and substrate control; and to isolate highly enriched C_3 -symmetric tris(phosphines) and their derivatives.

2. Results and discussion

2.1. Screening benzyl halides in Pt-catalyzed alkylation of **1**, and identification of a selective reaction with the substrate 2-cyanobenzyl bromide

An ideal triple alkylation of **1** would proceed with high selectivity for one C_3 -symmetric product (high *dr* and *er*). More realistically, this reaction should be diastereoselective in order to be practical; a high *er* is less valuable if the desired product is formed in low yield, especially if separation is challenging. As a benchmark, an unselective catalyst ($x = 0.5$ in Scheme 2) would give a 1:3 ratio of C_3 and C_1 products (*dr* = 0.33).

The rate and selectivity of the alkylation of **1** (Scheme 3) using the base $NaOSiMe_3$, commercially available benzyl halides, and the catalyst precursor $Pt((R,R)\text{-Me-DuPhos})(Ph)(Cl)$ was investigated using $^{31}P\{^1H\}$ NMR spectroscopy, as reported for the related double alkylation of bis(secondary phosphines).¹¹ The C_3/C_1 product ratio under these unoptimized reactions could be assessed from $^{31}P\{^1H\}$ NMR spectra of either the reaction mixtures or after work-up and the addition of sulfur to yield the tris(phosphine sulfides) $MeC(CH_2P(S)Ph(CH_2Ar))_3$. The rate and selectivity depended strongly on the benzyl halide. Chlorides reacted slowly, some bromides led to product mixtures, and the *dr* values for a small library of benzyl bromides which were alkylated smoothly ranged from 0.4 to 1.6. We were unable to identify structural features of the substrates $ArCH_2Br$ associated with high selectivity; sample *dr* values were 1.0 ($Ar = Ph$) and 0.6 ($Ar = o\text{-tolyl}$ or 2-naphthyl; see Experimental for details). The most promising substrates were $C_6F_5CH_2Br$ (*dr* = 1.3) and 2-cyanobenzyl bromide ($Ar = o\text{-C}_6\text{H}_4\text{CN}$; *dr* = 1.6); the latter was studied in more detail.

After scale-up of this fast reaction, crude tris(phosphine) **3** was isolated as an oil and identified spectroscopically, or oxidized with sulfur or H_2O_2 to give solid sulfide **4** or oxide **5** derivatives, which were more readily purified. For the sake of comparison, C_1 -enriched samples (*dr* = 0.5) were prepared using $CuCl$ or CuI as catalyst precursors (Scheme 4).¹²

Scheme 4. Pt- or Cu-catalyzed synthesis of tris(phosphine) **3** and its conversion into sulfide or oxide adducts **4** or **5** (Ar = *o*-C₆H₄CN; catalyst precursor = Pt(Me-DuPhos)(Ph)(Cl), CuCl, or CuI)

2.2. Determination of the diastereoselectivity and enantioselectivity of the Pt-catalyzed alkylation

The integration of the ³¹P{¹H} NMR spectra of **3**, **4** or **5** showed that the Pt-catalyzed alkylation was diastereoselective (dr ~ 2). The ³¹P{¹H} NMR analysis of the hydrogen-bonded adducts¹³ formed by tris(phosphine oxide) **5** with the commercially available chiral amino acid (*S*)-Fmoc-Trp(Boc)-OH (Chart 1)¹⁴ enabled the determination of the enantiomeric composition of the C₃/C₁ mixtures. Adducts of the (*R,R,R*)-, (*S,S,S*)-, (*R,R,S*)-, and (*S,S,R*)-diastereomers of **5** gave rise to one, one, three, and three ³¹P{¹H} NMR signals, respectively, for a total of eight peaks, which could be assigned by comparison of the samples with different levels of enrichment, as shown in Figure 1 (see Experimental for additional details). The dr measured by integration of these ³¹P{¹H} NMR spectra was consistent with results from **3**, **4**, or **5**, and similar integration yielded er values for the C₃ and C₁ products (Table 1).

Chart 1. ³¹P{¹H} NMR analysis of mixtures of a chiral amino acid and tris(phosphine oxide) **5** was used to determine the enantiomeric ratios of the C₃ and C₁ products

Table 1. Selectivity of Pt-catalyzed triple alkylation of **1**: dr and er values for tris(phosphine oxide) **5** determined by ³¹P{¹H} NMR integration

Entry ^a	dr (oxide) ^b	dr (oxide/amino acid) ^c	er (C ₃) ^d	er (C ₁) ^d
1	1.97	1.97	38.5	3.35
2	1.90	1.80	49.7	3.46
3	2.05	2.03	54.8	3.58
4	2.28	2.16	65.0	3.40
5	2.30	2.06	62.4	5.13
6	2.23	2.09	55.7	4.07
Average (standard deviation)	2.1(2)	2.0(1)	54(10)	3.8(7)

^a See the Experimental for details of the procedure and NMR spectroscopic analysis. The enantiomeric catalyst precursors Pt((*S,S*)-Me-DuPhos)(Ph)(Cl) and Pt((*R,R*)-Me-DuPhos)(Ph)(Cl) were used in entries 1-3 and 4-6, respectively. ^b The dr (C₃/C₁ ratio) was determined by integration of the ³¹P{¹H} NMR spectrum of phosphine oxide **5** in CDCl₃. ^c The dr was determined by integration of the ³¹P{¹H} NMR spectrum of a mixture of phosphine oxide **5** and (*S*)-Fmoc-Trp(Boc)-OH (2 equiv per P) in CDCl₃. ^d The er values (C₃/C₃' and C₁/C₁' ratios) were determined by integration of the ³¹P{¹H} NMR spectrum of a mixture of phosphine oxide **5** and (*S*)-Fmoc-Trp(Boc)-OH (2 equiv per P) in CDCl₃.

As can be seen in Table 1, repeated experiments gave consistent dr values, which were slightly greater than those observed in the original screening. There was more scatter in the er measurements, which can be ascribed to difficulties in accurate integration of the low-intensity broad ³¹P{¹H} NMR signals, especially for the minor C₃ isomer. Within experimental error, the results were the same for the enantiomeric catalyst precursors with (*S,S*)- and (*R,R*)-Me-DuPhos ligands (entries 1-3 and 4-6).¹

2.3. Catalyst or substrate control in Pt-catalyzed alkylation?

The measured dr and er values (Table 1) enabled us to test the substrate control hypothesis from Scheme 2. If the selectivity of the three Pt-catalyzed alkylations was the same (catalyst control), the dr of 2.1(2) must result from an *x*-value of 0.875, which predicts er values of 343 and 7 for the C₃- and C₁-tris(phosphines) **3**, respectively. The observed er values of 54(10) and 3.8(7) clearly did not match these predictions, thus indicating different selectivity in the three alkylations of **1** (substrate control). This could be described as negative cooperativity (lower er than expected in a catalyst-controlled reaction). In an alternative analysis, the measured er values matched those predicted (53 and 3.8) for a catalyst-controlled reaction with *x* = 0.79.⁸ However, the predicted dr of 1.0 is not consistent with the experimental value of 2.1(2), again

¹ We cannot exclude the possibility that the apparently higher stereoselectivity with the (*R,R*)-Me-DuPhos catalyst is due to higher stereochemical purity, either of one enantiomer of the commercial ligand (both are labelled as 98+%) or of one enantiomer of the Pt catalyst precursor, after recrystallization.

Figure 1. $^{31}\text{P}\{^1\text{H}\}$ NMR Spectra (243 MHz) of tris(phosphine oxide) **5**/chiral amino acid adducts, 21 °C, CD_2Cl_2 . Top: racemic **5**, prepared with CuI catalyst precursor; middle: enriched **5**, ($\text{Pt}((R,R)\text{-Me-DuPhos})(\text{Ph})(\text{Cl})$ precursor); bottom: enriched **5** ($\text{Pt}((S,S)\text{-Me-DuPhos})(\text{Ph})(\text{Cl})$ precursor).

demonstrating substrate control. This could be described as positive cooperativity (a higher dr than expected in a catalyst-controlled reaction).

These observations are consistent with previous results of asymmetric sulfide oxidations^{8b} and with the dependence of selectivity on benzyl halide structures. The diastereoselectivity of the alkylation with the achiral catalyst precursor CuCl (Scheme 4; dr = 0.5, instead of the 0.33 expected for an unselective catalyst) also demonstrates the substrate control, which is apparently typical of this tripodal system.

In order to explain the origin of this stereochemical substrate control, we propose the mechanism in Scheme 5, by analogy to our previous study of Pt-catalyzed alkylations of PHMe(Is) (Is = 2,4,6-(*i*-Pr)₃C₆H₂) using benzyl bromide and the same catalyst precursor, Pt((*R,R*)-Me-DuPhos)(Ph)(Cl).¹⁵ This reaction with NaOSiMe₃ and tris(secondary phosphine) **1** should yield diastereomeric complexes **A**₁ and **B**₁ (R = R' = H), which differ in the configuration of the Pt-phosphido group. Nucleophilic attack on a benzyl bromide yields

cationic tertiary phosphine complexes **R**₁ and **S**₁, which undergo intramolecular ligand substitution with a pendant secondary phosphine and the base to generate new Pt-phosphido complexes **A**₂/**B**₂ (R = H, R' = CH₂Ar). After two more P-alkylations, intermolecular substitution of **R**₃/**S**₃ with the new substrate **1** and base forms phosphines **C**₃/**C**₁₋₂ and regenerates **A**₁ and **B**₁.

The stereoselection in these reactions depends on rapid pyramidal inversion, which interconverts **A** and **B**.^{16,5e-f} If this step is much faster than P–C bond formation, then the relative abundance of the phosphido complexes (*K*_{eq}) and their rates of alkylation (*k*_R, *k*_S) determine the product ratio (Curtin-Hammett kinetics, Scheme 5).^{17, 5e-f} However, this discussion is oversimplified. Since the two pendant PPhR groups are also stereocenters, **A** and **B** would both actually exist as mixtures of four diastereomers; for the sake of clarity, only one of each is shown in Scheme 5. If the speciation and/or alkylation rates of the eight **A**/**B** isomers depended on the configuration of these stereogenic centers, which is plausible, the observed substrate control could occur.^{14b-c,8}

Scheme 5. Proposed origin of substrate control of stereochemistry in Pt-catalyzed alkylation of **1** ([Pt] = Pt(Me-DuPhos); only one of the four diastereomers of Pt-phosphido complexes **A**₁₋₃ and **B**₁₋₃ and their alkylation products **R**₁₋₃ and **S**₁₋₃ is shown.

2.4. Isolation and structure of C₃-4

Although the enantiopurity of C₃-tris(phosphine) **3** was lower than that predicted on the basis of the experimental dr by a catalyst control model, its separation from C₁-**3** would still afford highly enantiomerically enriched products (er = 54 translates to 96% ee). Therefore, we carried out the reaction on a large scale (3 g of **1**) using 3.3 mol % of Pt catalyst per P. After completion of the reaction, treatment with sulfur gave the crude

tris(phosphine sulfide) **4** in high yield. Repeated recrystallization gave highly diastereomerically enriched C₃-**4**, albeit in low yield (6%). In contrast, the chromatographic separation of the diastereomers of **4** or tris(phosphine oxide) **5**, or separation of the tris(phosphine borane) derivatives was unsuccessful.

The high symmetry of C₃-**4** simplified its NMR characterization (see the Experimental); its composition was also confirmed by X-ray crystallography (Figure 2). However,

because of twinning and disorder problems, this structure was useful only to confirm the atom connectivity.

Figure 2. ORTEP diagram of one of the two molecules of C_3 -**4** in the unit cell of $4 \cdot CHCl_3 \cdot 1.5H_2O$. The other, disordered, molecule and solvent are not shown.

Phosphine sulfides have an extensive coordination chemistry,¹⁸ and the closely related tris(phosphine sulfide) $MeC(CH_2PPh_2(S))_3$ has been reported as a ligand in rhodium complexes¹⁹ and gold or palladium nanoparticles,²⁰ all of which are catalytically active. Since chiral derivatives of such ligands are unknown, C_3 -**4** is potentially useful as a tridentate chelate in asymmetric catalysis.

Unfortunately, our attempts to remove sulfur from C_3 -**4** were unsuccessful. Raney nickel²¹ and Si_2Cl_6 ²² were reacted with **4**, but the expected phosphine **3** was not observed in the resulting mixtures.

3. Conclusion

Herein we have attempted to determine which factors lead to catalyst control or substrate control in repeated catalytic reactions on a symmetrical multifunctional substrate.²³ Herein, substrate-controlled selectivity was observed in the alkylation of the tripodal substrate $MeC(CH_2PPh)_3$ by a chiral platinum catalyst. Substrate control in reactions on this conformationally constrained scaffold was expected, but enforcing positive cooperativity to improve the diastereoselectivity and enantioselectivity of such transformations remains a challenge.

Our results show the potential of this approach, although it is not yet synthetically useful; the C_3 -tris(phosphine) **3** was formed in 54(10) er (96% ee) and the potentially valuable tris(phosphine sulfide) C_3 -**4** was isolated by recrystallization. In future studies, we plan to increase the size of the P-substituent in order to improve differentiation between the P-R and P- CH_2 groups,²⁴ mediated by the chiral catalyst and/or by the steric demands of the other tripod arms. Improved selectivity should also make C_3/C_1

separation more efficient, which may enable a more practical synthesis of the very rare P-stereogenic tris(phosphines) and their derivatives.

4. Experimental

General Unless otherwise noted, all reactions and manipulations were performed in dry glassware under a nitrogen atmosphere at an ambient temperature in a glove box or using standard Schlenk techniques. Petroleum ether (bp 38-53 °C) or pentane, CH_2Cl_2 , ether, THF, and toluene were dried over alumina columns similar to those described by Grubbs.²⁵ NMR spectra were recorded with 300, 500 or 600 MHz spectrometers. 1H and ^{13}C NMR chemical shifts are reported vs Me_4Si and were determined by reference to the residual 1H or ^{13}C solvent peaks. ^{31}P NMR chemical shifts are reported versus H_3PO_4 (85%) used as an external reference. Coupling constants are reported in Hz, as absolute values. Unless indicated, peaks in NMR spectra are singlets. Quantitative technologies incorporated provided elemental analyses. Mass spectrometry was performed at the University of Illinois. Reagents were from commercial suppliers, except for compounds $Pt(Me-DuPhos)(Ph)(Cl)$ ²⁶ and $MeC(CH_2PPh)_3$ **1**,⁶ which were synthesized using literature procedures.

Screening benzyl halides in Pt-catalyzed alkylation of **1**. General procedure

A solution of $Pt((R,R)\text{-}Me\text{-}DuPhos)(Ph)(Cl)$ [10 mg, 0.016 mmol, 6.3 mol % per tris(phosphine), 2.1 mol % per P] in 1 mL of THF was treated with a solution of **1** (100 mg, 0.252 mmol) in 2 mL of THF to afford a homogeneous reaction mixture. Treatment of this solution with $NaOSiMe_3$ (85 mg, 0.76 mmol) in 2 mL of THF gave a bright yellow solution. The benzyl halides (0.76 mmol, 3 equiv, 1 per P) were then either added as a THF solution (solids) or injected (liquids) while the reaction progress was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. In some cases, the selectivity of the reaction could be determined at this stage by integration. When full conversion was reached, the reaction mixtures were placed inside the glove box and pumped down under vacuum.

The residue was dissolved in 20 mL of a 33% THF/petroleum ether solution and passed through a silica plug to remove the inorganic salt and the Pt catalyst. The filtrate was pumped down under vacuum and analyzed by $^{31}P\{^1H\}$ NMR spectroscopy ($CDCl_3$). The spectra of the crude tris(phosphine) product mixtures often contained significant peak overlap and/or were complicated by peaks due to unidentified side products. Therefore, the crude tris(phosphines) were dissolved in 3 mL of THF and added to a slurry of S_8 (27 mg, 0.11 mmol, 1.1 equiv per P) in a few drops of THF. The conversion into the tris(phosphine sulfides) was determined by $^{31}P\{^1H\}$ NMR spectroscopy (THF). The reaction mixtures were then filtered and pumped down under vacuum. The crude solids were analyzed by $^{31}P\{^1H\}$ NMR spectroscopy ($CDCl_3$) and the diastereomeric ratio was determined by integration. This procedure was also carried out on a smaller scale (0.1 mmol of **1**), with similar results.

Table 2. Diastereomeric ratios and $^{31}\text{P}\{^1\text{H}\}$ NMR data in Pt-catalyzed asymmetric alkylation of $\text{MeC}(\text{CH}_2\text{PPh})_3$ with ArCH_2Br ^a

Entry	Aryl	Diastereomeric ratio (dr = C_3/C_1)	$^{31}\text{P}\{^1\text{H}\}$ NMR (tris(phosphine))	$^{31}\text{P}\{^1\text{H}\}$ NMR (tris(phosphine sulfide))
1	Ph	1.0	-29.5 (C_1), -29.7 (C_3/C_1)	ND ^b
2	<i>o</i> -Tol	0.6	-31.06 (C_1), -31.12 (C_1), -31.3 (C_3)	40.6 (C_1), 40.4 (C_3), 40.3 (C_1), 40.2 (C_1)
3	<i>o</i> -IC ₆ H ₄	1.2	-27.6 to -28.2 (overlapping) ^c	41.7 (C_1), 41.6 (C_3), 41.2 (C_1), 40.8 (C_1) ^d
4	<i>o</i> -CNC ₆ H ₄	1.6	-23.1 (C_1), -23.2 (C_3)	41.3 (C_1), 41.0 (C_3/C_1), 40.9 (C_1)
5	<i>o</i> -PhC ₆ H ₄	0.75	-28.6 to -28.7 (C_1), -28.9 (C_3)	NA
6	<i>o</i> -NO ₂ C ₆ H ₄	ND	+22.8, -24.2	48.8-41.7 (overlapping) ^e
7	<i>o</i> -BrC ₆ H ₄	ND	-24.6, -25.3, -27.6 to -28.5 (broad) ^f	48.1-35.2 ^g
8	<i>o</i> -CF ₃ C ₆ H ₄	ND	-19.4 to -25.0 ^h	48.5-40.0 (m) ⁱ
9	3,5-(CF ₃) ₂ C ₆ H ₃	0.7	-27.2 (C_1), -27.8 (2 C_1), -28.0 (C_3)	ND
10	3,5-(<i>t</i> -Bu) ₂ C ₆ H ₃	0.4	-30.2 (C_1), -30.5 (C_1), -30.9 (C_3), -31.0 (C_1)	ND
11	<i>p</i> -CF ₃ C ₆ H ₄	0.9	-28.3 (C_1), -28.6 (2 C_1), -28.8 (overlapping, C_3)	ND
12	C ₆ F ₅	1.3	-25.6 (C_1), -25.9 to -26.3 (C_3/C_1 , overlapping)	40.1 (C_3/C_1), 39.3 (C_1)
13	2-naphthyl	0.6	-30.1 (C_1), -30.2 (C_1), -30.3 (C_3/C_1)	41.2 (C_1), 40.7 (C_3/C_1), 40.4 (C_1)

^a Reaction times ranged from a few hours to 24 h, but some reactions did not go to complete conversion (entry 6; > 90% conversion in entries 5, 7-8, and 11), while the reactions of benzyl chlorides (Ar = 1-naphthyl, 2-Me-1-naphthyl, and 9-anthracenyl) were extremely slow.

^b ND = not determined. Peak overlap and the presence of by-products precluded identification of the product signals; in some cases, the tris(phosphine sulfide) was not prepared. ^c Unidentified side products: -7.2, 22.6, 36.7 ppm. ^d Significant side products from 40-48 ppm. ^e Incomplete conversion into the tris(phosphine); unidentified by-product peak at 78.5 ppm. ^f By-product signals: 36.0, 22.6, -6.9 to -9.5, some starting material remained. ^g Unidentified by-product peaks at 78.0 and 70.0 ppm. ^h By-product signals: 39.2-32.6, 22.2, -5.8 to -9.8, -34.5 to -37.0. Some starting material remained. ⁱ By-product peaks: 88.5, 78.3, 55.0 ppm.

Pt-Catalyzed alkylation of **1** with 2-cyanobenzyl bromide. Synthesis of diastereo- and enantioenriched $\text{MeC}(\text{CH}_2\text{PPh}(\text{CH}_2\text{Ar}))_3$ **3** (Ar = *o*-C₆H₄CN)

Phosphine **1** (50 mg, 0.13 mmol), 2-cyanobenzyl bromide (84 mg, 0.43 mmol, 1.1 equiv per P), NaOSiMe₃ (48 mg, 0.43 mmol, 1.1 equiv per P) and Pt((*R,R*)-Me-DuPhos)(Ph)(Cl) (12 mg, 0.020 mmol, 5 mol % per P) were dissolved separately in four vials, each in 1 mL of THF. The phosphine solution was added dropwise to the catalyst precursor solution, followed by NaOSiMe₃; the solution turned bright yellow immediately. The benzyl bromide solution was then added dropwise to the bright yellow mixture. Another 1 mL of THF was used to rinse the vials and combined with the reaction mixture. The solution slowly turned orange and a precipitate formed. The reaction mixture was stirred for 3 h, after which it became pale yellow and cloudy. Pentane (10 mL, to give a 2:1 pentane/THF mixture) was added and the resulting solution was passed through a short silica plug. The solvent was removed under reduced pressure. In multiple reactions, this

gave 54-80 mg (0.073-0.11 mmol, 56-83%) of **3** as a white sticky oil (sometimes colorless). HRMS calcd for C₄₇H₄₃N₃P₃ (MH⁺): m/z 742.2670. Found: m/z 742.2682. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl₃): δ -24.1 (C_1), -24.3 (C_3), dr = 1.0:2.1. $^1\text{H}\{^{31}\text{P}\}$ NMR (CDCl₃): δ 7.40-6.99 (m, 24H, C_3/C_1 Ar), 6.77 (d, J = 8, 3H, C_3 Ar), 6.75-6.63 (m, 3H, C_1 Ar), 3.04-2.93 (m, 4H, C_1 P-CH₂, overlapping C_3 signals), 3.10 and 2.95 (AB quartet, J = 13, 6H, C_3 P-CH₂Ar), 2.87 and 2.80 (AB quartet, J = 13, 2H, C_1 P-CH₂Ar), 2.13-2.08 (m, 3H, C_1 P-CH₂, overlapping C_3 signals), 2.09 and 1.92 (AB quartet, J = 14, 6H, C_3 P-CH₂), 1.87 (d, J = 14, 1H, C_1 P-CH₂), 1.86 (d, J = 14, 1H, C_1 P-CH₂), 1.77 (d, J = 14, 1H, C_1 P-CH₂), 0.76 (3H, C_1 Me), 0.73 (3H, C_3 Me). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl₃): δ 141.1 (m, quat Ar, C_3/C_1), 135.9 (d, J = 15, C_3 quat Ar, overlapping m C_1 peaks), 132.3-131.8 (m, Ar), 131.2 (C_3 Ar), 131.1 (C_3 Ar), 128.7 (m, C_3 Ar), 128.2-128.1 (m, C_1 Ar), 128.0 (C_3 Ar), 127.1-127.0 (m, C_3/C_1 Ar), 124.8 (C_3 Ar), 116.8 (C_3 CN), 116.82-116.7 (m, C_1 CN, overlapping C_3 peak), 111.2 (C_3 quat Ar), 111.1-111.0 (m, C_1 quat Ar), 40.2 (m, C_3 MeC-CH₂), 40.1-39.8 (m, C_1 MeC-CH₂, overlapping C_3 signals), 37.0 (q, J = 14, C_3 quat MeC), 37.0 (q, J = 14, C_1 quat MeC, overlapping C_3 signals), 35.3

(d, $J = 16$, C_3 P-CH₂Ar), 35.2 (d, $J = 17$, C_1 P-CH₂Ar), 35.1 (d, $J = 17$, C_1 P-CH₂Ar), 34.8 (d, $J = 17$, C_1 P-CH₂Ar), 27.5 (q, $J = 8$, C_3 Me), 27.3 (q, $J = 9$, C_1 Me).

Cu-Catalyzed synthesis of a C_1 -enriched mixture of diastereomers of racemic **3 and its conversion into tris(phosphine sulfide) **4****

A solution of **1** (100 mg, 0.25 mmol) and 2-cyanobenzyl bromide (149 mg, 0.76 mmol) in 4 mL of THF was added to a solid mixture of NaOSiMe₃ (85 mg, 0.76 mmol) and CuCl (3 mg, 0.03 mmol, 10 mol %, 3.3 mol % per P). The resulting cloudy light yellow solution was stirred for 12 h and a white precipitate formed. The ³¹P{¹H} NMR spectrum of the mixture showed complete conversion of **1** to form the major product **3** (δ -22.9, -23.0 (overlapping)). The mixture was filtered through Celite and the filtrate was immediately treated with a slurry of S₈ (27 mg, 0.10 mmol, 1.1 equiv per P) in 1 mL of THF, resulting in a homogeneous, orange solution, which was stirred for 5 h. The ³¹P{¹H} NMR spectrum showed complete conversion to **4** (δ 41.3, 41.0 (C_3/C_1 overlap), 40.9). The reaction mixture was then pumped down under vacuum to afford a brown-orange solid (156 mg, 0.186 mmol, 74%; dr = 1:2 (³¹P{¹H} NMR)). Starting with 300 mg of **1** gave 490 mg of **4** (77%, dr = 1:2; see below for characterization data).

In a similar procedure using the catalyst precursor CuI (6 mg, 0.03 mmol, 10 mol %, 3.3 mol % per P), the reaction mixture was passed through Celite, and the filtrate was concentrated under vacuum. The residue was redissolved in 10 mL of 1:2 THF/pentane and passed through a short silica plug, which was washed with 2 $\times$ 2 mL of 1:2 THF/pentane. The resulting solution was concentrated under vacuum to give 144 mg (0.20 mmol, 80%) of tris(phosphine) **3** as a sticky white oil.

Large-scale Pt-catalyzed triple asymmetric alkylation of **1 with 2-cyanobenzyl bromide and isolation of **4****

A solution of Pt(*R,R*-Me-DuPhos)(Ph)(Cl) (469 mg, 0.764 mmol, 10 mol %, 3.3 mol % per P) in 10 mL of THF was treated with **1** (3.029 g, 7.642 mmol) in 100 mL of THF, resulting in a clear, homogeneous solution. Solid NaOSiMe₃ (2.572 g, 22.92 mmol) in a vial was then added to afford a bright yellow solution. The remaining base stuck to the walls of the vial was washed into the reaction mixture with approximately 45 mL of THF. The bright yellow solution was rapidly stirred for 2 min. Solid 2-cyanobenzyl bromide (4.494 g, 22.92 mmol) in a vial was then added to the reaction mixture to give a bright orange solution; the residual solid was washed into the reaction mixture with an additional 45 mL of THF. Within minutes, the bright orange solution became cloudy and in 30 min, a precipitate formed. In 2 h, more precipitation was noted and the mixture was significantly lighter in color. After overnight stirring, the mixture was pale yellow. The ³¹P{¹H} NMR spectrum showed that all of **1** had reacted. The reaction mixture was filtered through a Celite plug and the filtrate was immediately treated with a slurry of S₈ (807 mg, 3.15 mmol, 1.1 equiv per P) in 10 mL of THF to give a bright orange mixture, which contained some solid. After 12 h, ³¹P{¹H} NMR spectroscopy revealed that the reaction was complete and the reaction mixture was passed through a

silica plug to give a bright orange homogeneous solution. The plug was eluted once more with 100 mL of THF and the two fractions were combined and pumped down under vacuum to afford crude tris(phosphine sulfide) **4** as a brown-orange solid (6.683 g, 7.98 mmol, 104%; dr = 1.5 (³¹P{¹H} NMR)).

Isolation of C_3 -4** by recrystallization of C_3 -enriched **4**.**

This crude orange solid was recrystallized several times from chloroform/petroleum ether to yield C_3 -**4** as a white solid. This process was challenging because of the formation of viscous oils. In air, the crude product was dissolved in 30 mL of chloroform. The rapid addition of 50 mL of petroleum ether on top of the solution resulted in the formation of an oily precipitate. The flask was vigorously shaken by hand until almost all of the oil went back into solution; more chloroform was then added via pipette with vigorous manual stirring until the orange oil fully dissolved. The orange solution was then cooled in a refrigerator at -10 °C for 2-3 weeks to give a small portion of enriched C_3 -**4**, whose dr was typically 7-10. This enriched material was then recrystallized from chloroform layered with petroleum ether (1:3 ratio) to give the more highly enriched C_3 -**4** after 2 d. The procedure was repeated (typically 0-3 times) until the dr was greater than 100:1 (³¹P{¹H} NMR), to give a total of 364 mg (0.434 mmol, 6%). HRMS m/z calcd for C₄₇H₄₃N₃P₃S₃ (MH)⁺: 838.1832. Found: 838.1832. Anal. Calcd. for C₄₇H₄₂P₃N₃S₃·CHCl₃·1.5H₂O (same batch used for the X-ray structure): C, 59.11; H, 4.65; N, 4.31. Found: C, 57.06; H, 4.18; N, 4.09. ³¹P{¹H} NMR (CDCl₃): δ 41.0. ¹H NMR (CDCl₃): δ 7.82 (dd, $J = 8, 13$, 6H, Ar), 7.53 (d, $J = 8, 3$ H, Ar), 7.44 (t, $J = 7, 6$ H, Ar), 7.35 (m, 6H, Ar), 7.31 (t, $J = 8, 3$ H, Ar), 7.25 (m, 3H, Ar), 3.70 (m, 9H, CH₂), 3.28 (apparent t, $J = 14, 3$ H, CH₂), 0.59 (3H, CH₃). ¹H{³¹P} NMR (CDCl₃): δ 3.70 (overlapping AB with half of AX, $J = 14, 6$ H, CH₂), 3.28 (d, AX pattern, $J = 15, 6$ H, CH₂). ¹³C{¹H} NMR (CDCl₃): δ 135.3 (d, $J = 8$, Ar), 133.0 (d, $J = 2$, Ar), 132.4 (d, $J = 3$, Ar), 132.1-132.0 (overlapping, 2Ar), 131.3 (d, $J = 5$, Ar), 130.6 (d, $J = 75$, ipso Ar), 128.6 (d, $J = 12$, Ar), 127.8 (d, $J = 3$, Ar), 118.4 (CN), 114.1 (d, $J = 6$, ipso Ar), 42.8 (d, $J = 49$, CH₂), 41.4 (q, $J = 4$, quat MeC), 40.0 (dd, $J = 11, 51$, CH₂), 27.3 (m, CH₃).

Data for C_1 -4** in a mixture of C_3/C_1 -**4****

³¹P{¹H} NMR (CDCl₃): δ 41.3, 41.02, 40.9. ¹H{³¹P} NMR (CDCl₃): δ 8.00-7.00 (m, 27 H, C_1/C_3 Ar, overlapping; some distinct C_1 signals could be identified: 8.00-7.97 (m, 2H), 7.16-7.14 (m, 2H), 7.00 (d, $J = 8, 1$ H)), 3.79-3.57 (m, 9H, CH₂, overlapping C_3), 3.47 (dd, $J = 15, 4, 1$ H, CH₂), 3.32 (d, $J \sim 20, 1$ H, CH₂, overlapping C_3), 3.16 (d, $J = 13, 1$ H, CH₂), 1.29 (3H, Me). ¹³C{¹H} NMR (CDCl₃): δ 135.4 (d, $J = 8$, Ar), 135.3 (d, $J = 8$, Ar, overlapping C_3), 135.2 (d, $J = 8$, Ar), 133.0-132.9 (m, Ar, overlapping C_3), 132.7 (Ar), 132.4 (m, overlapping C_3), 132.2 (d, $J = 4$, Ar), 132.3 (overlapping m, Ar), 132.2-131.9 (m, overlapping C_3 , Ar), 131.2 (d, $J = 4$, Ar), 131.1 (d, $J = 4$, Ar), 130.9 (d, $J = 4$, Ar), 130.8 (d, $J = 58$, Ar), 130.5 (Ar), 130.1 (Ar), 130.0 (Ar), 129.0 (d, $J = 12$, Ar), 128.9 (d, $J = 12$, Ar), 128.8 (d, $J = 12$, Ar), 127.9-127.7 (m, overlapping C_3 , Ar), 126.5 (Ar), 118.3 (d, $J = 2$, CN), 118.3 (d, $J = 2$, CN), 118.2 (d, $J = 2$, CN), 114.2 (d, $J = 6$, Ar), 114.1 (d, $J =$

6, Ar), 114.1 (d, J = 6, Ar, overlapping), 42.7 (d, J = 48, CH₂), 42.6 (d, J = 48, CH₂), 42.2 (d, J = 47, CH₂), 41.4 (m, quat, overlapping C₃), 41.0-40.0 (m, CH₂, overlapping C₃ signals), 27.0 (m, CH₃). Note: especially in the aryl region, many signals overlapped those due to the C₃ isomer, but some distinct C₁ signals could be identified. IR(Nujol): 2221 cm⁻¹ (CN).

Oxidation of 3. Synthesis of MeC(CH₂P(O)Ph(CH₂Ar))₃ 5 (Ar = *o*-C₆H₄CN) An excess of 30% hydrogen peroxide solution (0.20 mL, 3.3 mmol of H₂O₂, 15 equiv per P) was added dropwise to a solution of **3** (54 mg, 0.073 mmol) in 10 mL of THF. The solution was stirred overnight after which the solvent was removed under vacuum to obtain a colorless (sometimes yellow) oil. The oil was dissolved in the minimum amount of CH₂Cl₂ and loaded onto a silica column, then purified using a step gradient eluent. First, 30:70 ethyl acetate/hexane was used to remove any less polar materials, after which 30:70 ethyl acetate/ethanol was used to elute tris(phosphine oxide) **5**. The eluent was treated with molecular sieves for at least 12 h in order to remove H₂O₂.²⁷ The solution was decanted to remove the molecular sieves, then pumped down under vacuum to give a white solid (45 mg, 0.057 mmol, 78%). Note: overnight air oxidation of **3** also gave **5**, but with more impurities present. HRMS calcd for C₄₇H₄₃N₃O₃P₃ (MH⁺): m/z 790.2517. Found: m/z 790.2507. ³¹P{¹H} NMR (CDCl₃): δ 37.4 (C₃), 37.4-37.3 (m, C₁), 35.7 (C₁), dr = 2.1:1. ¹H{³¹P} NMR (CDCl₃): δ 7.55-7.11 (m, 30H, C₃/C₁ Ar), 3.66 and 3.38 (AB q, J = 15, 6H, C₃ P-CH₂Ar), 3.57 (d, J = 15, 1H, C₁ P-CH₂Ar), 3.47 (d, J = 15, 1H, C₁ P-CH₂Ar), 3.32 (d, J = 15, 1H, C₁ P-CH₂Ar), 3.31 (d, J = 15, 1H, C₁ P-CH₂Ar), 3.26 (2H, C₁ P-CH₂Ar), 2.94 and 2.88 (AB q, J = 15, 6H, C₃ P-CH₂), 2.98-2.86 (m, 3H, overlapping C₃ signals, C₁ P-CH₂), 2.75 (d, J = 15, 1H, C₁ P-CH₂), 2.70 (d, J = 15, 1H, C₁ P-CH₂), 2.48 (d, J = 15, 1H, C₁ P-CH₂), 1.08 (C₁ Me), 0.68 (C₃ Me). ¹³C{¹H} NMR (CDCl₃): δ 135.5 (d, J = 8, C₃ quat Ar), 135.5-135.4 (m, C₁ quat Ar), 132.7 (C₃ Ar), 132.5 (C₃ Ar), 132.4 (m, C₁ Ar), 132.3-131.4 (m, C₁ Ar), 131.9 (d, J = 108, C₃ quat Ar), 131.9 (d, J = 1, C₃ Ar), 131.0 (d, J = 4, C₃ Ar), 130.9 (m, C₁ Ar), 130.7 (d, J = 9, C₃ Ar), 130.5 (m, C₁ Ar), 117.84 (C₃ CN), 117.79, 117.74, 117.70 (C₁ CN), 113.3 (d, J = 5, C₃ quat C-CN), 113.3-113.1 (m, C₁ quat C-CN), 41.2 (dd, J = 66, 8, C₁ P-CH₂), 39.9 (dd, J = 66, 10, C₃ P-CH₂), 39.6 (br dm, J ~ 67, 2 C₁ P-CH₂), 39.1 (d, J = 61, C₃ P-CH₂Ar), 39.2-39.0 (br m, C₃/C₁ quat MeC), 38.9 (d, J = 59, C₁ P-CH₂Ar), 38.8 (d, J = 61, C₁ P-CH₂Ar), 38.7 (d, J = 64, C₁ P-CH₂Ar), 29.6 (br m, C₁ Me), 29.4 (q, J = 6, C₃ Me). IR (Nujol): 2223 cm⁻¹ (CN).

NMR Assay of the enantiomeric composition of mixtures of C₃/C₁ tris(phosphine oxide) **5**

A CDCl₃ solution containing 15 mg (0.018 mmol) of **5** and 60 mg (0.11 mmol, 2 equiv per P) of (*S*)-Fmoc-Trp(Boc)-OH was prepared. ³¹P{¹H} NMR (CDCl₃): δ 39.62

(C₃), 39.89 (C₃'), 39.38, 39.38, 39.22 (C₁), 39.66, 39.59, 38.94 (C₁').

The ³¹P{¹H} NMR spectra of these mixtures, using both racemic and enriched samples of **5**, were examined in several different solvents. CD₂Cl₂ gave the best separation, and the expected eight peaks were observed with racemic **5** (Figure 1, top panel). In contrast, greater peak overlap was observed for CDCl₃ (Figure 3, top panel). Consistent results were obtained by integration of the ³¹P{¹H} NMR spectra in these solvents, but we found those in CDCl₃ were more reliable, and so they are reported here. In CD₂Cl₂, the C₁' signal at 39.2 ppm was baseline resolved, so that the amount of the major C₃ isomer (see Figure 1, middle) could be determined by subtraction of the C₁' contribution to the 39.9 peak. Similarly, integration of the C₁ signals at 39.45 and 39.6 ppm gave consistent results. However, integration of the low-intensity, broad C₃' signal at 40.1 ppm was challenging, especially with samples of **5** prepared via air oxidation; these contained unidentified impurities with ³¹P{¹H} NMR signals in this region. In CDCl₃, despite the peak overlap in Figure 3, similar analyses were possible, including integration of the baseline resolved C₁ and C₁' signals, and determination of the amount of C₃ isomer by subtraction. While integration of the minor C₃' signal remained difficult, overlap with trace impurity signals was reduced in comparison to the spectra in CD₂Cl₂. Figure 4 shows the spectrum of a similar, but less-enriched, sample, for which the minor C₃' signal intensity is greater. Note: samples of **5** prepared with the Pt((*S,S*)-Me-DuPhos)(Ph)(Cl) catalyst precursor and treated with the (*S*)-amino acid gave the spectra in the bottom panels of Figures 1 and 3. For consistency in analysis, these samples were also treated with the (*R*)-amino acid, yielding spectra similar to those in Figure 3 (middle), for which samples were prepared with the enantiomeric (*R,R*)-Me-DuPhos catalyst precursor and the (*S*)-amino acid.

Crystallographic data

Crystallographic data for C₃-**4**•CHCl₃•1.5H₂O have been deposited with the Cambridge Crystallographic Data Centre (CCDC number 1419755).

Acknowledgments

We thank the National Science Foundation for support, and the Department of Education for a GAANN fellowship to M.F.C. A.V.R. thanks Dartmouth College for a Presidential Scholarship, a Zabriskie Fellowship, and a Waterhouse research grant and acknowledges additional support from a Goldwater Scholarship.

Figure 3. ³¹P{¹H} NMR Spectra (243 MHz) of tris(phosphine oxide) **5**/chiral amino acid adducts, 21 °C, CDCl₃. Top: racemic **5** (CuI catalyst precursor); middle: enriched **5**, (Pt((*R,R*)-Me-DuPhos)(Ph)(Cl) precursor); bottom: enriched **5** (Pt((*S,S*)-Me-DuPhos)(Ph)(Cl) precursor).

Tetrahedron: Asymmetry

Figure 4. $^{31}\text{P}\{^1\text{H}\}$ NMR Spectra (243 MHz) of tris(phosphine oxide) **5**/chiral amino acid adducts, 21 °C, CDCl_3 . Top: enriched **5**, $(\text{Pt}((R,R)\text{-Me-DuPhos})(\text{Ph})(\text{Cl}))$ precursor; this spectrum is the same as the middle one in Figure 3). Bottom: a less-enriched (lower dr and er) sample of **5** (note the increased relative intensity of the C_3' and C_1' signals).

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Graphical Abstract

Selective Formation of a C_3 -Symmetric P-Stereogenic Tris(phosphine) *via* Platinum-Catalyzed Asymmetric Alkylation of a Tris(Secondary Phosphine)

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Zhiming Xu,^a Matthew F. Cain,^a Alexander V. Rupert,^a David S. Glueck,^a James A. Golen,^b and Arnold L. Rheingold^b

^aDepartment of Chemistry, Dartmouth College, Hanover, New Hampshire, 03755, USA ^bDepartment of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093, USA