

Biaryl-Like CATPHOS Diphosphines via Double Diels–Alder Cycloaddition between 1,4-Bis(diphenylphosphinoyl)buta-1,3-diyne and Anthracenes: Efficient Ligands for the Palladium-Catalyzed Amination of Aromatic Bromides and α -Arylation of Ketones

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Summary: A mixture of palladium(0) and CATPHOS, the 1,3-butadiene-bridged diphosphine generated via double Diels–Alder cycloaddition between bis(diphenylphosphinoyl)buta-1,3-diyne and anthracene, catalyzes the amination of a range of aromatic bromides as well as the α -arylation of ketones, giving conversions that either rival or exceed those obtained with BINAP.

Biaryl and biaryl-like diphosphines (Chart 1) have evolved into a highly versatile class of ligand for a host of carbon–carbon and carbon–heteroatom bond-forming reactions.¹ While enantiopure *atropos* biaryl-based diphosphines² can be used directly in asymmetric catalysis, their *tropos* counterparts can be resolved only after coordination to a substitutionally inert metal.³ Even so, BIPHEP, NUPHOS, and related *tropos* diphosphines (Chart 1) have been used to effect a host of platinum group metal catalyzed asymmetric transformations, including Diels–Alder⁴ and hetero Diels–Alder reactions,⁵ the carbonyl-ene reaction,⁶ asymmetric hydrogenation,⁷ and rhodium-catalyzed ene-type cyclizations,⁸ in the majority of cases with excellent levels of enantiocontrol. In addition, biaryl diphosphines are also proving to be the ligands of choice for a host of achiral transformations, including the palladium-catalyzed inter- and intramolecular amination of aryl halides⁹ and alkenyl bromides,¹⁰ the α -ary-

lation of ketones,¹¹ iridium- and rhodium-catalyzed chemo- and regioselective intermolecular cyclotrimerization of terminal alkynes,¹² cycloaddition and cycloisomerization of 1,6-enynes,¹³ rhodium-catalyzed isomerization of secondary propargylic alcohols to α,β -enones,¹⁴ the palladium-catalyzed carbonylation of heteroaromatic chlorides,¹⁵ and the iridium-catalyzed cross-coupling of terminal alkynes with internal alkynes.¹⁶ Given the effectiveness of biaryl-based diphosphines in platinum group metal catalysis, there is likely to be considerable interest in the development of alternative diphosphines which possess a similar basic skeletal architecture, particularly if their synthesis is operationally straightforward, modular, and more cost-effective.

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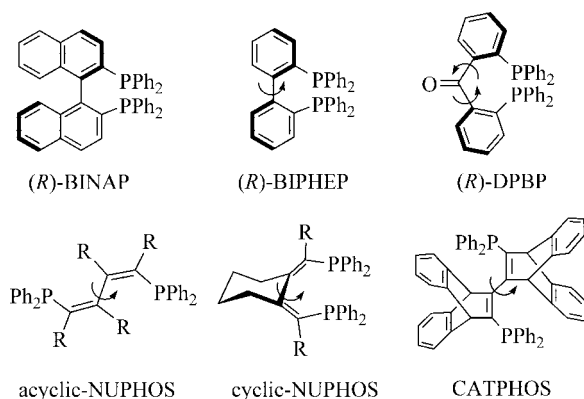
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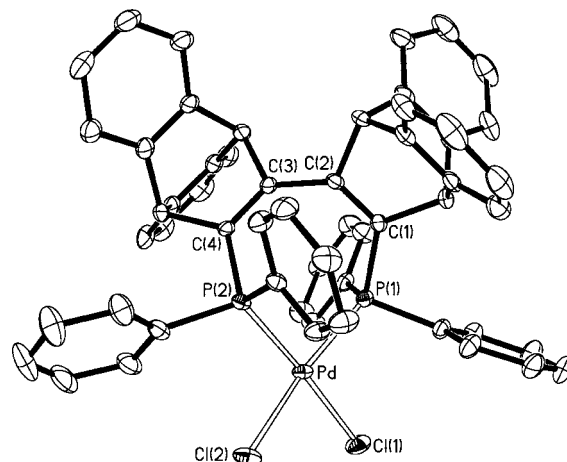
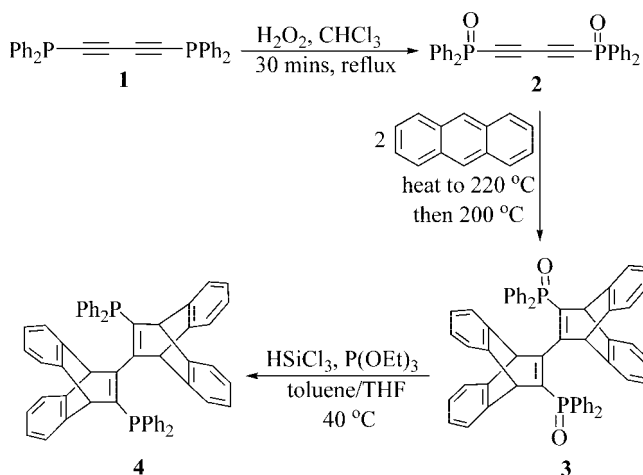
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Chart 1. Selected *atropos* and *tropos* Diphosphines

In this regard, we report here that the 1,3-butadiene-bridged diphosphine generated via double Diels–Alder cycloaddition between bis(diphenylphosphinoyl)buta-1,3-diyne and anthracene can be reduced under exceptionally mild conditions to afford CATPHOS, a biaryl-like diphosphine that forms a highly efficient catalyst for the amination of aryl bromides and the α -arylation of ketones, giving conversions that either rival or exceed those obtained with BINAP.

Our interest in bicyclic diphosphine **4** began after recognizing the close similarity with the core structural architecture of NUPHOS diphosphines¹⁷ (Chart 1): namely, two diphenylphosphino groups bridged by a substituted 1,3-butadiene tether. While attempts to prepare **4** by direct cycloaddition of anthracene with diphosphine **1** proved unsuccessful, the phosphine oxide **3** can be prepared in high yield via the thermal double cycloaddition between bis(diphenylphosphinoyl)buta-1,3-diyne and anthracene, as previously described (Scheme 1).¹⁸ Reduction of **3** also proved to be extremely problematic, as the use of trichlorosilane and triethylamine at elevated temperature gave a multitude of products, one of which was identified as diphenylphosphine. After repeated modification of the reaction, optimum conditions for the reduction were eventually identified and mild heating (40 °C) of a mixed toluene–tetrahydrofuran solution of **3** in the presence of trichlorosilane and triethyl phosphite gave **4** in near-quantitative yield as a spectroscopically and analytically pure white solid. The ³¹P NMR spectrum of **4** contains a single resonance at δ –15.3, while two sharp signals at δ 5.04 and 4.94 in the ¹H NMR spectrum are characteristic of the protons attached to the exo- and endo-bridgehead carbon atoms. The identity of **4** was unequivocally established by a single-crystal X-ray study, full details of which are provided in the Supporting Information.

With a particular interest in using the CATPHOS diphosphine **4** as a surrogate for more conventional biaryl diphosphines, we next investigated its platinum group metal coordination chemistry. Dropwise addition of a dichloromethane solution of **4** to a dichloromethane solution of [(cycloocta-1,5-diene)MCl₂] (M = Pd, Pt) resulted in quantitative formation of [(CATPHOS)MCl₂] (M = Pd, **5a**; M = Pt, **5b**). As the natural bite angle and the dihedral angle of biaryl-based diphosphines are both believed to influence catalyst performance, the X-ray single-crystal

**Figure 1.** Molecular structure of [(CATPHOS)PdCl₂] (**5a**) showing the conformation of the 1,3-butadiene tether. Hydrogen atoms have been omitted for clarity. Ellipsoids are at the 40% probability level.**Scheme 1**

structures of **5a,b** were determined to compare these parameters with the corresponding values for BIPHEP and related diphosphines. A perspective view of the molecular structure of **5a** is shown in Figure 1.¹⁹ The molecular structure of **5a** shows that the coordination around Pd is close to square planar with a dihedral angle of 7.4° between the PdP₂ and PdCl₂ planes. The natural bite angle of 94.27(3)° is comparable to that of 94.06(3)° reported for [Pd{MeO-BIPHEP}Br(*p*-NCC₆H₄)]²⁰ and is characteristic of a diphosphine bridged by a four-carbon sp²-hybridized tether. The dihedral angle of 21.1° between the least-squares planes defined by the double bonds and their substituents, C(1)C(2)C(5)C(12) and C(3)C(4)C(25)C(32), is markedly smaller than those found in biaryl-based diphosphines, which are typically much closer to 65–75°.

Since palladium(0)/BINAP is a highly effective catalyst for the amination of a range of aryl bromides with primary amines^{9a,b} as well as the α -arylation of ketones,^{11b} these two transformations were considered ideal candidates with which to undertake a comparative study between CATPHOS and BINAP. Our preliminary evaluation focused on the amination

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Table 1. Comparative Study of the Palladium-Catalyzed Arylation of Aniline Using Catalyst Generated from Pd₂(dba)₃ and either *rac*-BINAP or CATPHOS^a

entry	diphosphine	aryl bromide	time (h)	conversion (%) ^b
1	BINAP	4-MeC ₆ H ₄	8	80
2	CATPHOS	4-MeC ₆ H ₄	8	79
3	BINAP	2-MeC ₆ H ₄	4.5	80
4	CATPHOS	2-MeC ₆ H ₄	4.5	95
5	BINAP	4- <i>tert</i> -BuC ₆ H ₄	5	67
6	CATPHOS	4- <i>tert</i> -BuC ₆ H ₄	5	98
7	BINAP	3,5-Me ₂ -C ₆ H ₃	2	51
8	CATPHOS	3,5-Me ₂ -C ₆ H ₃	2	100
9	BINAP	4-MeOC ₆ H ₄	6	50
10	CATPHOS	4-MeOC ₆ H ₄	6	94
11	BINAP	4-ClC ₆ H ₄	3	60
12	CATPHOS	4-ClC ₆ H ₄	3	95
13	BIPHEP	4-ClC ₆ H ₄	5	77
14	JOHNPHOS	4-ClC ₆ H ₄	1	100
15	BINAP	4-CNC ₆ H ₄	3	100
16	CATPHOS	4-CNC ₆ H ₄	3	93

^a Reaction conditions: 1.0 equiv of Ar-Br, 1.1 equiv of amine, 1.4 equiv of NaO-*t*-Bu, 0.5 mol % Pd₂(dba)₃, 1.5 mol % BINAP, CATPHOS, or JohnPhos, toluene (2 mL), 80 °C. ^b Conversions were determined by GC analysis of the reaction mixture and are based on aryl bromide; average of three runs.

of 4-bromotoluene with aniline using Pd₂(dba)₃/(diphosphine) (1.0 mol % Pd) in toluene at 80 °C with NaO-*t*-Bu as base, full details of which are given in Table 1. Under these conditions the catalyst based on *rac*-BINAP gave 80% conversion after 8 h, compared to 79% for the corresponding CATPHOS-based catalyst; both gave complete conversion within 20 h. Interestingly, amination of the sterically more demanding 2-bromotoluene proceeded smoothly and more efficiently with the Pd₂(dba)₃/CATPHOS combination, which gave 95% conversion after 4.5 h compared to a conversion of only 80% obtained with the corresponding BINAP-based catalyst (entries 3 and 4). Having established that the catalyst based on palladium(0) and CATPHOS can compete effectively with its BINAP counterpart, the aminations were extended to include a range of electron-deficient and electron-rich aryl bromides. As expected, good conversions were obtained with electron-poor substrates, while electron-rich substrates were markedly more challenging; nevertheless, good conversions could be obtained after sufficiently long reaction times. The difference in performance between CATPHOS- and BINAP-based catalysts was most evident in the amination of electron-rich substrates. For example, reaction of 4-*tert*-butyl-1-bromobenzene with aniline using 1.0 mol % Pd(0)/CATPHOS gave 98% conversion after 5 h, whereas its BINAP counterpart achieved only 67% conversion in the same time (entries 5 and 6). Similarly, the corresponding amination of 4-bromoanisole with Pd/CATPHOS gave 94% conversion to the desired product after 6 h, compared to only 50% with Pd/BINAP (entries 9 and 10), while the reaction between 3,5-dimethyl-1-bromobenzene and aniline catalyzed by Pd/CATPHOS went to completion in 2 h but only reached 51% conversion with Pd/BINAP (entries 7 and 8). The comparative catalyst testing was extended to include systems based on BIPHEP and 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos), the former because it belongs to the *tropos* class of biaryl diphosphine and in this regard resembles CATPHOS, and the latter because it forms a highly active catalyst for the room-temperature amination

Table 2. Palladium-Catalyzed Arylation of *n*-Hexylamine and 2-Aminopyridine Using Catalyst Generated from Pd₂(dba)₃ and CATPHOS^a

Entry	Diphosphine	Amine	Aryl bromide	Product	Time (h)	% conv ^b
1	CATPHOS	<i>n</i> -Hex-NH ₂			4.5	94
2	CATPHOS	<i>n</i> -Hex-NH ₂			7	93
3	CATPHOS	<i>n</i> -Hex-NH ₂			7	81
4	CATPHOS	<i>n</i> -Hex-NH ₂			2	95
5	BIPHEP	<i>n</i> -Hex-NH ₂			24	28
6	JohnPhos	<i>n</i> -Hex-NH ₂			7	71
7	CATPHOS	2-PyNH ₂			24	100
8	CATPHOS	2-PyNH ₂			48	75
9	CATPHOS	2-PyNH ₂			48	72

^a Reaction conditions: 1.0 equiv of Ar-Br, 1.1 equiv of amine, 1.4 equiv of NaO-*t*-Bu, 0.5 mol % Pd₂(dba)₃, 1.5 mol % BINAP, CATPHOS, or JohnPhos, toluene (2 mL), 80 °C. ^b Conversions were determined by GC analysis of the reaction mixture and are based on aryl bromide; average of three runs.

and Suzuki coupling of aryl halides.²¹ In parallel experiments, the reaction of 4-chloro-1-bromobenzene with aniline was investigated with catalysts generated from BIPHEP and JohnPhos. Gratifyingly, the Pd(0)/CATPHOS catalyst system was significantly more active than its BIPHEP counterpart (entries 12 and 13). In contrast, Pd(0)/JohnPhos was highly active and gave complete conversion within 1 h (entry 14), whereas Pd(0)/CATPHOS required 3 h to reach 95% conversion.

Encouraged by these conversions, catalyst testing was extended to include the arylation of *n*-hexylamine and 2-aminopyridine. As shown in Table 2, good conversions were typically obtained with *n*-hexylamine within 4–8 h (entries 1–4), whereas reactions involving 2-aminopyridine required significantly longer times, reaching a similar level of conversion after 24–48 h with the same catalyst loading (entries 7–9). As described above, a comparative study showed that Pd(0)/CATPHOS gave much higher conversions than Pd(0)/BIPHEP for the amination of 4-bromoanisole with *n*-hexylamine (entry 5). In contrast, most surprisingly, the same reaction only reached 67% conversion after 6 h using 1.0 mol % Pd(0)/JohnPhos (entry 7) compared with a conversion of 94% for the corresponding CATPHOS system in the same time. However, further studies are clearly required to fully evaluate the relative merits of CATPHOS versus JohnPhos and related diphosphines. As found for Pd(0)/BINAP, the ratio of monoarylated/bisarylated product was typically greater than 30/1, as determined by ¹H NMR analysis of the crude reaction mixture.

The promising performance of Pd(0)/CATPHOS catalyst for the amination of aryl bromides prompted us to extend our studies

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Table 3. Palladium-Catalyzed α -Arylation of Ketones Using Catalyst Generated from $\text{Pd}_2(\text{dba})_3$ and CATPHOS^a

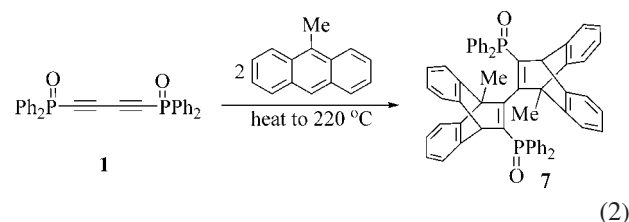
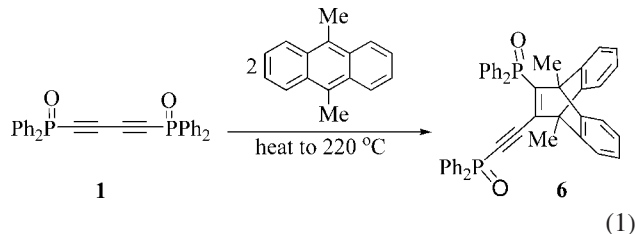
Entry	Aryl bromide	ketone	Product	Time (h)	Mono:Di ^b	% conv ^c
1				3	92:9	84
2 ^d				3	90:10	87
3				1	89:11	91
4				3	92:8	97
5				3	-	90
6				5	-	90
7				5	-	85
8				5	-	87
9				24	-	65
10				48	-	88
11				9	92:8	95

^a Reaction conditions: 1.0 equiv of Ar-Br, 1.2 equiv of ketone, 1.3 equiv of NaO-*t*-Bu, 1.5 mol % $\text{Pd}_2(\text{dba})_3$, 3.6 mol % CATPHOS, THF (3 mL), 70 °C. ^b Monoarylation–diarylation ratio determined by ¹H NMR spectroscopy. ^c Conversions were determined by GC analysis of the reaction mixture and are based on aryl bromide; average of three runs. ^d Catalyst generated from 1.5 mol % $\text{Pd}_2(\text{dba})_3$ and 3.6 mol % *rac*-BINAP.

to include the α -arylation of enolizable ketones (Table 3), a reaction that is efficiently catalyzed by a combination of $\text{Pd}_2(\text{dba})_3$ and Tol-BINAP or BINAP. Following a protocol described by Buchwald,^{11b} a THF solution of $\text{Pd}_2(\text{dba})_3$, CATPHOS, and NaO-*t*-Bu (3 mol % Pd) catalyzed the arylation of cyclohexanone with 4-bromo-1-chlorobenzene at 70 °C to give 84% conversion to the desired arylated ketone, which is comparable to that of 87% obtained with the corresponding BINAP system under the same conditions. As shown in Table 3, electron-rich and electron-poor aromatic bromides both couple with cyclohexanone, acetophenone, and heteroaryl ketones with good to excellent conversion to the desired α -arylated product. For each pair of coupling partners, good conversions were typically obtained within 1–5 h, with the exception of 2-acetylfuran, which required a reaction time of 24–48 h to reach an acceptable level of conversion with the same catalyst loading. For all substrates examined, the ratio of monoarylation to diarylation was typically greater than 8:1 and ketones containing α,α' -hydrogen atoms were regioselectively arylated at the least hindered position, again with high selectivity for monoarylation. For example, a 8:1 mixture of monoarylation–diarylation was obtained from the reaction between cyclohexanone and 4-*tert*-butylbromobenzene (entry 3), while the coupling of 3-methyl-2-butanone with 4-bromo-1-chlorobenzene occurred exclusively at the methyl carbon to afford a 12:1 ratio of monoarylated to diarylated product (entry 11).

As the parent CATPHOS diphosphine **4** is likely to be *tropos* in nature, we reasoned that introduction of substituents at the bridgehead carbon atoms would increase the barrier to rotation about C2–C3 of the butadiene tether to afford an atropisomeric

version for use in asymmetric catalysis. To this end, the corresponding Diels–Alder cycloaddition between 9,10-dimethylantracene²² and bis(diphenylphosphinoyl)buta-1,3-diyne resulted in selective monocycloaddition to afford **6** in high yield after 40 min with no evidence for any double cycloaddition adduct even after heating for 24 h at 200 °C (eq 1). While 9,10-dimethylantracene appears to be sterically too demanding to undergo double cycloaddition with **1**, the corresponding reaction between 9-methylantracene and bis(diphenylphosphinoyl)buta-1,3-diyne at 200 °C for 40 min results in highly regioselective double cycloaddition to afford the C₂-symmetric adduct **7** (eq 2), with the more bulky methyl-substituted bridgehead carbon atoms attached to C2 and C3 of the 1,3-butadiene tether, as confirmed by a single-crystal X-ray study.



In conclusion, palladium(0) complexes of the inexpensive and easy-to-prepare biaryl-like CATPHOS diphosphine, formed via double Diels–Alder cycloaddition between bis(diphenylphosphinoyl)buta-1,3-diyne and 2 equiv of anthracene, are highly efficient catalysts for the amination of aryl bromides as well as the α -arylation of enolizable ketones. Comparative catalyst testing with selected substrates revealed that Pd(0)/CATPHOS either rivals or outperforms its BINAP counterpart. The corresponding Diels–Alder reaction with 9-methylantracene occurs in a highly regioselective manner to afford a C₂-symmetric version (DM-CATPHOS) with the methyl-substituted bridgehead carbon atoms located on C2 and C3 of the butadiene tether, while the use of 9,10-dimethylantracene results in selective monocycloaddition. Studies are currently underway to investigate the *tropos/atropos* character of these phosphines for applications in asymmetric catalysis and to explore the range of alkynylphosphines that undergo Diels–Alder cycloaddition with the aim of preparing electron-rich monodentate derivatives for use in palladium-catalyzed cross-couplings.

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Supporting Information Available: Text, figures, a table, and CIF files giving full details of experimental procedures and characterization data for all compounds, details of catalyst testing, and, for compounds **4**, **5a,b**, and **7**, details of crystal data, structure solution and refinement, atomic coordinates, bond distances, bond angles, anisotropic displacement parameters. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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