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Generation of an Aromatic Amide-Derived Phosphane (Aphos) Library by Self-Assisted Molecular Editing and Applications of Aphos in Room-Temperature Suzuki–Miyaura Reactions

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Abstract: Aromatic amide-derived phosphanes (Aphos) are hemilabile P,O-coordinating ligands, which, when combined with a Pd precursor, yield a promising precatalyst system for Suzuki–Miyaura cross-coupling reactions. A focused library of Aphos ligands has been constructed for structural optimization, with the target of improving catalytic efficacy. By using microwave irradiation at accurately regulated temperature, an expeditious and reproducible one-pot synthesis and screening protocol was designed and experimentally validated. The success is based on a unique self-assisted molecular editing (SAME) process in which both the substrate and the product molecules catalyze formation of the product. Thus, starting from a 4-chlorobenzamide-derived Aphos as the substrate, parallel reactions with a selected set of arylboronic acids, in the absence of an added *external phosphane ligand* to Pd, produced a family of structurally edited Aphos ligands. The resultant reaction mixture containing the new Aphos, the Pd species, and the base could be used for in situ screening of the Aphos efficacy in a reference Suzuki–Miyaura coupling reaction. The structures of all Aphos ligands were characterized by ^{31}P NMR spectroscopy and their catalytic profiles in the reference reaction were evaluated by HPLC analysis. These data allowed the identification of an efficient Aphos ligand, capable of promoting room-temperature Suzuki–Miyaura coupling of unactivated and sterically hindered aryl chlorides with arylboronic acids under mildly basic conditions.

Keywords: heterogeneous catalysis · microwave-assisted reactions · palladium · phosphanes · Suzuki–Miyaura coupling

Introduction

Undoubtedly one of the most extensively studied palladium-catalyzed cross-coupling reactions for carbon–carbon bond formation is the Suzuki–Miyaura protocol[1,2] through which an organic halide or pseudohalide combines with an organic boronic acid or equivalent boron-derived reagent. Typically, aryl and vinyl electrophiles are preferred in the cross-coupling reactions with alkyl, aryl, and vinyl boron compounds for assessing biaryls, 1,3-dienes, alkyl/aryl-substituted alkenes, and alkyl-substituted aromatics. Recent advancement in reactive catalyst design has extended the Suzuki–Miyaura cross-coupling to alkyl electrophiles.[3,4] As a consequence of the intrinsic lower reactivity of the C_{Ar}–Cl bond, aryl chlorides are believed to undergo oxidative addition onto Pd^0 with much more difficulty compared with aryl iodides and bromides. Development of reactive palladium catalysts for activating aryl chlorides in cross-coupling reactions remains a hot thematic area.[5] During the past decade significant advances have been made in the rational design of bulky and electron-rich ligands capable of forming monoligated palladium species.[6] In 1997, Shen first reported tricyclohexylphosphane (PCy_3, **1a**) as the ligand in the Pd-catalyzed coupling of activated aryl chlorides with arylboronic acids at 100 °C in the presence of CsF in NMP.[7] In 1998, Fu and coworkers used tri-*tert*-butylphosphane ($PtBu_3$, **1b**) in combination with $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) as the precatalyst for Suzuki–Miyaura coupling of unactivated aryl chlorides at 80–90 °C (Cs_2CO_3, dioxane)[8a] or at room tem-

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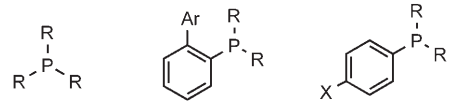


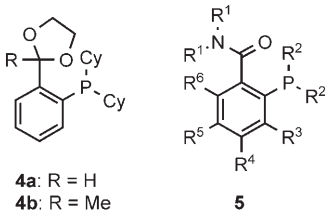
1a: R = Cy
1b: R = *t*Bu

2a: R = Cy
2b: R = *t*Bu

3a: X = H, R = Cy
3b: X = Me_2N, R = *t*Bu

perature (KF, THF).[8b] First reported in 1998 by Buchwald, was the biphenyl-derived phosphane **2a** (Ar = 2-dimethylaminophenyl),[9a] which forms a precatalyst system with $Pd(OAc)_2$ and demonstrates high activity in promoting room-temperature Suzuki–Miyaura coupling of unactivated aryl chlorides in the presence of CsF or K_3PO_4 in dioxane. Since then, a number of biaryl-derived phosphanes of the types **2a**,**b** have been prepared and applied to highly efficient Suzuki–Miyaura coupling of unactivated aryl chlorides at room temperature ($Pd(OAc)_2$ in THF with KF, K_3PO_4, or $K_3PO_4 \cdot H_2O$).[9] Dialkylarylphosphanes such as **3a** have been used along with $[Pd_2(dba)_3]$ for cross-coupling of 4-chlorotoluene with phenylboronic acid at 110 °C to give the product in 48 % yield (K_3PO_4, PhMe).[10] It is interesting to note that the dimethylamino-substituted **3b** remarkably improved efficacy of the precatalyst, $[PdCl_2(\mathbf{3b})_2]$, in the Suzuki–Miyaura coupling of heteroaryl chlorides with arylboronic acids (> 89 % yields; K_2CO_3, 10–20 % H_2O in PhMe, reflux for 12 h).[11a] In the literature, a variety of bulky and electron-rich dialkylphosphino-substituted heterocycles[11b] and trialkylphosphanes[11c] have been disclosed for the Suzuki–Miyaura cross-coupling reactions of aryl chlorides under mild conditions.[2f,6,11d] Moreover, *N*-heterocyclic carbenes (NHCs)[12,13] represent another class of electron-donating monodentate ligands, which have demonstrated excellent catalytic efficacy in room-temperature Suzuki–Miyaura coupling reactions of unactivated aryl chlorides.[14–18] However, a strong base, KO*t*Bu, was often required.[15,16,18]

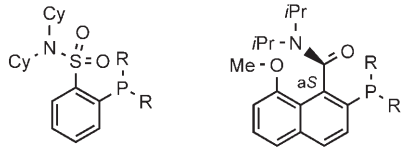
Hybrid ligands with phosphorus–oxygen donor groups have been used in many types of transition-metal-catalyzed reactions.[19a] The hemilability of these P,O-ligands enables diverse coordination behavior and the ligands form monodentate and chelating complexes with the metal. In particular, when bulky phosphorus and/or oxygen donor groups are incorporated into P,O-ligands, the monoligated metal species should be preferentially formed and could be highly reactive toward catalysis.[19] The first efficient ether-type P,O-ligand **4b** was reported by Bei, Gruam, and co-workers in 1999 for



4a: R = H
4b: R = Me

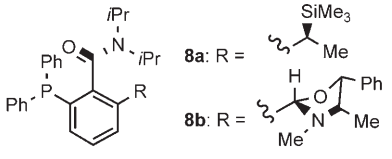
5

the Suzuki–Miyaura coupling of unactivated aryl chlorides ($[Pd(dba)_2]$, CsF, 110–110 °C in dioxane or toluene).[20a] However, the analogous ligand **4a** was inferior.[20b] We first reported the *N*,*N*-dialkyl aromatic amide-derived phosphanes (Aphos) of the type **5** as air-stable hemilabile P,O-ligands for Suzuki–Miyaura cross-coupling reactions of unactivated aryl chlorides (92–99 % yields; 0.5 mol % $[Pd_2(dba)_3]$, K_3PO_4, PhMe, 110 °C, < 5 h)[10,21a,c] and aryl bromides (86–99 % yields; 0.005 mol % $[Pd_2(dba)_3]$, $KF \cdot 2H_2O$ or K_3PO_4, PhMe, 60–80 °C, < 40 h).[21b] The phosphanes crafted on sulfonamide derivatives, atropisomeric *N*,*N*-dialkyl benzamide, and 1-naphthamide scaffolds (**6**–**8**) are known. Our design of Aphos **5** was inspired by the structures of **7** and **8**. Clayden and co-workers reported the *N*,*N*-diisopropyl benzamide-derived phosphanes **8a**,**b**, which display both central and axial chirality and applied them in the palladium-catalyzed asymmetric allylic alkylation (AAA) with up to 90 % *ee* (*ee* = enantiomeric excess).[22] We prepared the enantiomerically pure atropisomeric 1-naphtha-



6a: R = Ph
6b: R = Cy

(a*S*)-**7a**: R = Ph
(a*S*)-**7b**: R = Cy
(a*S*)-**7c**: R = *t*Bu



8a: R =

8b: R =

Abstract in Chinese:

芳基酰胺衍生的膦化合物(Aphos)是半稳定的膦、氧配位配体，它与钯可组成有潜力的催化剂前体用于 Suzuki–Miyaura 偶联反应。本文报道一个 Aphos 配体定向化合物库的合成，用于优化配体结构来改良催化效率。利用微波辐射及精确控温技术，我们设计了一种用于快速、具重现性的一锅法合成和筛选原型，并在实验中得到了验证。它是基于一种称为"自助分子剪裁"(SAME)的过程，其中底物和产物分子均能催化产物的形成。我们以一个 4–氯苯甲酰胺衍生的 Aphos 为原料，在没有外加与钯络合的膦配体的条件下同选定的一组芳基硼酸进行平行反应，产生了一个结构剪裁过的 Aphos 配体家族。上述反应混合物含有新合成的 Aphos、钯、及所用的碱，可直接催化一个对照 Suzuki–Miyaura 偶联反应而用于筛选其中 Aphos 的催化效率。合成的 Aphos 配体均经 ^{31}P 核磁共振谱学鉴定结构，它们在对照反应中的催化性能则用高效液相色谱分析来评价。这些数据给出一个有效的 Aphos 配体，它能催化室温及温和碱性条件下不活泼、大位阻氯代芳烃同芳基硼酸的 Suzuki–Miyaura 偶联反应。

mide-derived phosphanes (A^2phos) (a*S*)-**7a–c** and their antipodes by means of a chemical resolution process and used them in AAA (up to 94.7% *ee*),[23a] the asymmetric Heck reaction (AHR),[23b] and asymmetric Suzuki–Miyaura cross-coupling.[23c] In our initial screening of the *N*,*N*-dialkyl aromatic scaffolds by using the reference Suzuki–Miyaura reaction of 4-chlorotoluene with phenylboronic acid,[10] we found that:

1) The benzamide-derived Aphos provides better catalytic efficacy than the 1-naphthamide analogues.
2) *N*,*N*-Diisopropyl 2-dicyclohexylphosphinobenzamides **5** (Cy-Aphos; $R^1 = i$Pr, $R^2 =$ Cy) are in general much more active in catalysis than the corresponding di-*tert*-butylphosphino derivatives **5** (*t*Bu-Aphos; $R^1 = i$Pr, $R^2 = t$Bu).
3) An aryl substituent at C4 of **5** ($R^4 =$ Ph) enhances Aphos performance in the Suzuki–Miyaura coupling as compared to C4-alkyl- ($R^4 =$ Cy) and C6-aryl- ($R^6 =$ Ph) substituted analogues.

Recently, the aromatic sulfonamide-derived phosphane **6b** was reported and tested in the coupling reaction of 4-chlorophenyl toluenesulfonate with phenylboronic acid at 80 °C in dioxane (77% yield; 2 mol% $Pd(OAc)_2$, Cs_2CO_3).[24] We report here a detailed account of our studies on the synthesis and screening of an Aphos library for discovery of a highly efficient precatalyst that promotes room-temperature Suzuki–Miyaura cross-coupling of unactivated and sterically hindered aryl chlorides.[25]

Results and Discussion

In our early studies, the beneficial effect of the *N*,*N*-dialkyl amide moiety [$R^1R^1NC(O)$-] in Aphos **5** has been clearly established with respect to $PhPCy_2$ (**3a**). Not only does the amide improve stability towards air oxidation, but it also remarkably enhances catalytic efficacy in the Suzuki–Miyaura cross-coupling reaction.[10] Aphos **5** can be synthesized, purified, and stored as a normal organic compound. Special oxygen-free operations are not necessary and solid-state oxidation of Aphos by air is minimal. We took the following criteria into our design and selection of the *N*,*N*-dialkylbenzamide scaffolds **5**:

1) The *N*,*N*-dialkyl amide moiety should facilitate directed *ortho*-lithiation[26] for easy incorporation of the dialkylphosphino (R^2R^2P-) subunit.
2) The *N*,*N*-dialkyl amide moiety should have a balanced steric bulkiness for achieving an appropriate oxygen donor function, while allowing formation of both P-monodentate and P,O-chelating Pd species (**9**–**11**) as given in Figure 1 (see below).
3) The dialkylphosphino subunit should possess complimentary steric and electron-rich properties in respect to the *N*,*N*-dialkyl amide moiety.

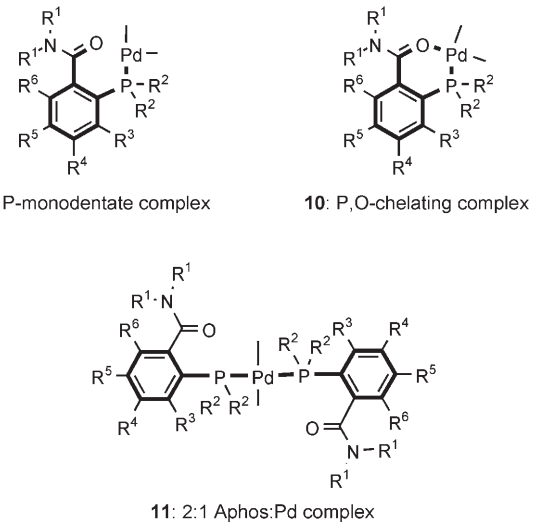


Figure 1. Possible coordination modes of Aphos **5** with palladium.

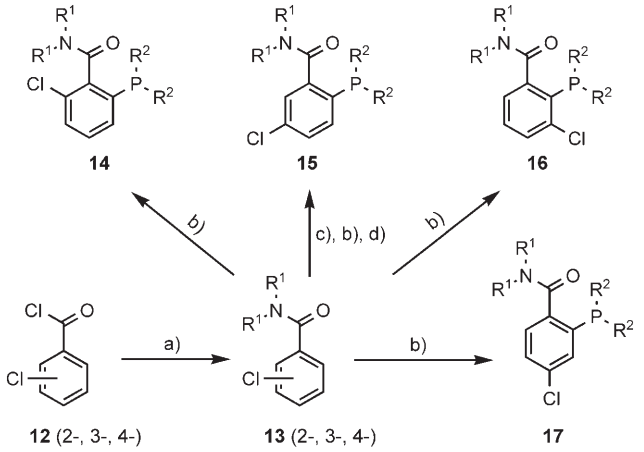
4) The substituents (R^3, R^4, R^5, and R^6) on the aromatic ring offer additional structural elements for fine tuning the chemical and physical properties of Aphos, such as crystallinity, solubility, and steric and electronic perturbations.

The substituent effect on Aphos performance has been clearly established.[10] It warrants a detailed study in the current work.

Structural evidence on the palladium complexes of secondary aromatic amide-derived P,O-ligands has been disclosed in the literature.[27] Sánchez and co-workers carried out extensive studies on the versatile coordination behavior of *o*-$Ph_2PC_6H_4CONHR$ (R = *i*Pr, Ph) with palladium(II) by X-ray crystal structural analysis, revealing P-monodentate, P,O-bidentate, and anionic P,N-bidentate coordination modes.[27c,d] Addition of a base can induce a switch from P,O-bidentate to anionic P,N-bidentate coordination. This observation is characteristic for the secondary aromatic amide-derived P,O-ligands.[27c,d,f] We established the solid structure of [Pd(allyl){(a*S*)-**7a**}][PF_6] by X-ray crystallographic analysis and confirmed the P,O-coordination pattern of (a*S*)-**7a** with the Pd^{II} center.[28] A similar P,O-chelating Pd^{II} complex of the sulfonamide phosphane **6a** was characterized by X-ray crystal structural analysis.[24] Moreover, the P-monodentate Pd^{II} complex of **6a** was established in the solid state, but it demonstrated dynamic behavior in the solution phase and was possibly in equilibrium with the P,O-chelating complex.[24] Such fluctuation in P-monodentate and P,O-bidentate coordination modes of tertiary aromatic amide/sulfonamide phosphanes is believed to be the structural basis for the observed catalytic efficacy in Suzuki–Miyaura cross-coupling reactions. It is advantageous that tertiary aromatic amides can offer steric bulkiness through the *N*,*N*-dialkyl unit and do not exhibit an N-donor function. Therefore, Aphos **5** should be limited to the P-monodentate and P,O-bidentate coordination modes (Figure 1) and

cannot form the P,N-chelating complex, which is possible with secondary aromatic amide-derived phosphanes.[27c,d,f]

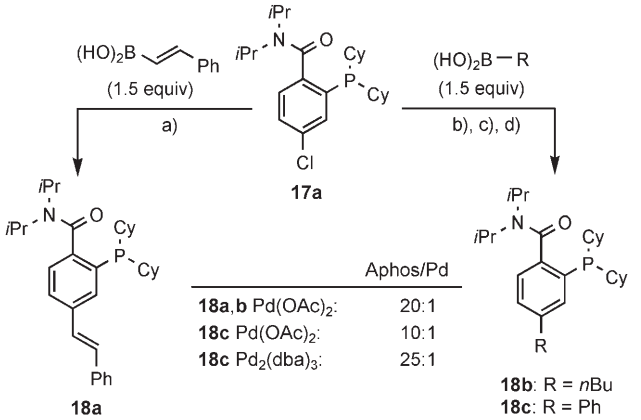
We designed a global synthetic strategy for accessing different substitution patterns in Aphos **5** as outlined in Scheme 1. The reaction of 2-, 3-, and 4-chlorobenzoyl chlorides **12** with dialkylamines lead to the formation of 2-, 3-, and 4-chlorobenzamides **13**. In our initial syntheses, reaction with various dialkylamines was attempted with reference to our early work on *N*,*N*-diethyl-, di-*n*-hexyl-, diisopropyl-, and dicyclohexyl-1-naphthamides.[29] We also tried cyclic secondary amines, such as pyrrolidine and piperidine, and found that the pyrrolidine-derived benzamides underwent *ortho*-lithiation (*s*BuLi-TMEDA, (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) THF, −78 °C) and subsequent trapping by R^2R^2PCl with difficulty, while the piperidine-derived Aphos ligands were not very air stable. Therefore, we focused on acyclic and symmetrical tertiary benzamide derivatives. On the other hand, a number of bulky dialkylphosphino subunits could be incorporated into **5** including diisopropyl-, dicyclohexyl-, dicyclopentyl-, and di-*tert*-butyl-substituted phosphanes. We found that it was not advantageous when both R^1 and R^2 in Aphos **5** were very bulky concurrently. For example the *i*Pr/Cy pairing in Cy-Aphos **5** (R^1 = *i*Pr, R^2 = Cy) demonstrates much better catalytic efficacy than the combination of *i*Pr/*t*Bu in *t*Bu-Aphos **5** (R^1 = *i*Pr, R^2 = *t*Bu).[10] Described here are the representative Cl-Cy-Aphos **14**–**17** with R^1 and R^2 being *i*Pr and Cy, respectively. Treatment of 2-, 3-, and 4-chlorobenzamides **13** with *n*BuLi or *s*BuLi in the presence of TMEDA[30a,b] in THF at −78 °C followed by trapping the resultant lithium species with chlorodicyclohexylphosphane (Cy_2PCl) afforded Cl-Cy-Aphos **14**, **16**, and **17** (R^1 = *i*Pr, R^2 = Cy). For the synthesis of **15**, a modified procedure was adopted.[30b] Thus, first the *ortho*-lithiated species was trapped with Me_3SiCl to form *N*,*N*-diisopropyl 3-chloro-2-trimethylsilylbenzamide,[30c] which was subjected to a second *ortho*-lithiation at the C6 position followed by incorporation of the Cy_2P-subunit. Finally, the Me_3Si group was removed upon treatment with tetrabutylammonium fluoride (TBAF) to furnish the C5-Cl-Cy-Aphos **15** (R^1 = *i*Pr, R^2 = Cy).



Scheme 1. Global synthetic strategy toward chlorobenzamide-derived Aphos **14**–**17**. a) R^1R^1NH, Et_3N. b) *n*BuLi or *s*BuLi, TMEDA, THF, −78 °C; then R^2R^2PCl. c) *s*BuLi, TMEDA, THF, −78 °C; then Me_3SiCl. d) TBAF, THF, RT.

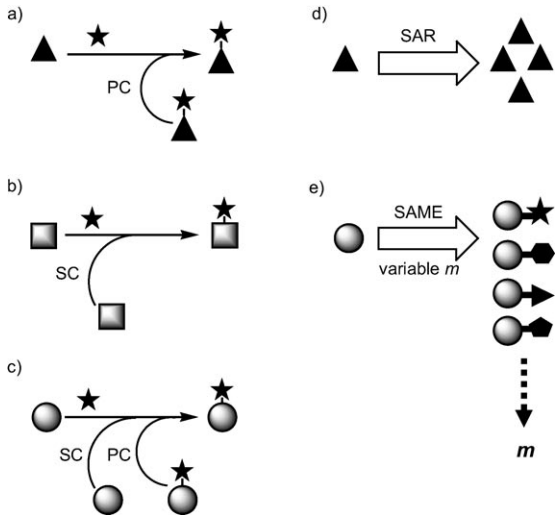
Self-assisted molecular editing (SAME): Taking C4-Cl-Cy-Aphos **17a** as the representative substrate, a novel structural editing protocol was designed and experimentally validated as shown in Scheme 2. The Suzuki–Miyaura couplings of vinyl, alkyl, and aryl boronic acids were used to replace C4-Cl in **17a** by vinyl, alkyl, and aryl groups to produce the new C4-substituted Cy-Aphos **18a**–**c** in 83–87 % yields. The three cross-coupling reactions of **17a** were catalyzed by the precatalyst system consisting of Pd, the substrate Aphos **17a** and the newly formed product Aphos **18a**–**c**. The ratios of Aphos/Pd were 10:1–20:1 for the reactions at 80 °C in THF. At elevated reaction temperature in PhMe, the Aphos/Pd ratio could reach as high as 25:1 for the formation of **18c**. These results imply that at temperatures of 80–110 °C the Pd complex(es) of this class of aromatic amide-derived P,O-ligands can be catalytically active even with such incredibly high Aphos/Pd ratios. However, the Aphos/Pd ratio had a significant effect on the coupling reactions at room temperature (see below). According to Fu's observation, a P*t*Bu_3/Pd ratio of 2:1 leads to sluggish Suzuki–Miyaura coupling reactions between aryl bromides and aryl chlorides at room temperature due to exclusive formation of the catalytically inactive complex $[Pd(PtBu_3)_2]$.[8b] In the case of Buchwald's biphenyl-derived phosphanes **2a**,**b**, ligand/Pd ratios of 1:1–5:1 were used for Suzuki–Miyaura couplings with the ligand/Pd ratio of 2:1 being preferred.[9d]

The reactions described in Scheme 2 represent an interesting type of chemical transformations in which both the substrate and the product concurrently catalyze formation of



Scheme 2. Synthesis of C4-substituted Cy-Aphos **18a**–**c**. a) 5 mol % $Pd(OAc)_2$, 3 equiv K_3PO_4, THF, 80 °C, 4 h, **18a**, 83 %. b) 5 mol % $Pd(OAc)_2$, 3 equiv K_3PO_4, THF, 80 °C, 8 h, **18b**, 87 %. c) 10 mol % $Pd(OAc)_2$, 3 equiv K_3PO_4, THF, 80 °C, 8 h, **18c**, 78 %. d) 2 mol % $Pd_2(dba)_3$, 3 equiv $KF{\cdot}2H_2O$, PhMe, 110 °C, 7 h, **18c**, 87 %.

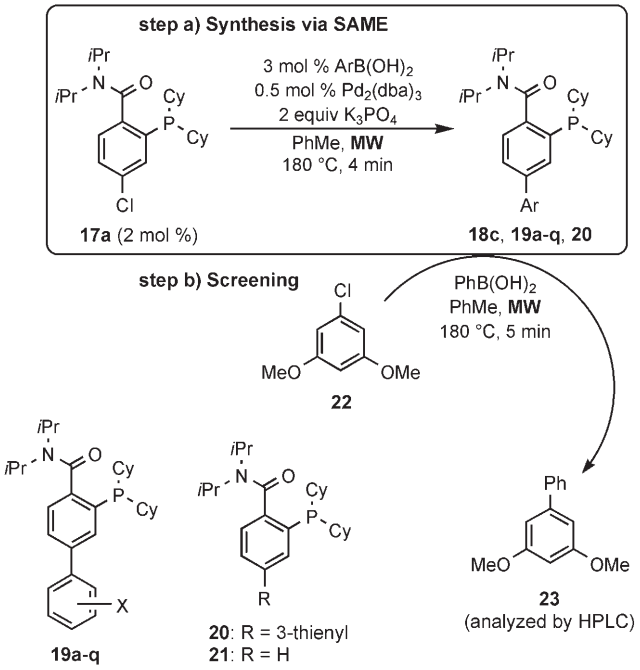
the product (Scheme 3c). This type of reaction is distinct from both product catalysis (PC) (Scheme 3a, or autocatalysis)[31] and substrate catalysis (SC) (Scheme 3b, or self-catalysis).[32] In an autocatalytic reaction the product catalyzes its own formation, while in a self-catalytic reaction, the substrate promotes its own conversion to the product. Thus, in order to initiate PC, seeding the reaction with preformed product molecules is required. In autocatalytic reactions with asymmetric amplification of stereochemical information (chirality),[31b–d] the seeding product molecules with low enantiomeric ratio can induce higher enantiomeric excess for the newly formed product. Such asymmetric autocatalysis with chirality amplification has been extensively studied in enantioselective synthesis and is considered as of mechanistic relevance to the origin of biochemical homochirality.[31b–d] In contrast to PC, a prefabricated catalyst is not required for SC. It operates when the reaction conditions are met, but the rate of product formation in SC is dependent on the substrate concentration and decreases with reaction progress, becoming very slow when the reaction approaches completion.[31a] As such, the combination of PC and SC in the same reaction offers a unique reaction system that proceeds without seeding with a tailor-made catalyst and the product formation should occur at a nearly constant rate if the rate laws and rate constants k_{SC} and k_{PC} for SC and PC are similar. In a special case in which k_{PC} overrides k_{SC}, the reaction shown in Scheme 3c becomes autocatalytic after initiation by SC.



Scheme 3. Illustrations of different reaction types and chemical processes. a) Product-catalysis (PC). b) Substrate-catalysis (SC). c) Both substrate- and product-catalysis. d) Schematic presentation of self-assisted replication (SAR). e) Self-assisted molecular editing (SAME).

Self-assisted replication (SAR) or self-replication is a process for generating a large number of perfect copies from a single original molecule (Scheme 3d).[33] For the minimal self-replicating systems, autocatalysis (or PC) is considered a key channel that duplicates the product molecule by means of template-directed synthesis.[33a] Theoretically, numerous mechanisms are possible for SAR, but a distinguishing profile of SAR is the specificity that a molecule only catalyzes or assists its own formation. Therefore, the information associated with the molecule can be passed on and preserved generation by generation. On the other hand, a chemical process or transformation capable of both SC and PC, referred to as self-assisted molecular editing (SAME),[34] is not specific for generating copies of a single molecular entity. The key feature of SAME is that a collection of new molecular entities (a compound library) can be self-generated from a single starting precursor. SAME is distinguished from combinatorial synthesis in the fundamental aspect that all reactions are both self- and autocatalytic. It is a unique strategy for generating molecular diversity. Indeed, a SAME process can be used for parallel or sequential synthesis of a library of single compounds (also compound mixtures if desired) simply by supplying different building blocks *m* (Scheme 3e).[35] It is emphasized that the library members are built upon a key scaffold capable of self-catalysis. Therefore, the characteristic features (identity) of the original molecule is carried on and preserved in the newly formed collection of molecular entities.

Synthesis and screening of an Aphos library: Illustrated in Scheme 4 is a one-pot synthesis and screening protocol for C4-Ar-Cy-Aphos **18c**, **19a–q**, and **20** by taking advantage of both SAME and controlled microwave heating.[36,37] Starting from Aphos **17a** as the substrate, a Suzuki–Miyaura cross-coupling with different arylboronic acids, $ArB(OH)_2$, was carried out in the presence of $[Pd_2(dba)_3]$ and K_3PO_4 in tolu-



Scheme 4. Microwave-assisted one-pot synthesis and screening of C4-Ar-Cy-Aphos **18c**, **19a–q**, and **20** by using the SAME process with C4-Cl-Cy-Aphos **17a**.

ene by using a pressurized process vial with microwave irradiation. After heating at 180 °C for 4 min, new C4-aryl-substituted Aphos ligands were obtained in 60–98 % yields, as checked by ^{31}P NMR spectroscopy (Table 1).[38] Except for

Table 1. Microwave-assisted synthesis of Aphos **18c**, **19a–q**, **20**, and **21** by SAME.

Entry	Aphos[a]	^{31}P NMR Signals in $CDCl_3$ (peak integration [%])[b]
1	**19a**: X = 3-Ph	−7.36 (98); −7.93 (2)
2	**20**	−7.72 (65); −7.94 (35)
3	**19b**: X = 2-OMe	−7.32 (82); −7.93 (18)
4	**19c**: X = 4-F	−7.51 (74); −7.93 (26)
5	**19d**: X = 2-Me,4-F	−7.76 (71); −7.93 (29)
6	**19e**: X = 4-Me	−7.46 (95); −7.92 (5)
7	**18c**	−7.43 (93); −7.93 (7)
8	**21**[c]	−7.92 (100)
9	**19f**: X = 4-OMe	−7.51 (90); −7.94 (10)
10	**19g**: X = 3-OMe	−7.45 (88); −7.93 (12)
11	**19h**: X = 2,6-Me_2	−8.32 (70); −7.93 (30)
12	**19i**: X = 2-Me	−7.64 (81); −7.93 (19)
13	**19j**: X = 3-CF_3	−7.36 (96); −7.90 (4)
14	**19k**: X = 3-Me,4-F	−7.45 (93); −7.92 (7)
15	**19l**: X = 3,4,5-F_3	−7.44 (86); −7.91 (14)
16	**19m**: X = 3,4-benzo	−7.36 (91); −7.92 (9)
17	**19n**: X = 3-F,4-Ph	−7.38 (82); −7.93 (18)
18	**19o**: X = 2,3-benzo	−7,79 (60); −7.91 (40)
19	**19p**: X = 4-SMe	−7.49 (85); −7.92 (7); −6.63 (8)[d]
20	**19q**: X = 3-NO_2	−7.36 (63); −7.92 (37)

[a] Aphos ligands were prepared as shown in Scheme 4. [b] Chemical shift values in ppm for the Aphos mixture. The Aphos structures were validated by ^{31}P NMR spectroscopy and the purities were estimated by the integration of ^{31}P signals of the Aphos mixture. The ^{31}P signals for authentic **17a**, **18c**, and **21** are −6.65, −7.45, and −7.97 ppm, respectively. [c] No arylboronic acid was added. [d] The remaining substrate Aphos **17a**.

4-methylthiobenzeneboronic acid (entry 19, Table 1), the substrate **17a** was completely converted. Because a 2:1 ratio of **17a** to Pd was used, dechlorination of **17a** might compete at such a high palladium loading (50 mol %). Indeed, **17a** was quantitatively transformed into **21** in the absence of an arylboronic acid (entry 8, Table 1). Moreover, formation of **21** (which had a ^{31}P NMR signal at approximately −7.93 ppm in the mixture) was observed as the background reaction in all couplings of **17a**. The yields of **21** varied within 2–40 % depending on the reactivity of the arylboronic acids. The Aphos synthesis was repeated for selected arylboronic acids and the product ratios could be reproduced, assuring reliability of the synthesis. According to the ratios of **21** listed in Table 1, arylboronic acids can be grouped by the increased reactivity order of: electron-deficient and/or sterically bulky subgroups (1-naphthyl ≈ 3-$NO_2C_6H_4$ ≈ 3-thienyl < 2,6-$Me_2C_6H_3$ ≈ 2-Me,4-FC_6H_3 ≈ 4-FC_6H_4) < moderately electron-deficient and/or less sterically bulky subgroups (2-MeC_6H_4 ≈ 2-$MeOC_6H_4$ ≈ 3-F,4-PhC_6H_3 ≈ 3,4,5-$F_3C_6H_2$ ≈ 3-$MeOC_6H_4$) < electron-rich and/or non-sterically bulky subgroups (4-$MeOC_6H_4$ ≈ 2-naphthyl ≈ 4-$MeSC_6H_4$ ≈ 3-Me,4-FC_6H_3 ≈ Ph < 4-MeC_6H_4 ≈ 3-$CF_3C_6H_4$ ≈ 3-PhC_6H_4).

The Aphos library synthesis and screening were performed on a technical microwave reactor in a sequential manner so that a single compound library was generated and screened. The molar ratios of all reagents used in the Aphos synthesis step were calibrated to the aryl chloride **22**, which is the substrate of the subsequent coupling reaction, designed for screening the efficiency of the newly formed Aphos. The reaction mixture from step a in Scheme 4, which contained the newly formed C4-Ar-Cy-Aphos, the palladium species, and K_3PO_4, was then directly used for screening the Aphos efficiency in the reference Suzuki–Miyaura cross-coupling reaction of the unactivated aryl chloride **22** as shown in step b of Scheme 4. Thus, 5-chloro-1,3-dimethoxybenzene (**22**, 1 equiv) and $PhB(OH)_2$ (1.5 equiv) together with an internal reference compound, *N*,*N*-diisopropyl 4-cyclohexylbenzamide, were added to the Aphos mixture and heated at 180 °C for 5 min under microwave heating. The resultant reaction mixture was filtered through Celite and silica gel, and the filtrate was subjected to HPLC analysis for determination of the conversion of **22** (see Supporting Information). In general, the conversion of **22** ranged from 63 % to 90 % for Aphos derivatives **19a–q** and **20**; the values for phosphanes **18c** and **21** are 77 % and 76 %, respectively. For selected runs, the biphenyl product **23** was purified and the isolated yields were consistent with the HPLC-determined conversion values of **22**. For comparison of Aphos efficiency, we normalized the conversion data of **22** obtained by HPLC analysis according to the Aphos ratios given in Table 1 (see Supporting Information). By using Aphos **21** as the reference, a relative order of catalytic efficiency is derived for the 20 Aphos ligands. As depicted in Figure 2, Aphos ligands **18c**,[39] **19a–e**, and **20** demonstrate reduced efficiency (1–14 %), while enhanced catalytic efficiency (3–20 %) is observed for Aphos ligands **19f–q** with a maximum increase of 20 % for the C4-(3-nitrophenyl)-Cy-Aphos **19q**.

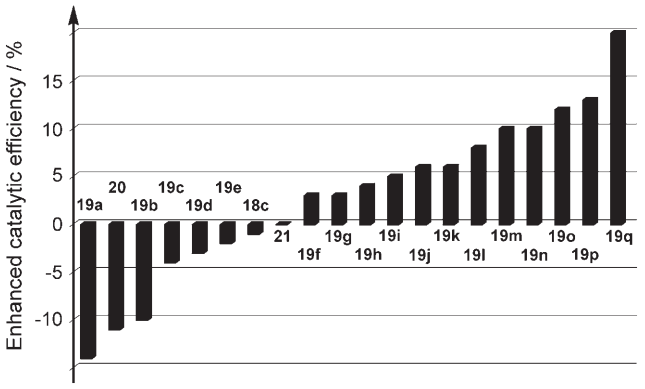
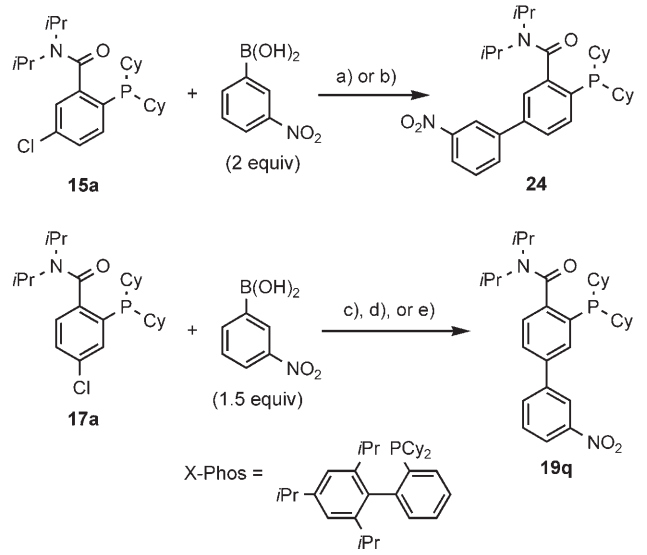


Figure 2. Relative efficiency of 4-Ar-Cy-Aphos **18c**, **19a–q**, and **20** with reference to C4-unsubstituted Cy-Aphos **21**. The values were estimated by HPLC analysis of the coupling product **23** formed in the reaction of **22** with $PhB(OH)_2$ in the presence of the Aphos synthesized in Scheme 4.

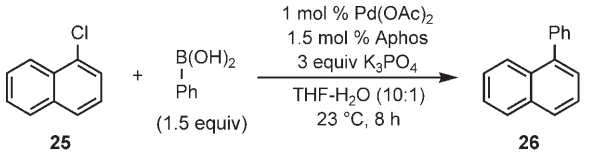
Synthesis and comparison of C4- and C5-(3-nitrophenyl)-Cy-Aphos ligands 19q and 24: With the Aphos library screening data in hand, the C4-(3-nitrophenyl)-Cy-Aphos ligand **19q** was synthesized and fully characterized (Scheme 5). The coupling reaction of **17a** with 1.5 equivalents of 3-nitrobenzeneboronic acid was first carried out in the presence of 5 mol% $Pd(OAc)_2$ and 3 equivalents of K_3PO_4 in THF at 80°C for 24 h to furnish the product Aphos ligand **19q** in 56% yield (Scheme 5, condition c). By using 10 mol% $Pd(OAc)_2$ the yield of **19q** could be improved to 82% with a reduced reaction time of 15 h (condition d). It was interesting to find that addition of 10 mol% X-Phos[9e] into the reaction system containing 4 mol% $Pd(OAc)_2$ could also speed up the coupling reaction (80°C, 8 h) to produce **19q** in 83% yield (condition e). The coupling of **15a** with 3-nitrobenzeneboronic acid was found to be slightly difficult and a higher temperature was found to be advantageous. With the use of 10 mol% of $Pd(OAc)_2$ the coupling was performed at 100°C for 8 h to afford the Aphos ligand **24** in 70% yield (condition a in Scheme 5). If 12 mol% X-Phos was added along with 5 mol% $Pd(OAc)_2$ the reaction occurred at 80°C for 10 h to give **24** in 75% yield (condition b). These results imply that X-Phos may act as a "seeding ligand" to initiate the coupling reaction or as a more efficient ligand for palladium presumably due to its electron-richness relative to the Aphos counterparts. It should be emphasized that the nitro-containing Aphos ligands could not be prepared by using the directed *ortho*-deprotonation approach as shown in Scheme 1 due to interference of the nitro group with the alkyllithium reagent. It further testifies to the synthetic potential of the SAME approach illustrated in Scheme 2.



Scheme 5. Synthesis of Cy-Aphos **19q** and **24**. a) 10 mol% $Pd(OAc)_2$, 3 equiv K_3PO_4, THF/H_2O (10:1), 100°C, 8 h, 70%. b) 5 mol% $Pd(OAc)_2$, 12 mol% X-Phos, 3 equiv K_3PO_4, THF/H_2O (10:1), 80°C, 10 h, 75%. c) 5 mol% $Pd(OAc)_2$, 3 equiv K_3PO_4, THF, 80°C, 24 h, 56%. d) 10 mol% $Pd(OAc)_2$, 3 equiv K_3PO_4, THF, 80°C, 15 h, 82%. e) 4 mol% $Pd(OAc)_2$, 10 mol% X-Phos, 3 equiv K_3PO_4, THF, 80°C, 8 h, 83%.

With the pure Aphos ligands **19q** and **24** in hand, a comparison of catalytic efficiency with other Aphos ligands was conducted by using the coupling reaction of 1-chloronaphthalene **25** with phenylboronic acid at room temperature. Reaction conditions were adopted according to our optimization described below and the coupling results are summarized in Table 2. By interrupting the reaction after 8 h, the residual **25** was recovered along with the isolated product **26**. A relative efficiency index E_{rel} was calculated on the basis of the conversion data by taking the unsubstituted Aphos ligand **21** as the reference. For C4-substituted Aphos ligands, an increasing order of catalytic efficacy can be derived: alkyl (**18b**) < vinyl (**18a**) < phenyl (**18c**) < 3-nitrophenyl (**19q**). The C5-(3-nitrophenyl)-Cy-Aphos ligand **24** is slightly more active than **19q** (entry 6, Table 2). These results reproduce the outcome depicted in Figure 2 for Aphos **19q** and our early findings.[10] Moreover, the Aphos ligand efficiency was found to be dependent on both coupling partners and reaction conditions (see below). For the room-temperature coupling of unactivated or sterically hindered aryl chlorides with arylboronic acids, C4- and C5-(3-nitrophenyl)-Cy-Aphos ligands **19q** and **24** are among the best performing ligands we have examined.

Table 2. Comparison of Cy-Aphos phosphanes **18a–c**, **19q**, **21**, and **24** in the Suzuki–Miyaura cross-coupling of 1-chloronaphthalene with phenylboronic acid at room temperature.



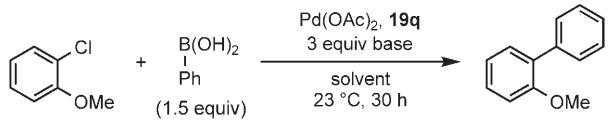
Entry	Aphos	Conversion [%][a]	Yield [%][b]	E_{rel}[c]
1	**18a**	41	35	0.9
2	**18b**	30	26	0.7
3	**18c**	48	41	1.1
4	**19q**	68	62	1.5
5	**21**	45	38	–
6	**24**	71	66	1.6

[a] Conversion of **25** based on recovered materials. [b] Isolated yield of **26**. [c] E_{rel} = [conversion of **25** for C4-substituted Aphos]/[conversion of **25** for Aphos **21**]. Similar E_{rel} values can be obtained according to the isolated product yields.

Room-temperature Suzuki–Miyaura cross-coupling of aryl chlorides: The room-temperature Suzuki–Miyaura cross-coupling of unactivated aryl chlorides with arylboronic acids poses a synthetic challenge for carbon–carbon formation. Advances in the design of electron-rich and sterically bulky phosphanes, such as **1b** and **2a**,**b** and NHCs[12,13] as the robust ligands have been made,[6] and the groups of Fu,[8b,c] Buchwald,[9] Hermann,[14] Nolan,[15] Glorius,[16] Ma and Andrus,[17] and Organ[18] have made significant contributions in this area. We initially reported the use of $[Pd_2(dba)_3]$–

Aphos systems with $KF{\cdot}2H_2O$[21b] or K_3PO_4[10] in toluene for Suzuki–Miyaura cross-coupling reactions of aryl bromides and unactivated aryl chlorides at heating temperatures. It was found that the $[Pd_2(dba)_3]$–Aphos combination could not promote the coupling of 2-chloro-1-methoxybenzene with phenylboronic acid at room temperature (Table 3, entry 19).[40] In contrast, $Pd(OAc)_2$ was a suitable palladium source for the room-temperature reaction. With 1 mol% $Pd(OAc)_2$ and 2 mol% of C4-(3-nitrophenyl)-Cy-Aphos **19q** in THF/H_2O (10:1), various bases were screened for the reaction of **27** with phenylboronic acid at 23 °C for 30 h. The isolated yields of the biphenyl **28** are listed in entries 1–5 and 9 of Table 3. The highest yield of 70% was obtained for K_3PO_4 (entry 9). Other commonly used mild bases, CsF, KF, and K_2CO_3, afforded the product in 27–47% yields. A lower palladium loading than 1 mol% resulted in a drop of the yield to 27% (entry 6 vs. entry 9).

Table 3. Screening of reaction conditions for room-temperature Suzuki–Miyaura coupling of 2-chloro-1-methoxybenzene with phenylboronic acid using Aphos **19q**.



27 28

Entry	Pd [mol%]	**19q**:Pd	Base[a]	Solvent[b]	Yield [%][c]
1	1	2:1	KOAc	THF/H_2O	<5
2	1	2:1	Cs_2CO_3	THF/H_2O	<5
3	1	2:1	K_2CO_3	THF/H_2O	47
4	1	2:1	CsF	THF/H_2O	27
5	1	2:1	KF	THF/H_2O	33
6	0.5	2:1	K_3PO_4	THF/H_2O	27
7	1	1:1	K_3PO_4	THF/H_2O	43
8	1	1.5:1	K_3PO_4	THF/H_2O	76
9	1	2:1	K_3PO_4	THF/H_2O	70
10	1	2.5:1	K_3PO_4	THF/H_2O	<5
11	1	3:1	K_3PO_4	THF/H_2O	<5
12	1	1.5:1	K_3PO_4	THF/H_2O	62[d]
13	1	2:1	K_3PO_4	THF	76
14	1.5	1.3:1	K_3PO_4	THF/H_2O	65
15	1.5	1.7:1	K_3PO_4	THF/H_2O	56
16	2	1.5:1	K_3PO_4	THF/H_2O	85[e]
17	1	1.5:1	K_3PO_4	*i*PrOH/H_2O	61[e]
18	1.5	1.7:1	K_3PO_4	*i*PrOH/H_2O	54[e]
19	2[f]	1.5:1	K_3PO_4	THF/H_2O	<5[e]

[a] $K_3PO_4{\cdot}H_2O$ can be used instead of K_3PO_4. [b] A 9 vol% aqueous solvent was used unless otherwise stated. [c] Isolated yields. [d] For 10 h. [e] For 24 h. [f] $[Pd_2(dba)_3]$ was used.

A remarkable effect of the Aphos/Pd ratio on the coupling reaction was observed (Figure 3). A 76% yield of **28** was produced at a 1.5:1 **19q**/Pd ratio (entry 8), while with **19q**/Pd ≥ 2.5:1 almost no reaction occurred (entries 10 and 11). This observation is quite different from those made in the coupling reactions carried out above room temperature. As described above in Scheme 2, at ≥80 °C, the Suzuki–Miyaura coupling of **17a** could take place at an Aphos/Pd ratio of up to 25:1. The possible structures of Aphos–Pd complexes at different ratios are discussed below based on ^{31}P NMR spectroscopic studies. At 1 mol% $Pd(OAc)_2$ with a **19q**/Pd ratio of 1.5:1, a slightly lower yield of 62% was obtained by reducing the reaction time from 30 h to 10 h (entry 12 vs. entry 8). However, the yield could be improved to 85% after a 24 h reaction time with a Pd loading of 2 mol% (entry 16 vs. entry 8). A fine adjustment of the **19q**/Pd ratio at either 1.3:1 or 1.7:1 confirmed that a 1.5:1 ratio of **19q**/Pd gave the optimal result (entries 14 and 15 vs. entry 8). Use of water as the co-solvent was not apparently beneficial (entry 13 vs. entry 9); however, it was generally added for operational convenience in dissolving the inorganic reagents. In addition to THF/H_2O (10:1), *i*PrOH/H_2O (10:1) could be used as the solvent without affecting the efficiency of the coupling reaction at 1.5 mol% palladium loading although a lower yield was obtained with 1 mol% $Pd(OAc)_2$ (entries 17 and 18 vs. entries 8 and 15). A final set of general reaction conditions was determined for the room-temperature Suzuki–Miyaura coupling of unactivated aryl chlorides in this study: 1–2 mol% $Pd(OAc)_2$, 1.5:1 Aphos/$Pd(OAc)_2$, 1 equivalent aryl chlorides, 1.5 equivalents arylboronic acids, and 3 equivalents K_3PO_4 in THF/H_2O (10:1).

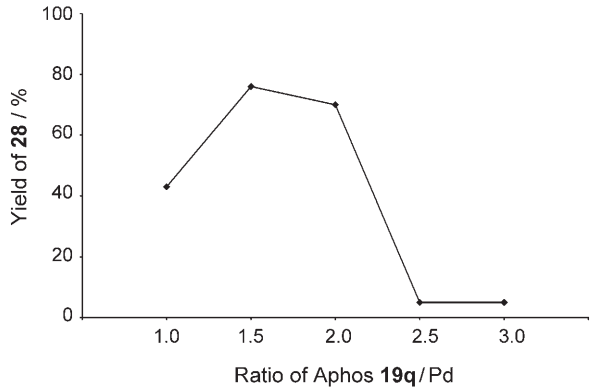
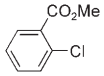
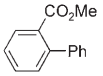
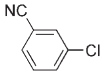
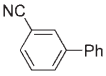
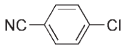
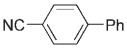
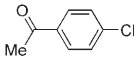
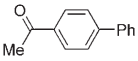


Figure 3. Effect of Aphos **19q**/Pd ratio on the coupling product yield of **28**. The data in this plot are based on the values in the entries 7–11 of Table 3.

Room-temperature Suzuki–Miyaura cross-coupling reactions of some selected activated aryl chlorides were first examined for Aphos **19q** and the results are summarized in Table 4. At 0.2 mol% $Pd(OAc)_2$, the coupling reactions were carried out for 24–40 h to afford the products in 87–92% yields (entries 2, 3, and 5). For some substrates, excellent yields were obtained at 0.1 mol% Pd loading (entries 1 and 4). With 1 mol% Pd, the reaction time could be significantly reduced, to 8 h (entry 1, Table 4).

Table 5 summarizes the results of room-temperature coupling reactions of unactivated aryl chlorides with arylboronic acids catalyzed by the precatalyst Aphos **19q**–$Pd(OAc)_2$ (1.5:1). For the reactions of 1-chloronaphthalene with phenyl, 2-tolyl, and 2-methoxyphenyl boronic acids, 82–95% yields were obtained at 1 mol% Pd loading (entries 1–3). For 2-, 3-, 4-chlorotoluenes, the coupling reactions with phenylboronic acid at 1 mol% $Pd(OAc)_2$ for 24 h afforded the products in 68–73% yields, but higher yields of 82–90%

Table 4. Room-temperature Suzuki–Miyaura coupling of activated aryl chlorides with phenylboronic acid using Aphos **19q**.[a]

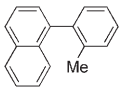
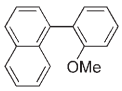
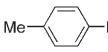
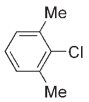
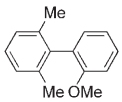
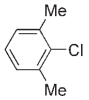
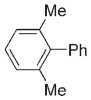
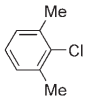
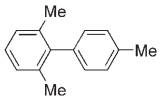
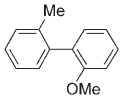
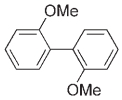
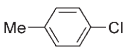
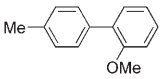
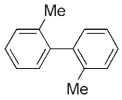
Entry	Aryl chloride	Product	Pd [mol%]	*t* [h]	Yield [%][b]
1			1.0 0.1	8 36	95 94
2			0.1 0.2	36 40	76 90
3			0.1 0.2	36 24	71 87
4			0.1	36	97
5			0.1 0.2	36 40	81 92

[a] Reaction conditions: 1 equiv aryl chloride, 1.5 equiv $PhB(OH)_2$, 3 equiv K_3PO_4, $Pd(OAc)_2$/**19q** = 1:1.5, 2 mL THF/H_2O (10:1) per mmol aryl chloride. Room temperature is approximately 23 °C. [b] Averaged isolated yields of two runs.

could be achieved by using 2 mol% of the palladium reagent (entries 4–6). Chloroanisoles demonstrated diminished reactivity in the room-temperature coupling with phenylboronic acid and moderate yields of 88% and 75% were obtained for 2- and 3-chloroanisoles after 36 h (entries 7 and 8). The yield for the reaction of 4-chloroanisoles with phenylboronic acid was 24% in the presence of 1 mol% Pd after 24 h (data not shown in Table 5). For the sterically hindered substrate, 2-chloro-1,3-dimethylbenzene, 84% yield was obtained for the coupling with 2-methoxybenzeneboronic acid (entry 9), but lower yields (53% and 28%) respectively, were obtained when phenyl and 4-tolyl boronic acids, were used (entries 10 and 11). For the reactions of aryl chlorides and arylboronic acids both possessing an *ortho*-methoxy or -methyl substituent, low yields were generally obtained (entries 13–16) except for the entry 12 in Table 5. It was found that the reactions of 2-methoxybenzeneboronic acid were faster and furnished better results than other arylboronic acids under the current catalytic system (entries 3, 9, and 12–14, Table 5).

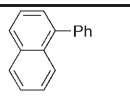
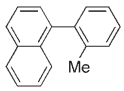
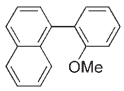
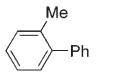
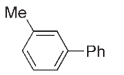
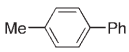
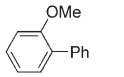
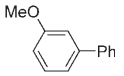
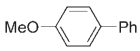
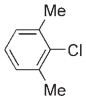
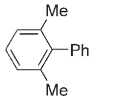
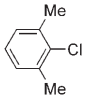
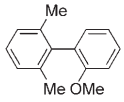
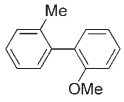
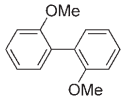
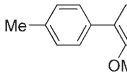
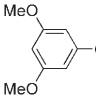
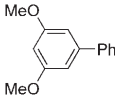
C5-(3-Nitrophenyl)-Cy-Aphos ligand **24** was found to be slightly more efficient than the C4 counterpart ligand **19q** in the comparison study given in Table 2. This was confirmed again in the room-temperature coupling reactions of unactivated aryl chlorides with arylboronic acids (Table 6). Nearly quantitative yields were obtained for the reactions of 1-chloronaphthalene with phenyl, 2-tolyl, and 2-methoxyphenyl boronic acids at 1 mol% $Pd(OAc)_2$ and 1.5 mol% of **24** for 6–18 h (entries 1–3). Similarly, the couplings of 2-, 3-, and 4-chlorotoluenes with phenylboronic acid furnished the products in quantitative yields by using 2 mol% palladium for 36 h (entries 4–6). The electron-rich 2-, 3-, and 4-chloroanisoles reacted smoothly with phenylboronic acid to provide the products in much higher yields (80–99%) than the analogous precatalyst consisting of Aphos **19q** and $Pd(OAc)_2$ (Table 6, entries 7–9 and 13 vs. Table 5, entries 7, 8, and 13). With this robust Aphos **24**, the hindered and electron-rich chlorobenzenes in entries 10–14 underwent the coupling reactions with phenyl and 2-methoxyphenyl boronic acids to afford good to excellent yields. In particular, a

Table 5. Room-temperature Suzuki–Miyaura coupling of unactivated aryl chlorides with arylboronic acids using Aphos **19q**.[a]

Entry	Aryl chloride	Product	Pd [mol%]	*t* [h]	Yield [%][b]
1			1	36	82
2			1	24	94
3			1	8	95[c]
4			1 2	24 24	68 90
5			2	24	87
6			1 2	24 24	73 82
7			2 2	24 36	75 88
8			2 2	24 36	71 75
9			2 2	24 36	78[c,d] 84[c,d]
10			2	36	53
11			2	36	28
12			2	24	86[c]
13			2	36	47[c]
14			1 2	24 24	52[c] 54[c]
15			2	36	35
16			2	36	28

[a] Reaction conditions: 1 equiv aryl chloride, 1.5 equiv $PhB(OH)_2$, 3 equiv K_3PO_4, $Pd(OAc)_2$/**19q** = 1:1.5, 2 mL THF/H_2O (10:1) per mmol aryl chloride. Room temperature is approximately 23 °C. [b] Averaged isolated yields of two runs. [c] In THF. [d] 2 equiv arylboronic acid were used.

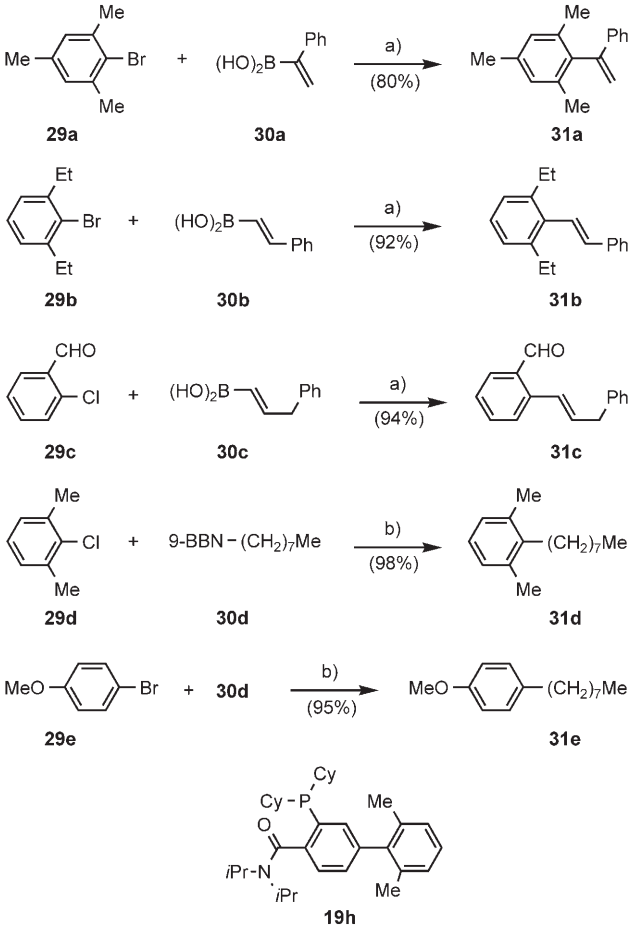
Table 6. Room-temperature Suzuki–Miyaura coupling of unactivated aryl chlorides with arylboronic acids using Aphos **24**.[a]

Entry	Aryl chloride	Product	Pd [mol%]	*t* [h]	Yield [%][b]
1			1	18	98
2			1	18	99
3			1	6	96
4			2	36	99
5			2	36	99
6			2	36	98
7			2	36	92
8			2	36	99
9			2	36	80
10			2	36	94
11			2 2	36 36	78 91[c,d]
12			2	36	85
13			2	36	78
14			2	36	92
15			2 1	36 23	36 97[e]

[a] Reaction conditions: 1 equiv aryl chloride, 1.5 equiv $PhB(OH)_2$, 3 equiv K_3PO_4, $Pd(OAc)_2$/**24** = 1:1.5, 2 mL THF/H_2O (10:1) per mmol aryl chloride. Room temperature is approximately 23 °C. [b] Averaged isolated yields of two runs. [c] In THF. [d] 2 equiv arylboronic acids were used. [e] The reaction was performed at 60 °C using Aphos **19q**.

91% yield was obtained by using two equivalents of the arylboronic acid to form the biphenyl product with three *ortho*-substituents (entry 11, Table 6). The reaction of 5-chloro-1,3-dimethoxybenzene with phenylboronic acid gave the product in 36% yield with 2 mol% $Pd(OAc)_2$ and 3 mol% Aphos **24** at room temperature for 36 h. The yield could be improved to 97% after a 23 h reaction at 60 °C by using 1 mol% Pd and 1.5 mol% of Aphos **19q** (entry 15, Table 6).

We found that C4-(2,6-dimethylphenyl)-Cy-Aphos **19h** was much more efficient for room-temperature Suzuki–Miyaura cross-couplings with vinylboronic acids and alkylboranes. Illustrated in Scheme 6 are some selected examples



Scheme 6. Aphos **19h**-$Pd(OAc)_2$-catalyzed coupling of hindered aryl bromides and chlorides with vinylboronic acids and alkylboranes. a) 1 mol% $Pd(OAc)_2$, 1.5 mol% Aphos **19h**, 1.5 equiv vinylboronic acids **30a–c**, 3 equiv K_3PO_4, THF, room temperature, 48 h for **29a**; 20 h for **29b**; or 8 h for **29c**. b) 1 mol% $Pd(OAc)_2$, 1.5 mol% Aphos **19h**, 1.5 equiv alkylborane **30d**, 3 equiv $K_3PO_4 \cdot 3H_2O$, THF, 50 °C, 12 h for **29d**; or room temperature, 12 h for **29e**.

of the couplings of aryl bromides and chlorides **29a–e** with the boron reagents **30a–d**. Sterically hindered aryl bromides **29a**,**b** were treated with the vinylboronic acids **30a**,**b** in the presence of 1 mol% $Pd(OAc)_2$ and 1.5 mol% Aphos **19h** at room temperature for 20–40 h to furnish the products **31a** and **31b** in 80% and 92% yield, respectively. The activated aryl chloride **29c** underwent room-temperature coupling with the vinylboronic acid **30c** in 8 h to produce **31c** in 94% yield. The reaction of the hindered aryl chloride **29d** with the alkylborane **30d** prepared in situ from 1-octene and 9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane) took place at

50 °C in 12 h at 1 mol % palladium loading to afford the product **31d** in 98 % yield. In contrast, the electron-rich aryl bromide **29e** reacted with **30d** at room temperature to give **31e** in 95 % yield after 12 h. Moreover, vinyl bromides could be coupled with alkylboranes at room temperature by using Aphos **19h**/$Pd(OAc)_2$ as the precatalyst and this protocol has been used in our synthesis of the tetrahydrofuran fragment required for total synthesis of amphidinolide Y.[41]

Studies on Aphos–Pd complexes by ^{31}P NMR spectroscopy: As described above, the room-temperature coupling reactions involving Aphos–$Pd(OAc)_2$ as the precatalyst in THF or THF/H_2O (10:1) were generally very slow in the initial several hours, with no visible formation of the product. After the induction period the reaction took place smoothly and gradually slowed down within 24 h with precipitation of Pd black in some cases. This may be the reason that doubling the palladium loading or prolonging the reaction time did not always lead to significant improvement of the yields (entries 6–8 and 14, Table 5). To understand the structures of complexes formed between Aphos and palladium(0), we performed a series of NMR experiments by using Aphos **21** and [$Pd_2(dba)_3$] in [D_8]THF. The ^{31}P NMR spectra at different Aphos/Pd ratios are depicted in Figure 4. The free Aphos **21** in [D_8]THF gives a single ^{31}P signal at −9.0 ppm (Figure 4a). After adding [$Pd_2(dba)_3$] to form a 0.5:1 mixture of **21**/Pd, the free Aphos signal (at −10.8 in the mixture instead of −9.0 ppm) almost disappeared and a new single signal at 42.0 ppm was seen (Figure 4b). Increasing the amount of **21** to a 1:1 ratio to palladium resulted in a similar spectrum except for enhancement in the intensities for the minor peaks a–d shown in the insert (Figure 4c). The broad peak c at 26.1 ppm is unique and it almost disappeared when the ratio of **21**/Pd reached 1.5:1 (Figure 4d). Free **21** appeared again when the **21**/Pd ratios were ≥1.5:1. The spectra in Figure 4e–g are almost identical and they differ only in the intensities of the two major peaks at 42.0 and −10.8 ppm after addition of more Aphos **21**.

According to the information gained from the ^{31}P NMR experiments and the results plotted in Figure 3, we can conclude that different ratios of Aphos and Pd only form one major Pd complex that is catalytically inactive at room temperature. On the basis of the relative peak intensities at 42.0 and −10.8 ppm in Figure 4d,e, the Pd complex should be monoligated. Scheme 7 shows two possible complex structures **9a** and **10a**, of which the P,O-chelating complex **10a** seems the most suitable candidate. We reasoned that the broad peak c at 26.1 ppm may be assigned for the P-monodentate complex **9a**, which might exhibit a dynamic ^{31}P NMR profile due to the conformational flexibility of the bulky and non-coordinated amide moiety.[24] Alternatively, the broad peak c seen in Figure 4b–d might be a consequence of the equilibrium between **9a** and **9a′** in which one Aphos molecule acts as both P- and O-monodentate donor to different Pd species. If this is true, it should account for the observation that the broad peak c disappeared in the presence of a large excess of **21**. We assign the most abun-

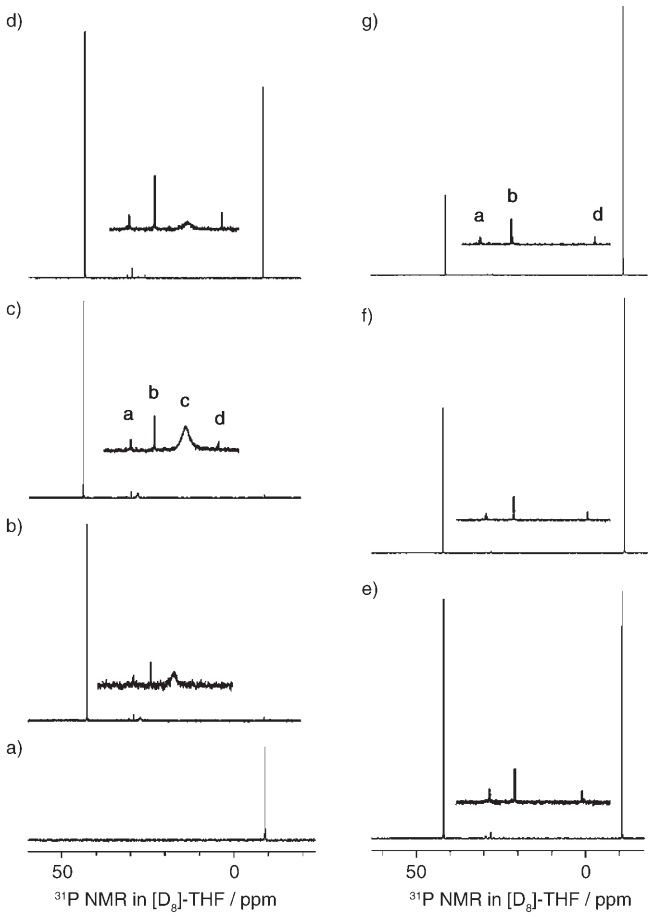
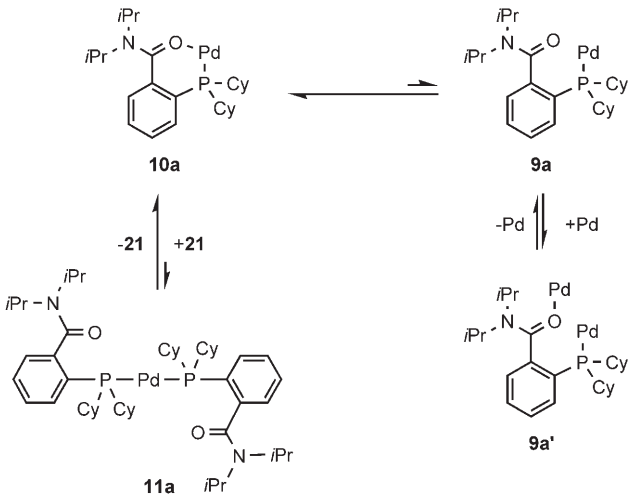


Figure 4. ^{31}P NMR charts of Aphos **21** and its complexes with [$Pd_2(dba)_3$] in [D_8]THF taken at room temperature. a) Aphos **21** alone. b) 0.5:1 mixture of Aphos **21** with Pd^0. c) 1:1 mixture of Aphos **21** with Pd^0. d) 1.5:1 mixture of Aphos **21** with Pd^0. e) 2:1 mixture of Aphos **21** with Pd^0. f) 2.5:1 mixture of Aphos **21** with Pd^0. g) 3:1 mixture of Aphos **21** with Pd^0. The spectra were taken 20 min later at room temperature after mixing. ^{31}P chemical shifts for the major complex and the free Aphos **21** are 42.0 and −9.0 ppm (or −10.8 ppm in the mixture). ^{31}P chemical shifts for the peaks a–d in the insert are 29.4, 28.0, 26.1, and 24.3 ppm, respectively.



Scheme 7. Proposed Pd complexes of Aphos **21**.

dant minor peak b (28.0 ppm) to the symmetrical 2:1 complex **11a** and the peaks a (29.4 ppm) and d (24.3 ppm) as the conformational isomer(s) of **11a** or the dba complexes of **9a**.[40a] We measured a ^{13}C NMR spectrum for the 3:1 mixture of **21** and Pd in [D_8]THF shown in Figure 4g and found two amide carbonyl signals at 167.3 (d, $J_{P\text{-}C}=4.0$ Hz) and 166.9 ppm (d, $J_{P\text{-}C}=2.8$ Hz) for the major (free **21**) and minor (the Pd complex) phosphorus-containing components. In view of the small difference in the ^{13}C NMR chemical shifts, coordination of the oxygen donor to Pd in **10a** should be quite weak. Moreover, only one ketone carbonyl signal at 185.1 ppm was observed, indicating that dba is not associated with **10a**. We tried to prepare Pd complexes of **21** for X-ray structural analysis. However, suitable single crystals have not been obtained so far. Although much more solid structural evidence is needed for a conclusive discussion of the Aphos–Pd complex structures, it is evident that the catalytically active Pd species is the complex which exhibits a broad ^{31}P signal at 26.1 ppm. We did similar ^{31}P NMR experiments with mixtures of **21** with [$Pd_2(dba)_3$] at different ratios in C_6D_6. In contrast to [D_8]THF, the Aphos–Pd complex formation was quite slow at room temperature in C_6D_6. This may explain the fact that heating was required for the coupling reactions of aryl chlorides with arylboronic acids in PhMe when Aphos–[$Pd_2(dba)_3$] was used as the precatalyst.[10] Similar heating conditions were used for the ether-type P,O-ligand **4b**[20b] and the ferrocene-based variants.[42]

Conclusion

Aromatic amide-derived phosphanes (Aphos) are hybrid hemilabile ligands that possess both phosphorus and oxygen donor groups. Aphos ligands are expected to form both P-monodentate and P,O-chelating metal (such as palladium) complexes in a dynamic relationship. With carefully selected *N*,*N*-dialkylaminocarbonyl [$(R^1)_2NC(O)$-] and dialkylphosphino [$(R^2)_2P$-] subunits in **5** the monoligated Pd complexes **10** are almost exclusively formed regardless of the Aphos/Pd ratio within the range from 0.5:1 to 3:1. However, for the Suzuki–Miyaura cross-coupling of unactivated aryl chlorides with arylboronic acids at room temperature, a remarkable effect of the Aphos/Pd ratio on catalysis is observed, suggesting that the catalytically active species may not be the P,O-chelating Pd complexes such as **10a** (Scheme 7). In contrast, on heating to temperatures of 80–100 °C, the coupling reactions take place smoothly with high Aphos/Pd ratios of up to 25:1. Such diverse properties of Aphos form the basis for development of the self-assisted molecular editing (SAME) protocol we used for generation of molecular diversity based on building blocks.

As an illustrative application of SAME, a focused C4-substituted Cy-Aphos library has been synthesized and screened by sequential microwave-assisted reactions starting from a single C4-Cl-Cy-Aphos **17a**. This one-pot Aphos synthesis and screening process in combination with controlled microwave chemistry provides reliable and reproducible results in a high-throughput manner, leading to the discovery of an efficient Cy-Aphos **19q** containing a 3-nitrophenyl group at the C4 position. Aphos **19q** and its C5-substituted analogue **24** promote room-temperature Suzuki–Miyaura coupling of unactivated and hindered aryl chlorides with arylboronic acids at 1–2 mol% $Pd(OAc)_2$ with a 1.5:1 Aphos/Pd ratio in THF or THF/H_2O in the presence of K_3PO_4 as the base. A related Cy-Aphos **19h** substituted with a 2,6-dimethylphenyl group at the C4 position in combination with 1 mol% $Pd(OAc)_2$ offers a highly reactive precatalyst for room-temperature reactions of hindered and electron-rich aryl bromides and chlorides with vinylboronic acids and alkylboranes, respectively. The effect of the substituent on the benzene ring of Aphos[10] was further validated in this study by using the C4-substituted Aphos ligands **18a–c**, **19a–q**, and **20**. The substituent effect, although moderate, is useful for fine tuning catalytic efficacy, which is important for asymmetric Suzuki–Miyaura cross-coupling to synthesize axially chiral biaryls possessing at least three *ortho* substituents.[23c,43] In order to achieve highly enantioselective reactions, temperatures below 40–60 °C are preferred for asymmetric Suzuki–Miyaura cross-coupling.[23c] We have applied the SAME protocol to access analogues of the Cy-A^2phos (a*S*)-**7b** and evaluated enantioselectivity in asymmetric Suzuki–Miyaura cross-coupling. The details will be reported elsewhere.

Experimental Section

General methods: All microwave reactions were carried out in closed 10 mL pressurized process vials on a technical microwave reactor (Emrys creator from Personal Chemistry AB or Initiator from Biotage AB, Uppsala, Sweden) with the reaction temperature measured by an IR sensor. NMR spectra were recorded on a 300, 400, or 500 MHz instrument in $CDCl_3$ using residual $CHCl_3$ as the internal reference for ^1H (δ 7.26 ppm) and ^{13}C (δ 77.2 ppm) or a routine external reference for ^{31}P. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by APCI, CI, ESI, or TOF methods. Elemental analyses were performed by Zhejiang University, Hangzhou, China. Melting points are uncorrected. Silica gel plates 60 F-254 (0.25 mm, E. Merck) were used for thin-layer chromatography by using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel 60 (particle size 0.040–0.063 mm, E. Merck) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Aryl boronic acids and other reagents were obtained commercially and used as received. Dry THF and toluene were freshly distilled from sodium and benzophenone under a nitrogen atmosphere. Toluene was degassed before use in all microwave-assisted reactions.

General procedure A—synthesis of Cl-Cy-Aphos 14, 16, and 17: *N*,*N*-Diisopropyl 2-, 3-, or 4-chlorobenzamide (500.0 mg, 2.08 mmol) and dry THF (20 mL) were added to a flame-dried flask with a stirring bar, under a nitrogen atmosphere. Freshly distilled TMEDA (0.38 mL, 2.5 mmol, 1.2 equiv) and *n*BuLi (1.56 mL, 1.6 M solution in hexanes, 2.5 mmol) were added sequentially and dropwise, by syringe over 5 min to the resultant solution cooled in a dry-ice/acetone bath (−78 °C). The resultant mixture was stirred at −78 °C for 30 min. Chlorodicyclohexylphosphane (0.55 mL, 2.5 mmol) was then added by a syringe. The resultant mixture was stirred at −78 °C for 1 h and then allowed to slowly warm to room temperature. The reaction mixture was filtered through a pad of silica gel topped with a layer of Celite while eluting with EtOAc. The filtrate was concentrated

under reduced pressure and the residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to provide **14a**, **16a**, or **17a**.

***N,N*-Diisopropyl 6-chloro-2-dicyclohexylphosphinobenzamide (14a)**: Compound **14a** was prepared in 99% yield according to general procedure A. White amorphous solid; m.p. 182–184°C; R_f=0.60 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ=7.34 (dt, J=7.6, 1.2 Hz, 1H), 7.31 (dd, J=7.6, 1.2 Hz, 1H), 7.20 (t, J=7.6 Hz, 1H), 3.55–3.45 (m, 2H), 2.14–1.50 (m, 12H), 1.60 (d, J=6.8 Hz, 3H), 1.56 (d, J=6.8 Hz, 3H), 1.50–1.00 (m, 10H), 1.22 (d, J=6.8 Hz, 3H), 1.15 ppm (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ=166.5 (d, $J_{P\text{-}C}$=4.0 Hz), 144.8 (d, $J_{P\text{-}C}$=36.7 Hz), 135.8 (d, $J_{P\text{-}C}$=25.4 Hz), 130.8, 130.7, 129.8, 127.7, 51.0, 46.0 (d, $J_{P\text{-}C}$=8.8 Hz), 35.7 (d, $J_{P\text{-}C}$=16.7 Hz), 32.7 (d, $J_{P\text{-}C}$=12.4 Hz), 30.1 (d, $J_{P\text{-}C}$=12.6 Hz), 30.0 (d, $J_{P\text{-}C}$=6.7 Hz), 29.9 (d, $J_{P\text{-}C}$=12.5 Hz), 29.4 (d, $J_{P\text{-}C}$=6.8 Hz), 27.7 (d, $J_{P\text{-}C}$=7.5 Hz), 27.6 (d, $J_{P\text{-}C}$=12.2 Hz), 27.0 (d, $J_{P\text{-}C}$=7.4 Hz), 26.9 (d, $J_{P\text{-}C}$=9.4 Hz), 26.4, 26.2, 21.4 (d, $J_{P\text{-}C}$=5.7 Hz), 20.7, 20.1, 20.0 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ=−7.15 ppm; IR (film): $\tilde{\nu}$=2927, 1634, 1446, 1333 cm^{-1}; HRMS (CI): m/z calcd for $C_{25}H_{40}ClNOP$: 436.2536; found: 436.2540 $[M+H]^+$.

***N,N*-Diisopropyl 3-chloro-2-dicyclohexylphosphinobenzamide (16a)**: Compound **16a** was prepared in 95% yield according to general procedure A. White amorphous solid; m.p. 170–172°C; R_f=0.27 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ=7.35–7.27 (m, 2H), 7.05 (d, J=7.2 Hz, 1H), 3.68 (septet, J=6.8 Hz, 1H), 3.53 (septet, J=6.8 Hz, 1H), 2.70–2.56 (m, 1H), 2.52–2.39 (m, 1H), 1.96–1.60 (m, 8H), 1.63 (d, J=6.8 Hz, 3H), 1.57 (d, J=6.8 Hz, 3H), 1.50–1.10 (m, 11H), 1.32 (d, J=6.4 Hz, 3H), 1.11 (d, J=6.4 Hz, 3H), 0.95–0.80 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ=169.5 (d, $J_{P\text{-}C}$=5.5 Hz), 150.9 (d, $J_{P\text{-}C}$=40.2 Hz), 141.5 (d, $J_{P\text{-}C}$=3.9 Hz), 131.7 (d, $J_{P\text{-}C}$=34.3 Hz), 130.2 (d, $J_{P\text{-}C}$=1.5 Hz), 129.6, 123.5 ($J_{P\text{-}C}$=9.6 Hz), 50.4, 45.6, 35.8 ($J_{P\text{-}C}$=13.5 Hz), 34.9 ($J_{P\text{-}C}$=14.2 Hz), 33.4 ($J_{P\text{-}C}$=30.1 Hz), 32.4 ($J_{P\text{-}C}$=24.0 Hz), 30.6 (d, $J_{P\text{-}C}$=9.6 Hz), 30.1 (d, $J_{P\text{-}C}$=6.1 Hz), 27.4 (d, $J_{P\text{-}C}$=7.2 Hz), 27.2 (d, $J_{P\text{-}C}$=7.4 Hz), 27.1 (d, $J_{P\text{-}C}$=13.8 Hz), 27.0 (d, $J_{P\text{-}C}$=16.1 Hz), 26.4, 26.0 (d, $J_{P\text{-}C}$=1.5 Hz), 21.3 (d, $J_{P\text{-}C}$=2.6 Hz), 20.6 (×2), 19.8 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ=9.43 ppm; IR (film): $\tilde{\nu}$=2925, 1631, 1447, 1337 cm^{-1}; HRMS (CI): m/z: calcd for $C_{25}H_{40}ClNOP$: 436.2536; found: 436.2540 $[M+H]^+$.

***N,N*-Diisopropyl 4-chloro-2-dicyclohexylphosphinobenzamide (17a)**: Compound **17a** was prepared in 91% yield according to general procedure A. White solid; m.p. 142–144°C (EtOAc/hexane); R_f=0.45 (9.1% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 23°C): δ=7.41 (s, 1H), 7.28 (dd, J=8.1, 2.1 Hz, 1H), 7.07 (dd, J=8.1, 2.7 Hz, 1H), 3.53–3.42 (m, 2H), 2.20–0.90 ppm (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$, 23°C): δ=169.4 (d, $J_{P\text{-}C}$=3.7 Hz), 145.7 (d, $J_{P\text{-}C}$=34.9 Hz), 135.6 (d, $J_{P\text{-}C}$=27.1 Hz), 133.2 (d, $J_{P\text{-}C}$=2.3 Hz), 132.4 (d, $J_{P\text{-}C}$=3.3 Hz), 129.1 (d, $J_{P\text{-}C}$=0.8 Hz), 126.8 (d, $J_{P\text{-}C}$=8.1 Hz), 51.0, 46.0, 35.8 (d, $J_{P\text{-}C}$=15.6 Hz), 33.1 (d, $J_{P\text{-}C}$=12.2 Hz), 30.7 (d, $J_{P\text{-}C}$=11.9 Hz), 30.5 (d, $J_{P\text{-}C}$=3.0 Hz), 30.2 (d, $J_{P\text{-}C}$=0.9 Hz), 29.3 (d, $J_{P\text{-}C}$=5.6 Hz), 28.1 (d, $J_{P\text{-}C}$=3.5 Hz), 28.0 (d, $J_{P\text{-}C}$=1.6 Hz), 27.4 (d, $J_{P\text{-}C}$=4.8 Hz), 27.2 (d, $J_{P\text{-}C}$=6.1 Hz), 26.8 (d, $J_{P\text{-}C}$=1.7 Hz), 26.6 (d, $J_{P\text{-}C}$=1.0 Hz), 21.3 (d, $J_{P\text{-}C}$=4.1 Hz), 21.0, 21.0, 20.5 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ=−6.65 ppm; IR (film): $\tilde{\nu}$=2926, 1634, 1437, 1336 cm^{-1}; MS (CI): m/z (%): 436 (100) $[M+H]^+$, 438 (37) $[M+2+H]^+$; elemental analysis calcd (%) for $C_{25}H_{39}ClNOP$ (436.0): C 68.87, H 9.02, N 3.21; found: C 68.82, H 9.02, N 3.22.

***N,N*-Diisopropyl 5-chloro-2-dicyclohexylphosphinobenzamide (15a)**: The known *N,N*-diisopropyl 3-chloro-2-trimethylsilylbenzamide[30c] (624.0 mg, 2.0 mmol) was added to a flame-dried flask with a stirring bar in dry THF (15 mL) under a nitrogen atmosphere. TMEDA (0.36 mL, 2.4 mmol, 1.2 equiv) and *n*BuLi (1.5 mL, 1.6 M solution in hexanes, 2.4 mmol) were added sequentially and dropwise by syringe over 5 min to the resultant solution cooled in a dry-ice/acetone bath (−78°C). The resultant mixture was stirred at −78°C for 2 h. Chlorodicyclohexylphosphane (0.49 mL, 2.2 mmol) was then added by syringe. The resultant mixture was stirred at −78°C for 2 h and then allowed to slowly warm to room temperature. The reaction mixture was filtered through a pad of silica gel topped with a layer of Celite while eluting with EtOAc. The filtrate was concentrated under reduced pressure and the yellow residue was recrystallized from CH_2Cl_2 and hexane to provide the silylated Aphos (946.0 mg, 93%). White crystalline solid; m.p. 204–206°C (CH_2Cl_2/hexane); R_f=0.30 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, 23°C): δ=7.35 (dd, J=8.0, 1.0 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H), 3.70–3.55 (m, 2H), 2.15–1.00 (m, 34H), 0.44 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 23°C): δ=169.8 (d, $J_{P\text{-}C}$=3.4 Hz), 153.0 (d, $J_{P\text{-}C}$=32.6 Hz), 142.8, 135.0 (d, $J_{P\text{-}C}$=4.8 Hz), 134.5, 132.6 (d, $J_{P\text{-}C}$=25.0 Hz), 128.6, 50.8, 46.8, 36.9 (d, $J_{P\text{-}C}$=17.7 Hz), 33.4 (d, $J_{P\text{-}C}$=14.7 Hz), 30.9 (d, $J_{P\text{-}C}$=7.2 Hz), 30.7 (d, $J_{P\text{-}C}$=14.7 Hz), 30.5 (d, $J_{P\text{-}C}$=11.9 Hz), 29.1 (d, $J_{P\text{-}C}$=8.4 Hz), 28.2 (d, $J_{P\text{-}C}$=9.8 Hz), 27.9 (d, $J_{P\text{-}C}$=9.9 Hz), 27.4 (d, $J_{P\text{-}C}$=8.9 Hz), 27.3 (d, $J_{P\text{-}C}$=11.7 Hz), 26.8, 26.6, 22.1, 21.4 (d, $J_{P\text{-}C}$=7.5 Hz), 21.2, 20.7 (d, $J_{P\text{-}C}$=7.8 Hz), 2.4 ppm (×3); ^{31}P NMR (202 MHz, $CDCl_3$, 23°C): δ=−10.53 ppm; IR (film): $\tilde{\nu}$=2928, 1623, 1445, 1308 cm^{-1}; MS (ESI): m/z (%): 530 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{28}H_{47}ClNOPSi$ (508.2): C 66.18, H 9.32, N 2.76; found: C 66.07, H 9.46, N 2.66.

TBAF (5 mL, 1.0 M in THF, 5.0 mmol) was added to a solution of the above silylated Aphos (508.0 mg, 1.0 mmol) in THF (5 mL) at room temperature followed by stirring at room temperature for 40 min. The reaction mixture was diluted with EtOAc and filtered through a pad of silica gel topped with a layer of Celite with elution by EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexane) to provide **15a** (414.0 mg, 95%). White crystalline solid, m.p. 172–174°C (EtOAc/hexane); R_f=0.20 (petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, 23°C): δ=7.39 (d, J=8.0 Hz, 1H), 7.24 (dd, J=8.0, 2.0 Hz, 1H), 7.09 (d, J=2.0 Hz, 1H), 3.54–3.42 (m, 2H), 2.10–0.99 ppm (m, 34H); ^{13}C NMR (125 MHz, $CDCl_3$, 23°C): δ=169.0 (d, $J_{P\text{-}C}$=3.4 Hz), 148.9 (d, $J_{P\text{-}C}$=37.1 Hz), 135.1, 134.4 (d, $J_{P\text{-}C}$=3.3 Hz), 131.5 (d, $J_{P\text{-}C}$=24.0 Hz), 127.5, 125.6 (d, $J_{P\text{-}C}$=8.7 Hz), 50.9, 45.9, 35.7 (d, $J_{P\text{-}C}$=16.9 Hz), 33.0 (d, $J_{P\text{-}C}$=13.2 Hz), 30.7 (d, $J_{P\text{-}C}$=15.5 Hz), 30.4 (d, $J_{P\text{-}C}$=18.9 Hz), 30.2 (d, $J_{P\text{-}C}$=13.7 Hz), 29.2 (d, $J_{P\text{-}C}$=4.8 Hz), 27.9 (d, $J_{P\text{-}C}$=6.8 Hz), 27.8, 27.2 (d, $J_{P\text{-}C}$=8.2 Hz), 27.2 (d, $J_{P\text{-}C}$=10.8 Hz), 26.7, 26.5, 21.2 (d, $J_{P\text{-}C}$=4.0 Hz), 20.9, 20.7, 20.3 ppm; ^{31}P NMR (202 MHz, $CDCl_3$, 23°C): δ=−8.83 ppm; IR (film): $\tilde{\nu}$=2926, 1630, 1443, 1332 cm^{-1}; MS (ESI): m/z (%): 458 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{25}H_{39}ClNOP$ (436.0): C 68.87, H 9.02, N 3.21; found: C 68.56, H 8.94, N 3.25.

General procedure B—synthesis of C4-substituted Cy-Aphos from C4-Cl-Cy-Aphos 17a: A 10 mL pressurized process vial containing a magnetic stirring bar was charged with $Pd(OAc)_2$ (5.6 mg, 2.5×10^{-2} mmol), **17a** (218.0 mg, 0.5 mmol), the boronic acid (7.5×10^{-1} mmol), and powdered K_3PO_4 (318.0 mg, 1.5 mmol). The loaded vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with nitrogen (this sequence was repeated three times). Degassed THF (2.0 mL) was added through the septum by syringe. The resultant mixture was stirred at 80°C until **17a** was completely consumed as determined by TLC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with EtOAc (5 mL), filtered through a thin pad of Celite and silica gel while eluting with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography over silica gel to provide the 4-substituted Cy-Aphos given in Schemes 2 and 5.

***N,N*-Diisopropyl 2-dicyclohexylphosphino-4-[(*E*)-2′-phenylvinyl)]benzamide (18a)**: Compound **18a** was prepared in 83% yield from **17a** and *trans*-2-phenylvinylboronic acid after 4 h at 80°C according to general procedure B. White amorphous solid; m.p. 127–130°C; R_f=0.23 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ= 7.57–7.50 (m, 4H), 7.37 (t, J=7.6 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.17–7.10 (m, 3H), 3.61 (septet, J=6.8 Hz, 1H), 3.48 (septet, J=6.8 Hz, 1H), 2.25–1.00 ppm (m, 34H); ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ= 170.1, 146.6 (d, $J_{P\text{-}C}$=35.8 Hz), 137.1, 135.9, 133.1 (d, $J_{P\text{-}C}$=22.5 Hz), 131.3, 129.1, 128.7 (×2), 128.4, 127.8, 126.6 (×2), 126.1, 125.7 (d, $J_{P\text{-}C}$=7.6 Hz), 50.6, 45.6, 35.5 (d, $J_{P\text{-}C}$=16.3 Hz), 32.8 (d, $J_{P\text{-}C}$=10.8 Hz), 30.5 (d, $J_{P\text{-}C}$=13.6 Hz), 30.2 (d, $J_{P\text{-}C}$=18.5 Hz), 30.1 (d, $J_{P\text{-}C}$=8.3 Hz), 29.1 (d, $J_{P\text{-}C}$=4.2 Hz), 27.7, 27.6, 27.1 (d, $J_{P\text{-}C}$=10.2 Hz), 27.0 (d, $J_{P\text{-}C}$=11.8 Hz), 26.5, 26.3, 21.0, 20.7, 20.6, 20.2 ppm; ^{31}P NMR (161 MHz, $CDCl_3$, 23°C): δ= −9.17 ppm; IR (film): $\tilde{\nu}$=2927, 1625, 1447, 1340 cm^{-1}; HRMS (CI): m/z: calcd for $C_{33}H_{47}NOP$: 504.3395; found: 504.3386 $[M+H]^+$.

***N,N*-Diisopropyl 4-*n*-butyl-2-dicyclohexylphosphinobenzamide (18b)**: Compound **18b** was isolated in 87% yield from **17a** and *n*-butylboronic acid after 8 h at 80°C according to general procedure B. White amorphous solid; m.p. 110–113°C; R_f=0.28 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ= 7.26 (s, 1H), 7.10 (d, J=8.0 Hz, 1H), 7.03 (dd, J=8.0, 3.2 Hz, 1H), 3.58 (septet, J=6.8 Hz, 1H), 3.46 (septet, J=6.8 Hz, 1H), 2.62 (t, J=7.2 Hz, 2H), 2.15–1.51 (m, 14H), 1.58 (d, J=6.8 Hz, 3H), 1.53 (d, J=6.8 Hz, 3H), 1.49–0.90 (m, 12H), 1.19 (d, J=7.2 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H), 0.92 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ=170.6 (d, $J_{P\text{-}C}$=3.0 Hz), 144.8 (d, $J_{P\text{-}C}$=35.5 Hz), 141.2, 132.6, 132.1 (d, $J_{P\text{-}C}$=21.4 Hz), 128.8, 125.1 (d, $J_{P\text{-}C}$=7.9 Hz), 50.6, 45.5, 35.5 (d, $J_{P\text{-}C}$=19.0 Hz), 35.4, 33.5, 32.9 (d, $J_{P\text{-}C}$= 12.0 Hz), 30.5 (d, $J_{P\text{-}C}$=15.4 Hz), 30.2 (d, $J_{P\text{-}C}$=18.8 Hz), 30.1 (d, $J_{P\text{-}C}$= 15.0 Hz), 29.0 (d, $J_{P\text{-}C}$=3.8 Hz), 27.7, 27.7, 27.1 (d, $J_{P\text{-}C}$=4.7 Hz), 27.0 (d, $J_{P\text{-}C}$=5.8 Hz), 26.6, 26.3, 22.1, 21.0 (d, $J_{P\text{-}C}$=3.6 Hz), 20.7, 20.6, 20.2, 13.9 ppm; ^{31}P NMR (161 MHz, $CDCl_3$, 23°C): δ= −9.90 ppm; IR (film): $\tilde{\nu}$=2926, 1632, 1439, 1338 cm^{-1}; HRMS (CI): *m/z*: calcd for $C_{29}H_{49}NOP$: 458.3552; found: 458.3549 $[M+H]^+$.

***N,N*-Diisopropyl 2-dicyclohexylphosphino-4-phenylbenzamide (18c).** Compound **18c** was prepared in 78% yield from **17a** and phenylboronic acid after 8 h at 80°C according to general procedure B by using 10 mol% $Pd(OAc)_2$. A higher yield of **18c** was obtained by using the following modified conditions. A 10 mL pressurized process vial containing a magnetic stirring bar was charged with phenylboronic acid (45.7 mg, 3.8×10^{-1} mmol), **17a** (109.0 mg, 2.5×10^{-1} mmol), $[Pd_2(dba)_3]$ (4.6 mg, 5.0×10^{-3} mmol) and $KF\cdot2H_2O$ (70.6 mg, 7.5×10^{-1} mmol). The loaded vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with nitrogen (this sequence was repeated for three times). Degassed dry toluene (2 mL) was added through the septum by a syringe, and the resultant mixture was stirred at room temperature for 2 min followed by stirring at 110°C for 7 h. Then, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (5 mL), and filtered through a thin pad of Celite and silica gel while eluting with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10% EtOAc/hexane) to afford **18c** (103.6 mg, 87%). White crystalline solid; m.p. 157–159°C (EtOAc/hexane); R_f=0.44 (9.1% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 23°C): δ=7.69 (s, 1H), 7.59–7.35 (m, 6H), 7.21 (dd, J=7.8, 3.0 Hz, 1H), 3.71–3.47 (m, 2H), 2.30–1.00 ppm (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$, 23°C): δ= 169.7 (d, $J_{P\text{-}C}$=4.0 Hz), 145.7 (d, $J_{P\text{-}C}$=35.0 Hz), 140.3, 139.2, 132.6 (d, $J_{P\text{-}C}$= 26.7 Hz), 130.7 (d, $J_{P\text{-}C}$=4.4 Hz), 128.4 (×2), 127.1, 127.0, 126.7 (×2), 125.2 (d, $J_{P\text{-}C}$=8.3 Hz), 50.3, 45.2, 35.2 (d, $J_{P\text{-}C}$=15.5 Hz), 32.5 (d, $J_{P\text{-}C}$= 11.7 Hz), 30.2 ($J_{P\text{-}C}$=14.3 Hz), 30.0 (d, $J_{P\text{-}C}$=8.6 Hz), 29.7 (d, $J_{P\text{-}C}$= 2.5 Hz), 28.8 (d, $J_{P\text{-}C}$=5.6 Hz), 27.4 (d, $J_{P\text{-}C}$=2.9 Hz), 27.3 (d, $J_{P\text{-}C}$= 3.2 Hz), 26.8 (d, $J_{P\text{-}C}$=9.9 Hz), 26.7 (d, $J_{P\text{-}C}$=10.9 Hz), 26.2, 26.0, 20.7 (d, $J_{P\text{-}C}$=4.1 Hz), 20.4, 20.3, 19.9 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ= −7.45 ppm; IR (KBr): $\tilde{\nu}$=2925, 1631 cm^{-1}; MS (CI): *m/z* (%): 478 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{31}H_{44}NOP$ (477.7): C 77.95, H 9.28, N 2.93; found: C 78.00, H 9.31, N 2.76.

***N,N*-Diisopropyl 2-dicyclohexylphosphino-4-(2′,6′-dimethylphenyl)benzamide (19h)**: Compound **19h** was prepared in 86% yield from **17a** and 2,6-dimethylbenzeneboronic acid in THF/H_2O (10:1) after 24 h at 100°C according to general procedure B by using 10 mol% $Pd(OAc)_2$. White crystalline solid; m.p. 181–182°C (EtOAc/hexane); R_f=0.31 (10% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 23°C): δ=7.31 (t, J= 1.8 Hz, 1H), 7.23–7.09 (m, 5H), 3.69 (septet, J=6.8 Hz, 1H), 3.51 (septet, J=6.8 Hz, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 1.95–1.00 ppm (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$, 23°C): δ=170.5 (d, $J_{P\text{-}C}$=3.5 Hz), 146.0 (d, $J_{P\text{-}C}$=35.0 Hz), 141.6, 139.8, 136.4 (d, $J_{P\text{-}C}$=46.2 Hz), 133.5 (d, $J_{P\text{-}C}$=3.6 Hz), 129.5 (d, $J_{P\text{-}C}$=1.3 Hz, ×2), 127.6, 127.4 (×3), 125.6 (d, $J_{P\text{-}C}$=8.8 Hz), 51.0, 45.9, 35.9 (d, $J_{P\text{-}C}$=15.5 Hz), 33.5 (d, $J_{P\text{-}C}$=11.9 Hz), 31.2 (d, $J_{P\text{-}C}$=15.2 Hz), 30.6 (d, $J_{P\text{-}C}$=12.8 Hz), 30.4 (d, $J_{P\text{-}C}$=7.7 Hz), 29.4 (d, $J_{P\text{-}C}$=3.5 Hz), 28.1 (d, $J_{P\text{-}C}$=10.9 Hz), 28.0 (d, $J_{P\text{-}C}$=4.2 Hz), 27.4 (d, $J_{P\text{-}C}$=3.2 Hz), 27.3 (d, $J_{P\text{-}C}$=2.6 Hz), 26.9, 26.8, 21.6 (d, $J_{P\text{-}C}$=4.2 Hz), 21.3, 21.2, 21.1, 21.0, 20.7 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ= −8.27 ppm; IR (KBr): $\tilde{\nu}$=2925, 1631, 1440, 1336 cm^{-1}; MS (TOF): *m/z* (%): 506 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{33}H_{48}NOP$ (505.7): C 78.37, H 9.57, N 2.77; found: C 78.30, H 9.58, N 3.24.

***N,N*-Diisopropyl 2-dicyclohexylphosphino-4-(3′-nitrophenyl)benzamide (19q)**: Compound **19q** was prepared in 82% from **17a** and 3-nitrophenylboronic acid after 15 h at 80°C according to general procedure B by using 10 mol% $Pd(OAc)_2$. Amorphous white solid; m.p. 91–93°C; R_f= 0.18 (9.1% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 23°C): δ= 8.40 (s, 1H), 8.23 (dt, J=7.2, 0.9 Hz, 1H), 7.88 (d, J=7.5 Hz, 1H), 7.68 (s, 1H), 7.65 (dd, J=7.8, 7.8 Hz, 1H), 7.56 (d, J=7.8 Hz, 1H), 7.27 (dd, J=8.1, 3.0 Hz, 1H), 3.63–3.49 (m, 2H), 1.94–0.84 ppm (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$, 23°C): δ=169.9 (d, $J_{P\text{-}C}$=3.9 Hz), 148.9, 147.5 (d, $J_{P\text{-}C}$=35.0 Hz), 142.7, 137.5, 134.1 (d, $J_{P\text{-}C}$=25.1 Hz), 133.3, 131.4 (d, $J_{P\text{-}C}$=3.8 Hz), 130.0, 127.8, 126.3 (d, $J_{P\text{-}C}$=8.0 Hz), 122.4, 122.3, 51.1, 46.0, 35.9 (d, $J_{P\text{-}C}$=15.2 Hz), 33.1 (d, $J_{P\text{-}C}$=12.2 Hz), 30.8 (d, $J_{P\text{-}C}$= 14.0 Hz), 30.6, 30.4 (d, $J_{P\text{-}C}$=3.6 Hz), 29.6 (d, $J_{P\text{-}C}$=5.3 Hz), 28.1 (d, $J_{P\text{-}C}$= 3.1 Hz), 28.0 (d, $J_{P\text{-}C}$=3.8 Hz), 27.4 (d, $J_{P\text{-}C}$=10.0 Hz), 27.2 (d, $J_{P\text{-}C}$= 7.3 Hz), 26.9 (d, $J_{P\text{-}C}$=2.4 Hz), 26.6, 21.4 (d, $J_{P\text{-}C}$=4.4 Hz), 21.1, 21.0, 20.5 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ=−7.35 ppm; IR (film): $\tilde{\nu}$=2926, 1630, 1531, 1441, 1342 cm^{-1}; MS (CI): *m/z* (%): 523 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{31}H_{43}N_2O_3P$ (522.7): C 71.24, H 8.29, N 5.36; found: C 71.08, H 8.28, N 5.28.

***N,N*-Diisopropyl 2-dicyclohexylphosphinobenzamide (21)**: *N,N*-Diisopropylbenzamide (454.0 mg, 2.2 mmol) and THF (4 mL) were added to a flame dried flask with a stirring bar under a nitrogen atmosphere. *n*BuLi (1.6 M in hexanes, 1.66 mL, 2.65 mmol) was added dropwise to the resultant solution which had been cooled in a dry ice-acetone bath (−78°C). After stirring the solution at −78°C for 20 min, chlorodicyclohexylphosphane (0.59 mL, 2.65 mmol) was added to the mixture, followed by stirring at −78°C for 2 h and at room temperature for 1 h. The reaction mixture was filtered through a pad of silica gel topped with a layer of Celite, and eluted with EtOAc. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (silica gel, 10% EtOAc/hexane) to afford **21** (635.2 mg, 72%). White solid; m.p. 168–169°C (CH_2Cl_2/hexane); R_f=0.49 (9.1% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 23°C): δ=7.48 (br s, 1H), 7.29 (t, J=3.4 Hz, 2H), 7.13 (br s, 1H), 3.59–3.43 (m, 2H), 2.20–0.90 ppm (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$, 23°C): δ=170.4 (d, $J_{P\text{-}C}$=3.9 Hz), 147.5 (d, $J_{P\text{-}C}$=34.5 Hz), 132.9 (d, $J_{P\text{-}C}$=3,3 Hz), 132.5 (d, $J_{P\text{-}C}$=2.0 Hz), 128.8, 127.2 (d, $J_{P\text{-}C}$=3.9 Hz), 125.5 (d, $J_{P\text{-}C}$=7.9 Hz), 50.9, 45.9, 35.8 (d, $J_{P\text{-}C}$=15.1 Hz), 33.1 (d, $J_{P\text{-}C}$=11.7 Hz), 30.8 (d, $J_{P\text{-}C}$= 14.2 Hz), 30.6 (d, $J_{P\text{-}C}$=14.5 Hz), 30.4 (d, $J_{P\text{-}C}$=9.5 Hz), 29.4 (d, $J_{P\text{-}C}$= 5.3 Hz), 28.1 (d, $J_{P\text{-}C}$=4.4 Hz), 28.0, 27.5 (d, $J_{P\text{-}C}$=4.2 Hz), 27.3 (d, $J_{P\text{-}C}$= 5.5 Hz), 26.9, 26.7, 21.4 (d, $J_{P\text{-}C}$=4.1 Hz), 21.0 (×2), 20.6 ppm; ^{31}P NMR (121 MHz, $CDCl_3$, 23°C): δ=−7.97 ppm; IR (KBr): $\tilde{\nu}$=2919, 1627 cm^{-1}; MS (CI): *m/z* (%): 402 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{40}NOP$ (401.6): C 74.77, H 10.40, N 3.49; found: C 74.64, H 10.20, N 3.40.

***N,N*-Diisopropyl 2-dicyclohexylphosphino-5-(3′-nitrophenyl)benzamide (24)**: Compound **24** was prepared in 70% yield from **15a** and 3-nitrophenylboronic acid after 8 h at 100°C according to general procedure B by using 10 mol% $Pd(OAc)_2$. White crystalline solid; m.p. 210–212°C (CH_2Cl_2/hexane); R_f=0.35 (9.1% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$, 23°C): δ=8.46 (t, J=2.0 Hz, 1H), 8.21 (dt, J=8.5, 1.0 Hz, 1H), 7.93 (t, J=1.5 Hz, 1H), 7.62 (t, J=8.0 Hz, 2H), 7.56 (dd, J= 8.0, 2.0 Hz, 1H), 7.36 (t, J=2.5 Hz, 1H), 3.62 (septet, J=7.0 Hz, 1H), 3.52 (septet, J=7.0 Hz, 1H), 2.25–1.00 ppm (m, 34); ^{13}C NMR (125 MHz, $CDCl_3$, 23°C): δ=170.0 (d, $J_{P\text{-}C}$=3.6 Hz), 149.0, 148.4 (d, $J_{P\text{-}C}$=35.3 Hz), 142.2, 139.3, 133.9 (br, ×2), 133.2 (d, $J_{P\text{-}C}$=4.2 Hz), 130.1, 126.0, 124.0 (d, $J_{P\text{-}C}$=8.8 Hz), 122.6, 122.2, 51.0, 45.9, 35.8 (d, $J_{P\text{-}C}$=14.8 Hz), 32.9 (d, $J_{P\text{-}C}$=11.4 Hz), 30.7 (d, $J_{P\text{-}C}$=13.1 Hz), 30.4 (d, $J_{P\text{-}C}$=18.5 Hz), 30.2 (d, $J_{P\text{-}C}$=21.6 Hz), 29.3, 27.9, 27.9, 27.2 (d, $J_{P\text{-}C}$=8.4 Hz), 27.2 (d, $J_{P\text{-}C}$= 10.7 Hz), 26.7, 26.5, 21.2, 21.1, 20.9, 20.3 ppm; ^{31}P NMR (202 MHz, $CDCl_3$, 23°C): δ=−8.26 ppm; IR (film): $\tilde{\nu}$=2927, 1626, 1532, 1447, 1348 cm^{-1}; MS (ESI): *m/z* (%): 545 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{31}H_{43}N_2O_3P$ (522.7): C 71.24, H 8.29, N 5.36; found: C 71.24, H 8.13, N 5.30.

Microwave-assisted synthesis and ^{31}P NMR characterization of Cy-Aphos 18c, 19a-q, and 20: A 10 mL pressurized process vial containing a magnetic stirring bar was charged with arylboronic acid (3.0×10^{-2} mmol), $[Pd_2(dba)_3]$ (4.6 mg, 5.0×10^{-3} mmol), **17a** (8.8 mg, 2.0×10^{-2} mmol), and

K_3PO_4 (424.6 mg, 2.0 mmol). The vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with nitrogen (this sequence was repeated six times). Degassed dry toluene (2 mL) was added through the septum by syringe and the resultant mixture was stirred at room temperature for 1 min. The loaded vial was then placed into the cavity of the technical microwave reactor and heated. The temperature was ramped from room temperature to 180 °C and then held at this temperature for 4 min. The time taken for the reaction mixture to reach the target temperature of 180 °C varied depending on the boronic acid used, but was within a period of 3–4 min. After cooling to room temperature, the reaction mixture was directly filtered through a plug of Celite and silica gel. The filtrate was condensed under reduced pressure and the residue was dissolved in $CDCl_3$ for ^{31}P NMR analysis. The results are summarized in Table 1 and the copies of ^{31}P NMR spectra are found in Supporting Information.

Microwave-assisted screening of Aphos 18c, 19a–q, 20, and 21 and HPLC analysis: Following the procedure for microwave-assisted synthesis of Aphos described above, the cap of the reaction vial was opened under a stream of nitrogen and the reference compound, *N,N*-diisopropyl 4-cyclohexylbenzamide (40.0 mg), **22** (172.6 mg, 1.0 mmol), and phenylboronic acid (182.9 mg, 1.5 mmol) were added quickly. The vial was sealed again with a new cap and evacuated through a needle under vacuum and backfilled with nitrogen twice. Degassed dry toluene (2 mL) was added through the septum by means of a syringe and the resultant mixture was stirred at room temperature for 1 min. The loaded vial was then placed into the cavity of the microwave reactor and heated. The temperature was ramped from room temperature to 180 °C and then held at this temperature for 5 min. The time taken for the reaction mixture to reach the target temperature of 180 °C was within the period of 1–2 min. After cooling to room temperature, the reaction mixture was diluted with EtOAc (5 mL), filtered through a plug of Celite and silica gel (eluting with EtOAc) and concentrated under reduced pressure. The residue was dissolved in acetonitrile (HPLC grade) and the solution was filtered directly through a PTFE (MFS-13) filter into a HPLC vial for quantitative analysis of the conversion of **22** by using the working curve given in Figure S1 of the Supporting Information. HPLC analysis was performed on a Waters HPLC system equipped with a Waters 600 Controller, Waters 717_{plus} Autosampler and Waters 2996 Photodiode Array Detector. Data acquisition and processing were controlled using Millennium[32] software. An Ultra C18 column (150×4.6 mm) with 5 μm diameter packing particles (cat. No.9174565) was used. Analysis was performed at 25 °C at a flow rate of 0.6 mL min^{-1}. Chromatograms were obtained using UV absorption at 240 nm. The mobile phase was acetonitrile/water (70:30). The sample injection volume was 1–6 μL. The data are found in Table S1 of the Supporting Information. A plot of the data on relative Aphos efficiency is given in Figure 2.

General procedure C—room-temperature Suzuki–Miyaura coupling of unactivated and hindered aryl chlorides using Aphos ligands 19q or 24: A 10 mL pressurized process vial containing a magnetic stirring bar was charged with $Pd(OAc)_2$ (2.2 mg, 1.0×10^{-2} mmol, 2.0 mol%), Aphos ligands **19q** or **24** (7.8 mg, 1.5×10^{-2} mmol, 3.0 mol%), the arylboronic acid (7.5×10^{-1} mmol, 1.5 equiv), and K_3PO_4 (318.0 mg, 1.5 mmol, 3.0 equiv). The vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with nitrogen (this sequence was repeated three times). Degassed THF (1 mL) was added by syringe and the mixture was stirred at room temperature for about 1 min. The aryl chloride (0.5 mmol, 1 equiv) was added by a syringe (solid aryl chlorides were added prior to the evacuation-backfill cycles). Degassed water (100 μL) was added by syringe and the resultant mixture was kept at room temperature with vigorous stirring for 6–36 h. The reaction mixture was diluted with EtOAc (5 mL), filtered through a thin pad of silica gel and concentrated under reduced pressure. The crude material was purified by flash column chromatography over silica gel to give the products. The reaction times and yields are found in Tables 5 and 6. The ^1H NMR data and copies of spectra of the products are found in the Supporting Information.

Room-temperature Suzuki–Miyaura coupling of activated aryl chloride using Aphos 19q: General procedure C was used but with reduced amounts of $Pd(OAc)_2$ and **19q**. The reaction conditions and product yields are found in Table 4. The ^1H NMR data and copies of spectra of the products are found in Supporting Information.

Comparison of Cy-Aphos Ligands 18a–c, 19q, and 24: General procedure C was used for the reaction of 1-chloronaphthalene (**25**) with phenylboronic acid but by using 1 mol% $Pd(OAc)_2$ and 1.5 mol% Aphos. The reaction was stopped after 8 h at room temperature and the remaining substrate **25** and the product **26** were isolated by flash column chromatography over silica gel. The results are listed in Table 2.

General procedure D—synthesis of compounds 31a–e: A 10 mL pressurized process vial containing a magnetic stirring bar was charged with $Pd(OAc)_2$ (1.1 mg, 5.0×10^{-3} mmol, 1.0 mol%), Aphos **19h** (3.8 mg, 7.5×10^{-3} mmol, 1.5 mol%), the boronic acid (7.5×10^{-1} mmol, 1.5 equiv) and K_3PO_4 (318.0 mg, 1.5 mmol, 3.0 equiv). The vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with nitrogen (this sequence was repeated three times). THF (1.5 mL) was added by syringe and the mixture was stirred at room temperature for about 1 min. The aryl halide (0.5 mmol, 1 equiv) was added by syringe (solid aryl halides were added prior to the evacuation-backfill cycles). The resultant mixture was kept at room temperature with vigorous stirring for 8–48 h. The reaction mixture was diluted with EtOAc (5 mL), filtered through a thin pad of silica gel and concentrated under reduced pressure. The crude material was purified by flash column chromatography over silica gel to give the products **31a–e** as shown in Scheme 6.

1-Mesityl-1-phenylethene (31a):[44] Prepared from compounds **29a** and **30a** in 80% yield after 48 h at room temperature according to general procedure D. Colorless oil; $R_f=0.78$ (5% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$, 23 °C): $\delta=7.34$–7.30 (m, 5H), 6.98 (s, 2H), 6.01 (d, $J=1.2$ Hz, 1H), 5.16 (d, $J=1.2$ Hz, 1H), 2.38 (s, 3H), 2.18 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): $\delta=147.1$, 139.8, 138.4, 136.6, 136.3, 128.6 (×2), 128.3 (×2), 127.8 (×2), 126.1 (×2), 114.8, 21.5, 20.6 ppm (×2); IR (film): $\tilde{\nu}=2918$, 1444 cm^{-1}; MS (CI): *m/z* (%): 222 (63) $[M]^+$, 207 (100) $[M-Me]^+$.

(*E*)-2,6-Diethylphenyl-2-phenylethene (31b): Prepared from compounds **29b** and **30b** in 92% yield after 20 h at room temperature according to general procedure D. Colorless oil; $R_f=0.55$ (hexane); ^1H NMR (300 MHz, $CDCl_3$, 23 °C): $\delta=7.57$ (d, $J=6.9$ Hz, 2H), 7.44 (t, $J=7.5$ Hz, 2H), 7.37–7.16 (m, 5H), 6.65 (dd, $J=16.5$, 3.3 Hz, 1H), 2.83–2.76 (m, 4H), 1.32–1.26 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): $\delta=$ 142.7, 137.8, 136.5, 134.1, 128.9 (×2), 127.8 (×2), 127.4, 126.8, 126.6 (×2), 126.2 (×2), 27.4 (×2), 15.8 ppm (×2); IR (film): $\tilde{\nu}=2963$, 1454 cm^{-1}; MS (CI): *m/z* (%): 237 (100) $[M+H]^+$; HRMS (APCI): *m/z*: calcd for $C_{18}H_{20}$: 236.1565; found: 236.1560 $[M]^+$.

2-[(*E*)-3-Phenylpropen-1-yl]benzaldehyde (31c): Prepared from compounds **29c** and **30c** in 94% yield after 8 h at room temperature according to general procedure D. Colorless oil; $R_f=0.31$ (5% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$, 23 °C): $\delta=10.30$ (s, 1H), 7.83 (d, $J=7.5$ Hz, 1H), 7.54–7.52 (m, 2H), 7.42–7.26 (m, 7H), 6.34 (dt, $J=8.7$, 6.9 Hz, 1H), 3.65 ppm (d, $J=6.9$ Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): $\delta=192.5$, 140.6, 139.8, 135.4, 133.9, 132.9, 131.4, 128.9 (×2), 128.8 (×2), 127.8, 127.5, 127.4, 126.6, 40.1 ppm; IR (film): $\tilde{\nu}=1692$ cm^{-1}; MS (CI): *m/z* (%): 223 (35) $[M+H]^+$, 131 (100) $[M\text{-}PhCH_2]^+$; HRMS (APCI): *m/z*: calcd for $C_{16}H_{15}O$: 223.1117; found: 223.1115 $[M+H]^+$.

1,3-Dimethyl-2-*n*-octylbenzene (31d). Prepared from compounds **29d** and **30d** in 98% yield according to general procedure D after 12 h at 50 °C instead of room temperature. Colorless oil; $R_f=0.75$ (petroleum ether); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): $\delta=6.98$ (s, 3H), 2.60 (t, $J=$ 6.8 Hz, 2H), 2.31 (s, 6H), 1.50–1.25 (m, 12H), 0.89 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): $\delta=139.8$, 135.9, 128.0 (×2), 125.4 (×2), 31.9, 30.3, 29.8, 29.4, 29.3, 29.1, 22.7, 19.8 (×2), 14.1 ppm; IR (film): $\tilde{\nu}=2924$, 1467 cm^{-1}; MS (CI): *m/z* (%): 218 (100) $[M]^+$.

4-Methoxyl-1-*n*-octylbenzene (31e):[45] Prepared from compounds **29e** and **30d** in 95% yield after 12 h at room temperature according to general procedure D. Colorless oil; $R_f=0.68$ (5% EtOAc in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$, 23 °C): $\delta=7.14$–7.11 (m, 2H), 6.88–6.84 (m, 2H), 3.89 (s, 3H), 2.58 (t, $J=7.6$ Hz, 2H), 1.68–1.55 (m, 2H), 1.40–1.25 (m, 10H), 0.92 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,

23 °C): $\delta = 157.4$, 134.9, 129.1 (×2), 113.5 (×2), 55.1, 34.9, 31.8, 31.6, 29.4, 29.1 (×2), 22.5, 14.0 ppm; IR (film): $\tilde{\nu} = 2925$, 1512, 1246 cm^{-1}; MS (CI): *m/z* (%): 220 (100) $[M]^+$.

^{31}P and ^{13}C NMR studies on Pd-Aphos complexes in solution: Aphos **21** (4.0 mg, 1.0×10^{-2} mmol) and $[Pd_2(dba)_3]$ (9.2 mg, 2.0×10^{-2} mmol) were added to an NMR tube followed by addition of $[D_8]$THF (0.75 mL). The solution was kept at room temperature for 40 min before taking a ^{31}P NMR spectrum. An additional portion of **21** (4.0 mg, 1.0×10^{-2} mmol) was added to the solution in the NMR tube and, after 40 min, a new ^{31}P NMR spectrum was recorded. The procedure was repeated. For the 3:1 mixture of **21**:Pd, a ^{13}C NMR spectrum was also taken. The ^{31}P NMR spectra are shown in Figure 4 and the original ^{31}P and ^{13}C NMR charts are found in the Supporting Information.

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