Organic Process Research & Development **2008,** *12,* 480–489

Streamlined Synthesis of the Bippyphos Family of Ligands and Cross-Coupling Applications

Gregory J. Withbroe, Robert A. Singer,* and Janice E. Sieser

Chemical Research and Development, Pfizer Global Research and Development, Groton Labs, Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

We describe the efficient preparation of Bippyphos, 1. The key precursor to Bippyphos, 5, was prepared via a one-pot bromination of diketone 2 followed by alkylation with pyrazole and condensation with phenylhydrazine. Lithiation of 5 and trapping with di-*tert*-butylchlorophosphine afforded Bippyphos, 1. Using this approach we have prepared several derivatives of Bippyphos to probe the structure and activity relationships of this family of phosphine ligands. We also demonstrate the utility of these ligands in Pd-catalyzed amination reactions and other cross-coupling reactions.

Introduction

Pd-catalyzed cross-couplings have found widespread utility in industry.[1] During our efforts to develop a Pd-catalyzed amination reaction for a late-stage drug candidate intended for the treatment of atherosclerosis, we embarked on development of our own nonproprietary phosphine ligands. We have previously disclosed some of our advancements in this area, though most notable is our work describing the utility of Bippyphos, **1**.[2] Bippyphos has been prepared by the four-step process shown below (Scheme 1). Originally we used this route to prepare over 4 kg of **1** to enable development work at Pfizer with this ligand.[3] While this route to **1** enables isolation of each intermediate, it suffers from the overall length of the synthesis and from stability issues with some of the process intermediates. In particular we recognized that intermediate **4** could readily degrade under alkaline or neutral conditions. Degradation was even observed during storage of intermediate **4**, further leading to concerns around isolation of this intermediate. In addition, we recognized that intermediate **3** was susceptible to debromination by reducing agents.[4] These observations prompted us to rethink our original process route to **1** and to consider an approach that would better enable the preparation of this family of ligands for closer examination.

Results and Discussion

A number of the steps in the synthesis of **1** (shown in Scheme 1) appeared amenable to sequential processing without isolation which we thought would alleviate the issue of unstable isolated process intermediates leading up to the preparation of **5**. Moreover, designing a one-pot process would also increase the efficiency of material throughput and ultimately lower the cost to prepare **1**. Toward this end we evaluated the bromination and subsequent alkylation in *N*-methyl-2-pyrrolidinone (NMP) (Scheme 2). For the bromination, we studied a variety of brominating reagents including bromine, pyridinium tribromide, and *N*-bromosuccinimide. Using a slight excess (1.2 equiv) of any of these reagents successfully pushed the bromination to completion in NMP. The addition of bromine was exothermic at the start of the reaction when preparing **3** and led to side products if the rate of addition and temperature were not controlled carefully. Once the bromination was complete, pyrazole (3.5 equiv) was added to the solution to effect the alkylation. The alkylation proceeded smoothly, although slowly under ambient conditions as originally reported.[5] We have now found that heating to 40–50 °C enables the alkylation to reach completion within 6−12 h.[6] Once the alkylation to afford **4** was complete, acetic acid was added followed by a solution of phenylhydrazine in methanol. Heating the reaction to about 40 °C allowed the condensation to reach completion within 10−16 h. After several hours, the product (**5**) began to precipitate from the reaction mixture as a yellow suspension. Once the condensation was complete, the reaction mixture was diluted with water and stirred under ambient conditions. The crude product was filtered and isolated as an NMP solvate. Washing the filtercake with water helped remove excess NMP, while washing with heptane significantly removed color. The crude bipyrazole **5**, was recrystallized by heating in toluene to achieve dissolution of **5** and then adding heptane to promote crystal formation. The recrystallization removed the NMP and produced crystals with a low bulk density that were pure by NMR. The product was typically isolated in 70−85% yield from this one-pot process after the recrystallization. The lithiation of **5** was carried out with *n*-butyllithium as reported in our prior communication.[2a] For our kilo laboratory campaign at Pfizer we had conducted the lithiation at −10 to −15 °C to enable use of conventional glass-lined vessels. One important detail is that the trapping of

* Corresponding author. E-mail: robert.a.singer@pfizer.com.

(1) (a) Tsuji, J. *Synthesis* **1990**, 739. (b) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (c) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(2) (a) Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A *Tetrahedron Lett.* **2006**, *47*, 3727. (b) Singer, R. A.; Tom, N. J.; Frost, H. N.; Simon, W. M. *Tetrahedron Lett.* **2004**, *45*, 4715. (c) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, 1727.

(3) Bippyphos is commercially available through Digital Specialty Chemicals or Sigma-Aldrich (catalogue number 676632).

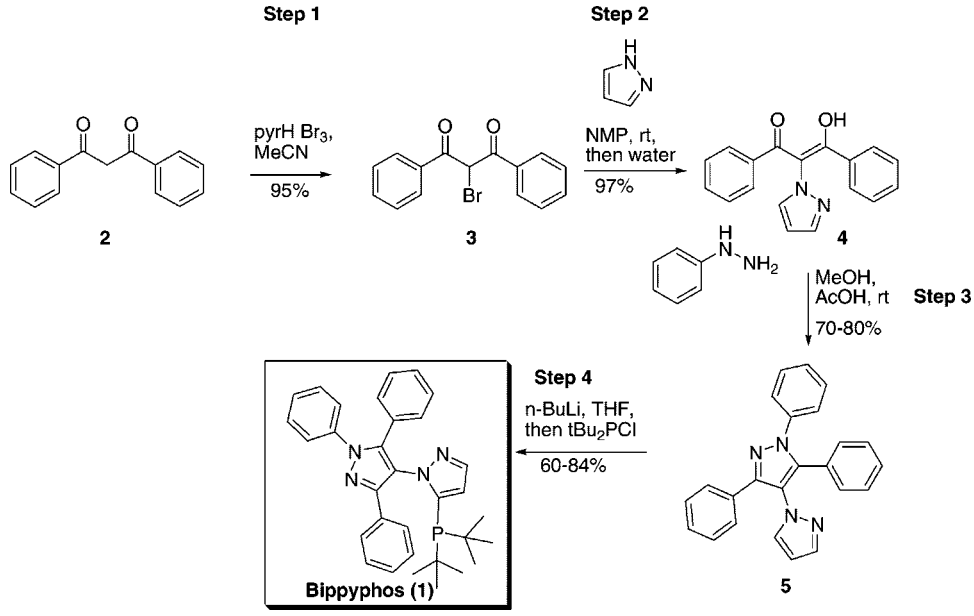
(4) During our original work we found that quenching the bromination with a reducing agent such as sodium thiosulfate led to debromination of **3**, converting the material back to **2**. To avoid this problem, the product, **3**, was precipitated from solution prior to quenching with the reducing agent.

(5) The alkylation requires 48 h to reach completion if carried out at room temperature.

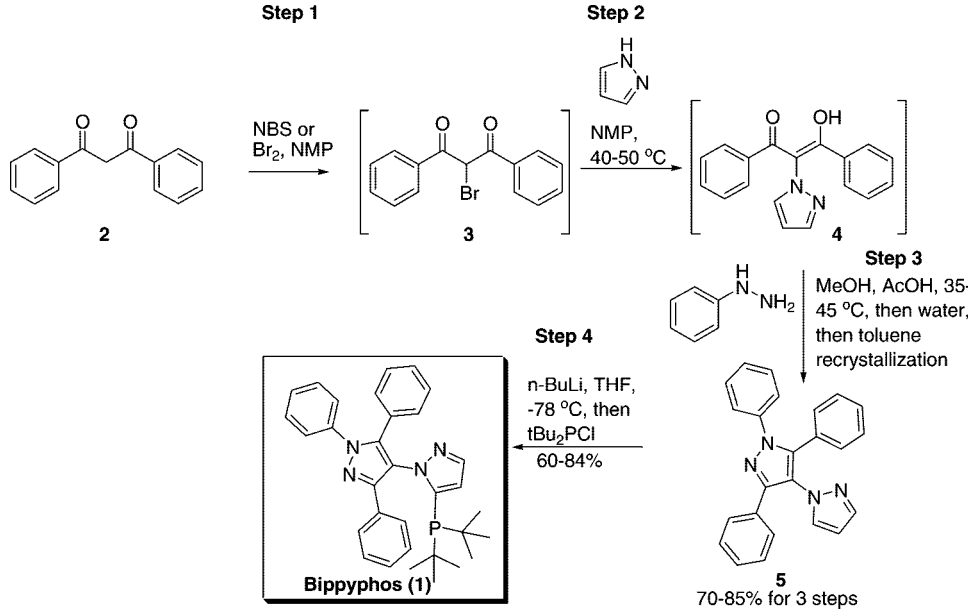
(6) We have even carried out the pyrazole alkylation of **3** at 55 °C without issue. At 55 °C the alkylation to afford **4** is complete within 3–5 h. Continued heating of the alkylation at 50–55 °C over 24 h only led to low levels of side products (1–2%).

Published on Web 03/20/2008
10.1021/op7002858 CCC: $40.75

Scheme 1



Scheme 2

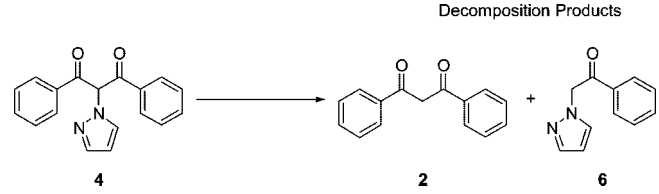


the chlorophosphine is highly exothermic and requires a slow addition to maintain the temperature in range and to avoid side products.

During the condensation for the formation of **5**, it was important to add the acetic acid prior to the phenylhydrazine to minimize side products that arise. Stability studies on **4** showed that addition of the acetic acid to maintain acidic conditions helped to avoid decomposition to **2** or **6**. It was also recognized that **4** is stable to the acidic alkylation reaction conditions under which it is produced (only buffered with excess pyrazole), but once the phenylhydrazine is added, the retroaldol side reaction or cleavage of pyrazole becomes more problematic.[7] Even the storage of **4** as a solid under ambient conditions was found to lead to decomposition to **2** and **6**!

(7) We suspect that the retroaldol side reaction is suppressed under acidic conditions due to the greater ease to protonate the tetrahedral intermediate and to lose water in the condensation.

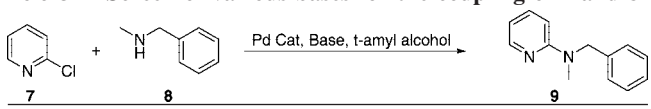
Scheme 3



Optimization of Pd-Catalyzed Amination

Having demonstrated a more efficient means of preparing our family of ligands, we next sought to optimize the conditions for use of Bippyphos in the Pd-catalyzed amination reaction. Frequently we encounter heterocyclic substrates such as chloropyridines in our development work at Pfizer[8] and require optimization of reactions for this problematic substrate class.[9] Secondary acyclic amines tend to be relatively more problematic in the Pd-catalyzed amination reactions due to the greater

Table 1. **Screen of various bases for the coupling of 7 and 8**

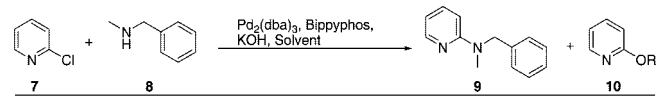


7 8 9

entry	base used (1.5 equiv)	conversion at 1 h (%)[a,c]	conversion at 16 h (%)[a,c]
1	KOH (88% pellets)	88	100
2	NaOH (99% pellets)	33	73
3	Cs_2CO_3	1	29
4	K_2CO_3	0	0
5	NaOtBu	70	96
6	NaOH (5% water)[b]	55	90
7	NaOH (15% water)[b]	74	100
8	NaOH (33% water)[b]	47	100

[a] Reaction conditions: used 1.0 equiv 2-chloropyridine, 1.25 equiv *N*-benzylmethylamine, 1.5 equiv base, 0.005 equiv $Pd_2(dba)_3$, 0.02 equiv Bippyphos in *tert*-amyl alcohol (1.25 M with respect to 2-chloropyridine) at reflux. [b] Amount of water is by weight % based on total weight of base used. [c] GC measured conversion based on integration of product relative to starting material.

Table 2. **Screen of various solvents**



7 8 9 10

entry	solvent [b]	conversion at 16 h (%)[a,c]	side product, **10** (%)
1	toluene	14	ND
2	dioxane	25	ND
3	THF or 2-Me-THF	22	ND
4	***tert*-amyl alcohol**	**100**	**ND**
5	MeOH	100	42 (R = Me)
6	20:1 THF/MeOH	100	14 (R = Me)
7	*sec*-butanol	100	22 (R = *sec*-Bu)
8	NMP	60	ND

[a] Reaction conditions: used 1.0 equiv 2-chloropyridine, 1.25 equiv *N*-benzylmethylamine, 1.5 equiv KOH, 0.005 equiv $Pd_2(dba)_3$, 0.02 equiv Bippyphos at reflux. [b] Solvent concentration was 1.25 M with respect to 2-chloropyridine. [c] GC measured conversion based on integration of all products relative to starting material.

propensity for β-hydride elimination.[10] For this reason, we elected to use 2-chloropyridine and *N*-benzylmethylamine (**8**) in our trials.

We found that we could make minor adjustments to our previously reported protocol to improve the success of couplings with pyridyl halides. Simply raising the reaction temperature from 80 to 90 °C to a reflux in *tert*-amyl alcohol (100–103 °C) helped drive reactions further. The source of Pd did not appear to impact performance of the Pd-catalyzed amination reactions as $Pd_2(dba)_3$ and $Pd(OAc)_2$ could be used interchangeably. We reexamined bases while using *tert*-amyl alcohol as solvent and confirmed that KOH pellets (88% assay)[11] are ideal for the process (Table 1, entry 1) as had been suggested previously in the literature.[12] As seen in Table 1, NaOH could perform equally as well as KOH, but a small amount of water was required. In addition, some water could be added to the process (up to 3% based on the weight of the KOH charge); however, additional water eventually led to a slower reaction, but still led to complete conversion. The extent of inhibition by water does eventually level out, and the process can be conducted as a biphase in water and *tert*-amyl alcohol but requires longer reaction times than if water is excluded.[13] The advantage of using more water is that the reactions can remain homogeneous, whereas in the absence of added water, the reactions become heterogeneous from the generation of salt byproduct.

After demonstrating that hydroxide salts provided optimal catalyst performance, solvents were evaluated. The higher catalytic efficiency with alcohol solvents was consistent across all substrate classes screened. Part of the reason for the increased reactivity is likely to be the superior solubility of KOH in alcohol over nonpolar solvents. The coupling between 4-bromo-*tert*-butylbenzene and **8** showed almost no product formation in toluene during the first hour, while the reaction was usually complete in *tert*-amyl alcohol during this time. This reactivity pattern was also observed with other amines such as 2,6-dimethylaniline and phenethylamine in couplings with 4-bromo-*tert*-butylbenzene. In couplings between pyridyl halides and amines, this reactivity pattern also held (Table 2). For the coupling between 2-chloropyridine (**7**) and *N*-benzylmethylamine (**8**), nonpolar solvents such as toluene (Table 2, entry 1) or dioxane were inferior to alcohols, with *tert*-amyl alcohol providing the cleanest purity profile (Table 2, entry 4). The more polar alcohol solvents possessed the highest catalyst activity but with some liabilities. Methanol appeared to be the best solvent for reactivity, but it was observed that methanol would couple with activated substrates, affording the methyl ether adduct as a side product! In the case of 2-chloropyridine coupling with *N*-benzylmethylamine, nearly a 1:1 ratio of product to methyl ether side product was observed, but for 3-chloropyridine (a less activated substrate) only about 2% of the methyl ether side product was observed. Using primary or secondary alcohols also led to coupling and reduction side products, with less hindered alcohols favoring coupling the most. For these reasons *tert*-amyl alcohol remains as the ideal solvent since side reactions are avoided,[14] but in selected substrates (electron-neutral systems) methanol could be a viable alternative. Using water as a cosolvent with *tert*-amyl alcohol did not

(8) (a) Pd-catalyzed amination reactions with pyridyl halides have been previously reported, see: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (b) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. N *Org. Lett.* **2002**, *4*, 3481. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L *J. Org. Chem.* **2000**, *65*, 1158. (d) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

(9) It has been shown that pyridyl substrates can displace phosphine ligands on Pd, see: Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(10) (a) Secondary acyclic amines have been shown to be more problematic substrates, see: Wolfe, J. P.; Wagaw, S.; Buchwald, S. L *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

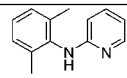
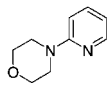
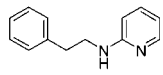
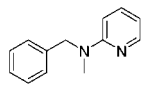
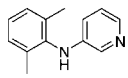
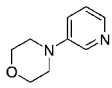
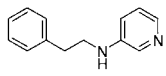
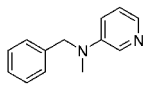
(11) The KOH pellets were used as supplied, without being ground to a powder. Grinding of the pellets was found to potentially lead to inferior performance, perhaps due to the ground pellets picking up water more readily.

(12) (a) Potassium hydroxide has been previously established as one of the most efficient bases for the Pd-catalyzed amination reaction, see: Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(13) The water was degassed with nitrogen to avoid oxidation of the catalyst. Water is more effective at retaining dissolved oxygen than organic solvents.

(14) Superior performance with tertiary alcohols as solvent or cosolvent has been reported in Pd-catalyzed amination reactions, see: (a) Reference 2c. (b) Huang, X.; Anderson, K.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

Table 3. **Couplings of various amines and chloropyridines catalyzed by Bippyphos[a]**

Entry	Chloropyridine	Product	Yield[b]
1			70%
2			89%
3			91%
4			89%
5			86%
6			92%
7			94%
8			92%

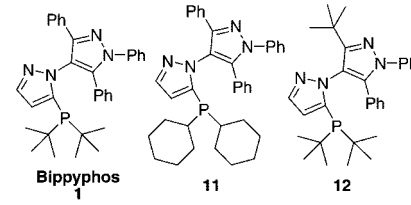
[a] Reaction conditions: used 1.0 equiv aryl halide, 1.25 equiv amine, 1.5 equiv KOH, 0.005 equiv $Pd_2(dba)_3$, 0.02 equiv Bippyphos at reflux in *tert*-amyl alcohol (1 M with respect to aryl halide) over 4 h. [b] Isolated yield.

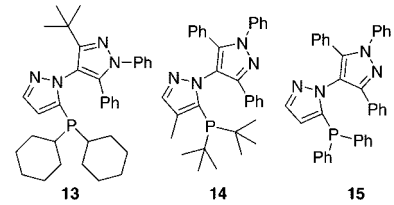
typically lead to hydroxy-substituted side products in the manner that alcohols would undergo coupling except in some cases when attempting to couple secondary amines with highly activated aryl halides.[15] For electron-rich aryl halides, reduction side products are more pronounced due to the slower reductive elimination step which enables competitive β-hydride elimination.[16]For example, when coupling 2-chloroanisole with *N*-benzylmethylamine in methanol at a reflux, a 2:1 ratio of product to reduction side product was observed. Reactions with NMP were considerably slower than with alcohol solvents due to competitive binding of the amide solvent blocking entry of the substrates to the catalyst. Blending small amounts of NMP with *tert*-amyl alcohol did not lead to noticeable inhibition and could be necessary for dissolution of highly crystalline substrates. We demonstrated that 2-chloropyridine and 3-chloropyridine could participate in the Pd-catalyzed amination reaction with a standard set of amine coupling partners. These results are shown in Table 3.

Preparation and Evaluation of Related Bipyrazole−Phosphine Ligands

We wanted to exploit the modular synthesis of Bippyphos and prepare analogues through substitution on the various building blocks to better understand structure and activity relationships. In general, substitution of the alkyl groups on phosphine appeared to have the largest impact on performance. Exchanging *tert*-butyl groups for cyclohexyl on the phosphine led to poorer performance for couplings of primary amines (Table 4, entries 8 and 10). On the other hand, secondary amines and anilines performed well with the less hindered dicyclohexylphosphine derivative **11**.[17] Increasing the steric environment further by substituting a *tert*-butyl group for one of the two phenyls on the pyrazole moiety (ligand **12**) led to no substantial improvement in couplings with primary amines (Table 4, entry 9).[18] Attenuating the electron-donating ability of the phosphine by exchanging the two alkyl groups for phenyl groups (ligand **15**) led to a relatively ineffective catalyst (Table 4, entries 12 and 17).

Introducing a methoxy group on the distal phenyl group of the pyrazole (through substitution on the phenylhydrazine fragment) led to no discernible change in performance from Bippyphos.[19] This study suggests that substrates can be matched with ligands based on the severity of the steric effects. Ideally, the least hindered primary amines perform best with ligands **1, 12** or **14**, while bulkier secondary amines perform better with ligand **11**. A clear diagonistic for the efficiency of the primary amine couplings is the ratio of the desired mono-arylated adduct to the bis-arylated adduct.





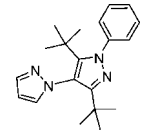
The less hindered ligands (**11** and **13**) have a relatively low branching ratio, while the most hindered ligands (**1**, **12** and **14**) tend to suppress the bis-arylation, especially ligand **14**. In contrast, the coupling between *N*-benzylmethylamine and 2-bromo-6-methoxypyridine gave almost exclusively the desired product using the less hindered dicyclohexylphosphines (Table 4, entries 14 and 16), while the di-*tert*-butylphosphine ligands afforded a small percentage of the hydroxyl adduct as a side product (Table 4, entries 13 and 15).

(15) While 2-chloropyridine could undergo substitution with hydroxide, this was not necessarily only Pd-catalyzed. Simply heating 2-chloropyridine with a hydroxide salt enables nucleophilic aromatic substitution to occur as a side reaction. Use of LHMDS as a base in THF can avoid this side reaction. To limit the Pd-catalyzed side reaction of hydroxyl substitution, use of a less hindered ligand, such as **11**, is appropriate in couplings with secondary amines.

(16) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.

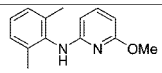
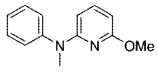
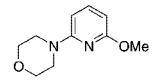
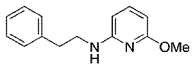
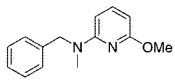
(17) The diisopropylphosphine analogue of **11** was also prepared in a related manner as described in the Experimental Section by lithiation with *n*-BuLi and trapping with *i*-Pr_2PCl. The diisopropylphosphine ligand performed identically to the dicyclohexyl ligand **11**. This diisopropylphosphine ligand was highly crystalline as was **11** and conveniently crystallized from isopropanol for isolation purposes.

(18) We had attempted to prepare the di-*tert*-butylpyrazole analogue of Bippyphos but found that the substrate (shown below)



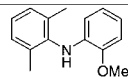
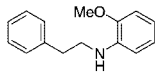
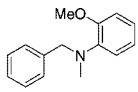
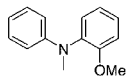
did not easily undergo lithiation to introduce the phosphine.

Table 4. **Pd-catalyzed aminations with 2-bromo-6-methoxypyridine**

Entry	Product	Ligand	Conversion[b]	Side product
1		**1**	99%	
2		**11**	99%	
3		**1**	99%	
4		**11**	99%	
5		**1**	99%	
6		**11**	99%	
7		**1**	96%	3% bis-arylated adduct
8		**11**	71%	24% bis-arylated adduct
9		**12**	97%	3% bis-arylated adduct
10		**13**	76%	24% bis-arylated adduct
11		**14**	99%	ND
12		**15**	8%	ND
13		**1**	92%	8% hydroxy adduct
14		**11**	99%	ND
15		**12**	93%	4% hydroxy adduct
16		**13**	96%	ND
17		**15**	43%	ND

[a] Reaction conditions: used 1.0 equiv aryl halide, 1.2 equiv amine, 1.5 equiv KOH, 0.005 equiv $Pd(OAc)_2$, 0.02 equiv Bippyphos at reflux in *tert*-amyl alcohol (1 M with respect to aryl halide) over 6 h. [b] Amount of desired product determined by GC relative to side productes and starting material.

Table 5. **Pd-catalyzed aminations with 2-chloroanisole using various bipyrazole phosphine ligands**

Entry	Product	Ligand	Conversion[b]	Side product
1		**1**	87%	ND
2		**11**	100%	ND
3		**12**	98%	ND
4		**13**	99%	ND
5		**1**	100%	ND
6		**11**	100%	ND
7		**1**	91%	6% anisole
8		**11**	45%	38% anisole
9		**1**	86%	ND
10		**11**	99%	ND

[a] Reaction conditions: used 1.0 equiv aryl halide, 1.2 equiv amine, 1.5 equiv KOH, 0.01 equiv $Pd(OAC)_2$, 0.02 equiv Bippyphos at reflux in *tert*-amyl alcohol (1 M with respect to aryl halide) over 6 h. [b] Amount of desired product determined by GC relative to side products and starting material.

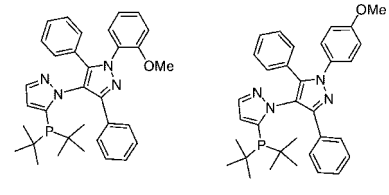
While ligand **11** outperformed Bippyphos for coupling substrate **8** with an electron-deficient aryl halide (2-bromo-6-methoxypryidine), we found that Bippyphos was more effective at suppressing β-hydride elimination when attempting to couple **8** with an electron-rich aryl halide such as 2-chloroanisole (Table 5, entries 7 and 8). Generally, reactions with electron-rich aryl halides are more prone to β-hydride elimination due to slower reductive elimination,[16] and so we decided that couplings with 2-chloroanisole could serve as a valuable benchmark. For couplings between 2-chloroanisole and amines other than **8** that are not as prone to β-hydride elimination, ligand **11** performed at least as well as Bippyphos (**1**) and in some cases appeared to be superior (Table 5, entries 2 and 10). While primary amines often have the liability of bis-arylation with less hindered ligands such as **11**, when coupling phenethylamine with 2-chloroanisole (Table 5, entries 5 and 6) bis-arylated side products were not observed, presumably due to the attenuated reactivity from the electron-rich nature of 2-chloroanisole.

We encountered a number of classes of substrates that did not perform well with Bippyphos. While unhindered cyclic secondary amines such as morpholine readily couple with aryl halides, we found that the more sterically hindered *cis*-2,6-dimethylpiperidine did not couple with either 2-chloroanisole nor with the more reactive 2-bromo-6-methoxypyridine. We also attempted couplings between amides and aryl halides which typically gave only trace product.[20] For example, the coupling between benzamide or 2-pyrrolidinone with 4-bromo-*tert*-butylbenzene only afforded about 2% product. Attempting these amide couplings with 2-chloropyridine led to slight improvement, but conversions of only about 10% was realized. Not only did amides generally fail to couple, but other non-nucleophilic heterocyclic amines failed to couple as well. Heterocyclic amines such as pyrazole, imidazole and indole did not produce any product with 4-bromo-*tert*-butylbenzene, nor with electron-deficient aryl halides such as 4-chlorobenzotrifluoride. Only in the case of 2,6-dibromopyridine did pyrazole couple to afford the desired product.

Ether Couplings

In an effort to better assess the side reactions with alcohols and to potentially take advantage of this reaction as an intended coupling, the scope of couplings between aryl halides and alcohols was briefly examined. Coupling alcohols with aryl halides is generally plagued with reduction side products due to the ease of β-hydride elimination.[21] Consequently, diaryl ethers are formed much more readily by cross-coupling methodology since they are not susceptible to β-hydride elimination.[22] In fact, bromo-*tert*-butylbenzene coupled cleanly

(19) We prepared methoxy-substituted derivatives of Bippyphos and observed no change in reactivity. The methoxy derivatives did tend to be more crystalline which could aid isolation. The structures are shown below:



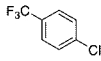
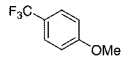
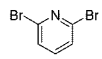
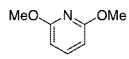
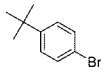
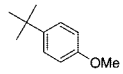
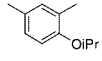
.

(20) The Buchwald group has successfully designed phosphine ligands to more generally catalyze couplings between aryl halides and amides and other non-nucleophilic amines, see: Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.

(21) (a) Vorogushin, A. V.; Huang, X.; Buchwald, S. L *J. Am. Chem. Soc.* **2005**, *127*, 8146. (b) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770.

(22) For a recent review on diaryl ether cross-coupling methodology, see: Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271.

Table 6. **Pd-catalyzed couplings with aryl halides and alcohols using Bippyphos (1)**

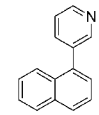
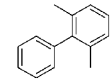
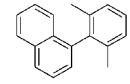
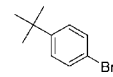
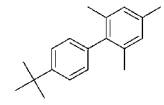
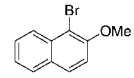
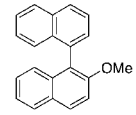
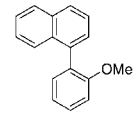
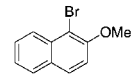
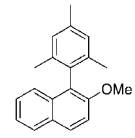
Entry	Aryl Halide	Product	Conversion[b]	Dehalogenation product
1			100%	ND
2			65%	35%
3			100%	ND
4			100%	ND
5			0%	100%
6			48%	52%
7			66%	34%
8			69%	31%
9			24%	76%
10			26%	74%
11			10%	90%

[a] Reaction conditions: used 1.0 equiv aryl halide, 1.5 equiv KOH, 0.005 equiv $Pd_2(dba)_3$, 0.02 equiv Bippyphos at reflux in alcohol (1 M with respect to aryl halide) over 3 h. [b] Amount of desired product determined by GC relative to side products and starting material.

with 1-napthol, *p*-cresol, and *o*-cresol when using Bippyphos without any evidence of reduction products as expected.[23] During our examination of alcohol couplings, electron-deficient aryl halides such as 2-chloropyridine or 4-chlorobenzotrifluoride performed optimally (Table 6, entries 1, 3, 4). Coupling electron-neutral substrates with methanol tended to afford 30−50% dehalogenated byproduct while couplings with isopropanol showed even higher levels of dehalogenation due the greater propensity for β-hydride elimination with a secondary alcohol. Electron-rich aryl halides, such as 2-bromoanisole, afforded solely reduction products (Table 6, entry 5). The steric hindrance of Bippyphos is essential to the success of these couplings to avoid reduction side products. As a comparison, when coupling 4-bromo-*tert*-butylbenzene with methanol, Bippyphos provides the desired ether and reduction products in a 1:1 ratio (Table 6, entry 6), and related ligands **12** and **14** provided similar results. In contrast, the use of the dicyclohexylphosphine analogue to Bippyphos (**11**) solely afforded the reduction product with no trace of the desired methyl ether product.

(23) The diaryl ether couplings were carried out with $Pd(OAc)_2$ and Bippyphos in *tert*-amyl alcohol using 1.0 equiv arylbromide, 1.2 equiv of the phenol and 1.5 equiv of K_2CO_3 at 100 °C over 8 h. Use of $Pd_2(dba)_3$ in diaryl ether couplings appeared to result in poorer reactivity.

Table 7. **Pd-catalyzed Suzuki−Miyaura couplings**

Entry	Aryl Halide	Product	Ligand	Conversion[a,b]
1			**1**	98% (98%[c])
2			**11**	89%
3			**15**	16%
4			**1**	35% (89%[c])
5			**11**	98% (99%[c])
6			**1**	2% (46%[c])
7			**11**	54% (99%[c])
8			**1**	55% (84%[c])
9			**11**	76% (99%[c])
10			**1**	5% (92%[c])
11			**11**	95% (99%[c])
12			**1**	45% (99%[c])
13			**11**	72% (98%[c])
15			**1**	5%[c]
16			**11**	91%[c]

[a] Reaction conditions: used 1.0 equiv aryl halide, 1.2 equiv aryl boronic acid, 1.5 equiv K_2CO_3, 0.01 equiv $Pd(OAc)_2$, 0.02 equiv ligand at reflux in *tert*-amyl alcohol (1 M with respect to aryl halide) over 3 h. [b] Amount of desired product determined by GC relative to side products and starting material. [c] Used 1.5 equiv KOH in place of K_2CO_3.

Suzuki−Miyaura Couplings

We examined Suzuki−Miyaura couplings with our ligands and applied similar reaction conditions to what we had used for the Pd-catalyzed amination reactions. Initially we examined KOH and K_2CO_3 as activating agents for the coupling and found no appreciable difference in performance (Table 7, entry 1); however, we did see improved reaction rates in *tert*-amyl alcohol over solvents such as dioxane. From this early optimization work, we decided to conduct the screen of reactions using *tert*-amyl alcohol and K_2CO_3. The source of Pd, whether $Pd(OAc)_2$ or $Pd_2(dba)_3$, did not appear to impact the performance of the couplings. While Bippyphos could efficiently catalyze reactions between coupling partners with a single *ortho* substituent (Table 7, entry 1), substrates with two or more *ortho* substituents performed better with **11** (Table 7, entries 5, 7, 9, 11, and 13). In the coupling between 2,6-dimethylchlorobenzene and phenylboronic acid, Bippyphos only achieved 35% conversion while **11** afforded the product in 98% conversion. In a more dramatic comparison, the coupling between 1-naphthylboronic acid and 1-bromo-2-methoxynaphthalene only reached 5% conversion with Bippyphos, whereas using **11** enabled 95% conversion to the desired product (Table 7, entries 10 and 11). We were pleased to find that when substituting KOH for K_2CO_3

Table 8. **Recommended applications for ligands 1 (Bippyphos) and 11 (Cy-Bippyphos)**

	ligand	
reaction type	Bippyphos (**1**)	Cy-Bippyphos (**11**)
Pd-catalyzed amination reactions	very general ligand, most effective with primary amines. Tends to suppress hydride elimination for electron-rich aryl halides.	most effective with electron-deficient aryl halides, anilines, and secondary amines (except with electron-rich aryl halides where hydride elimination occurs).
Suzuki−Miyaura couplings	most effective with unhindered aryl halides and boronic acids	highly effective with hindered aryl halides and boronic acids

in the couplings, the catalyst reactivity increased substantially. A number of the couplings that performed only moderately with K_2CO_3, provided excellent yields when switching to KOH (Table 7, entries 7–9, 12, 13). Even more remarkable was the successful coupling between 1-bromo-2-methoxynaphthalene and 1,3,5-trimethylbenzeneboronic acid with ligand **11** (Table 7, entry 16). This demonstrates that couplings to afford tetra-*ortho*-substituted biaryls are achievable with this ligand family.[24] We also examined the performance of the diphenylphosphine analogue of Bippyphos (**15**) and observed relatively poor performance as was the case with the amination reactions. In the coupling between 3-chloropyridine and 1-naphthalene boronic acid, only 16% product formed (Table 7, entry 3).

Conclusions

Bippyphos, **1**, is generally an effective phosphine ligand for Pd-catalyzed amination reactions, though the dicyclohexylphosphine analogue, **11**, is slightly more effective for some combinations of secondary amines and anilines with aryl halides (Table 8). In particular, Bippyphos is highly effective at suppressing β-hydride elimination which becomes more problematic in couplings involving secondary acyclic amines and electron-rich aryl halides. More dramatic differences in ligand performance were observed for Suzuki−Miyaura couplings, especially those involving sterically challenged substrates. The less hindered dicyclohexylphosphine ligand **11** outperformed Bippyphos, **1**, in all cases with substrates possessing multiple substituents *ortho* to the biaryl bridge. Both Bippyphos and **11** (Cy-Bippyphos) performed optimally in the Suzuki−Miyaura couplings with hindered substrates when using KOH as the base. In general, Cy-Bippyphos (**11**) successfully catalyzed couplings of aryl halides and boronic acids to afford tri-*ortho*-substituted biaryls and even one example of a tetra-*ortho*-substituted biaryl. Our modular design should enable us to continue to generate new members of this ligand family and design ligands suited to particular substrate combinations.

Experimental Section

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen.

General Procedure for Pd-Catalyzed Amination Reactions. To a flask under nitrogen was added $Pd_2(dba)_3$ (24 mg, 0.005 equiv, note 0.01 equiv Pd), or $Pd(OAc)_2$ (11 mg, 0.01 equiv), and Bippyphos (51 mg, 0.02 equiv, note 2:1 ligand to Pd molar ratio) in *tert*-amyl alcohol (5.0 mL). One can optionally add 0.10 mL of water to maintain a homogeneous reaction. After 5–15 min of stirring the dark purple reaction mixture (for $Pd(OAc)_2$ the reaction mixture was an orange color), KOH, 87–89% pellets (478 mg, 1.5 equiv) and the amine (6.00 mmol, 1.2 equiv) were added followed by the aryl halide (5.00 mmol, 1.0 equiv). The resulting reaction mixture became an orange color and was heated to ∼100 °C (reflux for *tert*-amyl alcohol is 100–103 °C). After 3 h the reaction was usually complete (consumption of aryl halide by GC). The reaction was cooled to rt and diluted with MTBE (20 mL) (note: may need 2-methyl-THF for more water-soluble substrates) and water (10 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo for purification by silica gel chromatography.

General Procedure for Suzuki−Miyaura Reactions. To a flask under nitrogen was added $Pd(OAc)_2$ (11 mg, 0.01 equiv), and **11** (56 mg, 0.02 equiv, note 2:1 ligand to Pd molar ratio) in *tert*-amyl alcohol (5.0 mL). After 5–15 min of stirring the orange reaction mixture, KOH (478 mg, 1.5 equiv), the aryl boronic acid (6.00 mmol, 1.2 equiv) and the aryl halide (5.00 mmol, 1.0 equiv) were added. The resulting reaction mixture was heated to ∼100 °C (reflux for *tert*-amyl alcohol is 100–103 °C). After 3 h the reaction was usually complete (consumption of aryl halide by GC). The reaction was cooled to rt and diluted with MTBE (20 mL) (note: may need 2-methyl-THF for more water-soluble substrates) and water (10 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo for purification by silica gel chromatography.

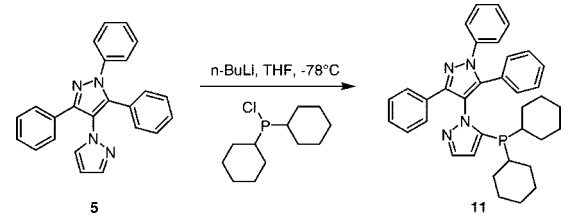
5-(Di-*tert*-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (1). Compound **5** (50.1 g, 138.3 mmol) was dissolved in THF (400 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (66.0 mL, 166 mmol) was added and the resulting reaction mixture was stirred at −78 °C for 1.5 h (note: the lithiation may be carried out at −10 to −20 °C, see alternative preparation below). The reaction started as an orange solution but after several minutes a suspension formed. After this time, di-*tert*-butylchlorophosphine (32 mL, 166 mmol) was added. The reaction mixture was allowed to gradually warm to 0 °C over 1 h and was stirred at 0 °C for an additional hour (maintaining the reaction cold seems to help with purity). The reaction was quenched with water (300 mL) and was diluted with *tert*-butyl methyl ether (600 mL). The organic layer was separated and washed with brine (200 mL). The organic layer was then dried over anhydrous sodium sulfate

(24) (a) Biaryls with four *ortho*-alkyl substituents have been prepared previously, see: Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L *J. Am. Chem. Soc.* **2005**, *127*, 4685. (d) Jensen, J. F.; Johannsen, M *Org. Lett.* **2003**, *5*, 3025. (e) Gereon, A.; Goddard, R.; Lehmann, C. W.; Glorius, F *J. Am. Chem. Soc.* **2004**, *126*, 15195. (f) Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V *Synlett* **2006**, 2908.

and concentrated in vacuo to a total volume of about 200 mL. The solution was diluted with *tert*-butyl methyl ether (400 mL) and was concentrated to a volume of about 300 mL. Crystals began to form, and the suspension was cooled to 0 °C to crystallize more material. After stirring for 2 h, the mixture was diluted with heptane (600 mL) to induce further crystallization, and the slurry was stirred for 4 h before filtration. The filtercake was washed with heptane to afford Bippyphos (**1**) as a white solid (59.0 g, 84%). Mp 191–193 °C; ^{1}H NMR ($CDCl_3$): δ 7.93 (d, J = 1.7 Hz, 1H), 7.48–7.11 (m, 15H), 6.62 (d, J = 1.7 Hz, 1H), 0.69 (d, J = 12.5 Hz, 9H), 0.57 (d, J = 12.5 Hz, 9H); ^{13}C NMR ($CDCl_3$): δ = 150.0, 143.5 (d, J = 26 Hz), 141.5, 140.4, 140.1, 132.3, 130.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 127.8, 127.7, 125.8, 121.1, 113.9 (d, J = 4.5 Hz), 32.1 (d, J = 18 Hz), 32.1 (d, J = 19 Hz), 30.0 (d, J = 27 Hz), 29.8 (d, J = 27 Hz). Anal. Calcd for $C_{32}H_{35}N_4P$: C, 75.86; H, 6.96; N, 11.06. Found: C, 75.62; H, 6.96; N, 10.86.

5-(Di-*tert*-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (1), Alternative Noncryogenic Process Used for Scale Up. Compound **5** (2.00 kg, 5.52 mol) was dissolved in THF (16 L) and cooled to −15 °C. A solution of 2.5 M *n*-hexyllithium in hexanes (2.68 L, 6.62 mol) was added over about 45 min between −15 and −10 °C, and the resulting reaction mixture was stirred at −15 °C for 1 h. The reaction mixture remained as an orange solution at this temperature range. After this time, di-*tert*-butylchlorophosphine (1.20 kg, 6.62 mol) was added over 1 h at −15 to −10 °C (could be beneficial to add this reagent as a solution to help reduce viscosity and minimize exotherm). The reaction mixture was held for 1 h at this temperature range after the addition and then allowed to gradually warm to ambient conditions. The reaction mixture was stirred at ambient conditions for an additional hour prior to the quench (note that maintaining the reaction cold after the phosphine addition seems to help with purity and the quench may proceed better at 0 °C than under ambient conditions). The reaction was quenched with dilute brine (7.2 L of water and 800 g of NaCl) and was further diluted with *tert*-butyl methyl ether (20 L). The organic layer was separated and was then dried over anhydrous sodium sulfate (2.00 kg). The sodium sulfate was removed by filtration. The organic solution was concentrated in vacuo to a total volume of about 8 L. The solution was diluted with *tert*-butyl methyl ether (20 L) and was concentrated to a volume of about 12 L. Crystals began to form during the vacuum distillation and the suspension was cooled to 0 °C to crystallize more material. After stirring for 2 h, the mixture was diluted with heptane (24 L) which was added over 30 min to induce further crystallization. The slurry was stirred for 3 h at about 0 °C, then cooled to −10 °C and stirred for another hour before filtration. The filtercake was washed with heptane (4 L) and transferred to a vacuum tray dryer held at 35 to 45 °C over 24 h to afford Bippyphos (**1**) as a white solid (2.24 kg, 80%).

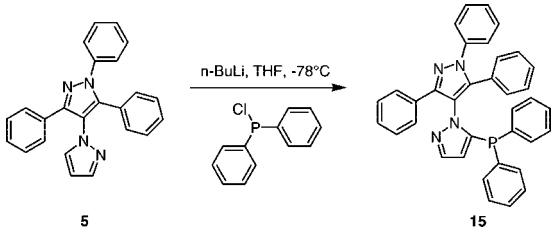
1-(1,3,5-Triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (5). To a solution of 1,3-diphenyl-1,3-propanedione, **2**, (50 g, 223 mmol) in NMP (200 mL, 4 mL/g LR) was added bromine (42.7 g or 13.7 mL, 1.2 equiv). Note that pyridinium tribromide or NBS may be used as alternatives to bromine for this step. The sustained red color was a sign that the reaction was complete near the end of the bromine dosing. Once reaction completion to form **3** was confirmed by TLC or HPLC, pyrazole (53.1 g, 3.5 equiv) was added. The reaction was heated to 35−55 °C and held for about 6−12 h. Once the reaction to form the alkylation adduct, **4**, was confirmed to be complete by HPLC, the reaction mixture was diluted with acetic acid (150 mL, 3 mL/g LR). Heating was continued at 35−45 °C, and then a solution of phenylhydrazine (36.2 g or 32.9 mL, 1.5 equiv) in methanol (250 mL, 5 mL/g LR) was added. Once the pyrazole condensation was nearly complete, the product precipitated from solution as a yellow suspension. After about 10 to 16 h the reaction was determined to be complete, and water (250 mL, 5 mL/g LR) was added to dilute the crystals. The crystals were stirred for at least 2 h and filtered. The filtercake was washed sequentially with water, then with cold methanol (to remove water), and then with heptane (the methanol and heptane washes removed color). The yellow solids were recrystallized by first dissolving in hot toluene (250 mL, 5 mL/g LR) and then adding heptane (500 mL, 10 mL/g LR) to the hot solution to promote the formation of crystals. The resulting suspension was stirred for at least 4 h and was filtered, washing the cake with heptane. Isolated 1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (**5**) as white crystals (64.7 g, 80%). Mp 168–169 °C; ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 2.1 Hz, 1H), 7.44–7.11 (m, 16H), 6.33 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 148.1, 141.2, 141.1, 140.0, 133.1, 131.1, 129.5, 129.3, 129.2, 128.7, 128.6, 128.1, 127.8, 127.0, 125.5, 121.2, 112.5, 107.1. Anal. Calcd for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46. Found: C, 79.16; H, 4.87; N, 15.30.



5 11

5-(Dicyclohexylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (11). Compound **5** (2.0 g, 5.3 mmol, 1.0 equiv) was dissolved in THF (20 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (2.6 mL, 6.4 mmol, 1.2 equiv) was added and the reaction allowed to stir at −78 °C for 1.5 h. After this time, dicyclohexylchlorophosphine (1.48 g, 6.38 mmol, 1.2 equiv) in THF (3 mL) was added. The mixture was kept at −78 °C for 30 min, gradually warmed to room temperature, and stirred overnight. The mixture was quenched with 1 M NaOH (10 mL) and extracted into MTBE (50 mL). The biphasic mixture was transferred to a separatory funnel for phase separation. The MTBE layer was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give an oily foam, which solidified upon standing. The solid was slurried in MTBE (10 mL) and granulated for 1 h (as an alternative, this ligand could be crystallized from isopropanol). The solids were filtered, rinsed with MTBE (5 mL), and allowed to dry overnight in a vacuum oven at 50–55 °C. This gave **11** as a white solid (1.5 g, 51%). Mp 173–174 °C; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H), 7.47−7.14 (m, 15H), 6.42 (d, 1H), 1.5−0.2 (m, 22H); ^{13}C NMR ($CDCl_3$): δ 149.6, 140.5, 140.2, 131.8, 129.8, 129.1, 128.8, 128.6, 128.5,

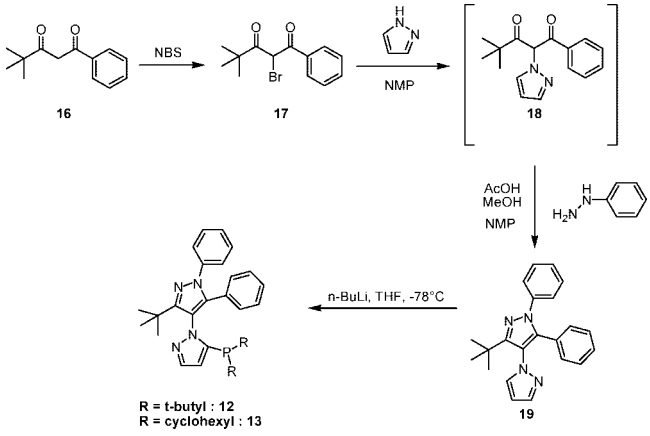
128.4, 127.8, 127.6, 125.5, 112.8, 33.6, 33.5, 29.7, 29.6, 28.8, 28.7, 28.4, 28.3, 27.2, 27.1, 27.0, 26.2. Anal. Calcd for: $C_{36}H_{39}N_4P$: C, 77.39; H, 7.04; N, 10.03. Found: C, 77.34; H, 7.01; N, 10.05.



5 15

5-(Diphenylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (15). Compound **5** (2.0g, 5.3 mmol, 1.0 equiv) was dissolved in THF (20 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (2.6 mL, 6.4 mmol, 1.2 equiv) was added and the reaction allowed to stir at −78 °C for 1.5 h. After this time, diphenylchlorophosphine (1.41 g, 6.38 mmol, 1.2 equiv) in THF (3 mL) was added. The mixture was kept at −78 °C for 30 min., then gradually warmed to room temperature, and stirred overnight. The mixture was quenched with 1 M NaOH (10 mL) and extracted into MTBE (50 mL). The biphasic mixture was transferred to a separatory funnel for phase separation. The MTBE layer was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give an oily foam. MTBE (10 mL) was added which gave an orange solution. Heptanes (2 mL) was added and the mixture stirred 4 h. The resulting slurry was filtered, rinsed with heptanes (5 mL), and allowed to dry overnight in a vacuum oven at 50–55 °C. This gave **15** as a yellow solid (2.1 g, 72%). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 1H), 7.40–6.99 (m, 21H), 6.86 (t, 2H), 6.75, (t, 2H), 6.02 (d, 1H); ^{13}C NMR ($CDCl_3$): δ 141.5, 133.4, 133.1, 133.0, 132.8, 129.7, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 127.9, 127.1, 125.4, 114.7. Anal. Calcd for: $C_{36}H_{27}N_4P$: C, 79.10; H, 4.98; N, 10.25. Found: C, 78.80; H, 4.87; N, 10.10.

2-Bromo-4,4-dimethyl-1-phenylpentane-1,3-dione (17). *N*-Bromosuccinimide (5.1 g, 28.6 mmol, 1.3 equiv) was added to a solution of 4,4-dimethyl-1-phenyl pentane-1,3-dione (4.5 g, 22.0 mmol, 1.0 equiv) dissolved in CH_3CN (23 mL). The reaction was allowed to stir at 50 °C overnight. Once reaction



16 17 18 19

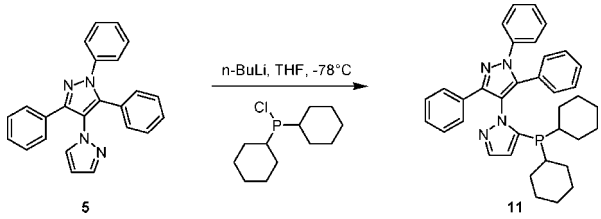
completion was confirmed by TLC or HPLC, the solution was cooled to rt and concentrated under reduced pressure to give a white solid. The solid was slurried in MTBE (70 mL) and stirred for 30 min. at rt. The white solid was filtered off and discarded. The filtrate, containing the product, was washed with aqueous saturated $NaHCO_3$ (50 mL), water (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give **17** as a white solid (6.1 g, 97%). Mp 96–97 °C; ^{1}H NMR ($CDCl_3$): δ 8.02−7.99 (d, 2H), 7.65−7.60 (m, 1H), 7.52−7.49 (m, 2H), 6.1 (s, 1H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 202.8, 189.9, 134.4, 129.5, 129.2, 49.4, 45.0, 27.2. Anal. Calcd for: $C_{13}H_{15}BrO_2$: C, 55.14; H, 5.34. Found: C, 55.23; H, 5.38.

1-(3-*tert*-Butyl-1,5-diphenyl-1H-pyrazol-4-yl)-1H-pyrazole (19). Pyrazole (5.0 g, 74.3 mmol, 3.5 equiv) was added to a solution of **17** (6.0 g, 21.2 mmol, 1.0 equiv) in NMP (18 mL) and warmed to 50 °−55 °C overnight to give **18**. Once reaction completion was confirmed by TLC or HPLC, the pot was cooled to room temperature and diluted with acetic acid (10 mL). A solution of phenylhydrazine (3.4 g, 31.8 mmol, 1.5 equiv) in methanol (10 mL) was added. The mixture was warmed to 55–60 °C for 24 h. Once reaction completion was confirmed by TLC or HPLC, the pot was cooled to room temperature and concentrated under reduce pressure to remove the methanol. The remaining orange solution was diluted with water (20 mL) and MTBE (50 mL). The biphase was allowed to stir for 1.5 h. The resulting precipitate was filtered, rinsed with MTBE (10 mL), and allowed to dry overnight in the vacuum oven. This gave **19** as a white solid (4.8 g, 66%). Mp 140–141 °C; ^{1}H NMR ($CDCl_3$): δ 7.78 (d, 1H), 7.49 (m, 5H), 7.20 (m, 5H), 6.41 (d, 1H), 1.0 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 149.6, 147.9, 143.4, 140.5, 134.1, 131.2, 129.7, 129.2, 128.8, 128.6, 128.3, 127.0, 107.2, 33.6, 30.4. Anal. Calcd for: $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 76.70; H, 6.26; N, 16.23.

1-(3-*tert*-Butyl-1,5-diphenyl-1H-pyrazol-4-yl)-5-(di-*tert*-butylphosphino)-1H-pyrazole (12). Compound **19** (1.2 g, 3.5 mmol, 1.0 equiv) was dissolved in THF (12 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (1.7 mL, 4.2 mmol, 1.2 equiv) was added and the reaction allowed to stir at −78 °C for 1.5 h. At this time, di-*tert*-butylchlorophosphine (760 mg, 4.2 mmol, 1.2 equiv) in THF (2 mL) was added. The mixture was kept at −78 °C for 2 h, gradually warmed to room temperature, and stirred overnight. The mixture was quenched with 1 M NaOH (10 mL) and extracted into MTBE (40 mL). The biphasic mixture was transferred to a separatory funnel for phase separation. The MTBE layer was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give an oily foam. The oily foam was purified by flash chromatography (3:1 Heptane: EtOAc). The fractions containing pure product were combined and concentrated under reduced pressure to give **12** as a white foam (740 mg, 43%). Mp 70–71 °C; ^{1}H NMR ($CDCl_3$): δ 7.82 (d, 1H), 7.53–7.46 (m, 5H), 7.29–7.27 (m, 2H), 7.15–7.13 (m, 3H), 6,71 (d, 1H), 1.23–1.20 (d, 9H), 1.09 (s, 9H), 0.74–0.71 (d, 9H); ^{13}C NMR ($CDCl_3$): δ 139.5, 129.5, 129.4, 128.9, 128.4, 128.2, 128.0, 31.4, 31.2, 30.3, 30.1, 30.0. Anal. Calcd for: $C_{30}H_{39}N_4P$: C, 74.04; H, 8.08; N, 11.51. Found: C, 73.47; H, 8.11; N, 11.02.

1-(3-*tert*-Butyl-1,5-diphenyl-1H-pyrazol-4-yl)-5-(dicyclohexylphosphino)-1H-pyrazole (13). Compound **19** (1.2 g, 3.5 mmol, 1.0 equiv) was dissolved in THF (12 mL) and cooled to

−78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (1.7 mL, 4.2 mmol, 1.2 equiv) was added, and the reaction was allowed to stir at −78 °C for 1.5 h. After this time, dicyclohexylchlorophosphine (760 mg, 4.2 mmol, 1.2 equiv) in THF (2 mL) was added. The mixture was kept at −78 °C for 2 h, gradually warmed to room temperature, and stirred overnight. The mixture was quenched with 1 M NaOH (10 mL) and extracted into MTBE (40 mL). The biphasic mixture was transferred to a separatory funnel for phase separation. The MTBE layer was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give a waxy yellow solid. To the solid was added isopropyl ether (10 mL) and the mixture allowed to granulate for 1 h at rt. The solid was filtered, rinsed with isopropyl ether (5 mL), and allowed to dry overnight in the vacuum oven at 50–55 °C. This gave **13** as a cream-colored solid (1.3 g, 71%). Mp 205–206 °C; ^{1}H NMR ($CDCl_3$): δ 7.82 (d, 1H), 7.47 (m, 5H), 7.19 (m, 5H), 6,46 (d, 1H), 0.50 – 2.0 (m, 31 H); ^{13}C NMR ($CDCl_3$): δ 149.0, 143.0, 139.8, 132.2, 129.6, 129.2, 129.0, 128.7, 128.2, 127.5, 112.5, 33.6, 33.4, 30.6, 30.3, 27.2, 27.1, 27.0, 26.5, 26.1. Anal. Calcd for: $C_{34}H_{43}N_4P$: C, 75.80; H, 8.05; N, 10.40. Found: C, 75.41; H, 8.11; N, 10.26.



4-Methyl-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (21). *N*-Bromosuccinimide (3.2 g, 18.0 mmol, 1.3 equiv) was added to a solution of 1,3-diphenyl-1,3-propanedione, **2**, (3.1 g, 13.9 mmol, 1.0 equiv) in NMP (12 mL) and allowed to stir for 4 h at rt to give **3**. Once reaction completion was confirmed by TLC or HPLC, 4-methylpyrazole (4.0 g, 48.7 mmol, 3.5 equiv) was added. The resulting solution was allowed to stir overnight at 50–55 °C to give the 4-methylpyrazole-substituted intermediate, **20**. Once reaction completion was confirmed by TLC or HPLC, the pot was cooled to room temperature and diluted with acetic acid (9 mL). A solution of phenylhydrazine (2.2 g, 20.7 mmol, 1.5 equiv) in methanol (9 mL) was added. The reaction solution was allowed to stir at rt overnight which resulted in an orange slurry. Once reaction completion was confirmed by TLC or HPLC, the orange slurry was filtered and rinsed with H_2O (10 mL). The damp cake was charged to a clean flask along with MeOH (15 mL) and H_2O (15 mL) where the slurry was allowed to granulate for 1 h at rt. The slurry was filtered and rinsed with H_2O (10 mL), followed by a rinse with heptane (10 mL). The damp cake was again charged to a clean flask. Toluene (28 mL) was added and heated to 95 °C to give a yellow solution. Heptane (70 mL) was added dropwise. Once addition was complete, the pot was slowly cooled to rt and stirred 1 h. The resulting slurry was filtered, rinsed with heptane (10 mL), and dried in the vacuum oven at 50–55 °C overnight. This gave **21** as a white crystalline solid (3.7 g, 71% yield). Mp 198–199 °C; ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H), 7.45−7.14 (m, 15H), 7.09 (s, 1H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.0, 131.6, 129.6, 129.2, 129.1, 128.7, 128.6, 128.0, 127.0, 125.5, 117.8, 9.5. Anal. Calcd for: $C_{25}H_{20}N_4$: C, 79.76; H, 5.35; N, 14.88. Found: C, 79.78; H, 5.29; N, 14.94.

5-(Di-*tert*-butylphosphino)-4-methyl-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (14). Compound **21** (1.7 g, 4.4 mmol, 1.0 equiv) was dissolved in THF (25 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (2.1 mL, 5.3 mmol, 1.2 equiv) was added and the reaction allowed to stir at −78 °C for 1.5 h. After this time, di-*tert*-butylchlorophosphine (950 mg, 5.3 mmol, 1.2 equiv) in THF (2 mL) was added. The mixture was kept at −78 °C for 2 h, gradually warmed to room temperature, and stirred overnight. The mixture was quenched with 1 M NaOH (10 mL) and extracted into MTBE (50 mL). The biphasic mixture was transferred to a separatory funnel for phase separation. The MTBE layer was washed with water (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow foam. The oily foam was purified by flash chromatography (3:1 heptane/EtOAc). The fractions containing pure product were combined and concentrated under reduced pressure to give a **14** as a yellow foam (475 mg, 21%). Mp 95–96 °C; ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 1H), 7.51 (d, 2H), 7.40 (d, 2H), 7.33−7.15 (m, 11H), 2.24 (s, 3H), 0.73 (d, 9H), 0.61 (d, 9H); ^{13}C NMR ($CDCl_3$): δ 142.6, 130.3, 129.0, 128.8, 128.5, 128.4, 128.2, 127.9, 127.6, 125.7, 30.8, 30.7, 13.5. Anal. Calcd for: $C_{33}H_{37}N_4P$: C, 76.13; H, 7.16; N, 10.76. Found: C, 76.05; H, 7.39; N, 10.54.

Acknowledgment

We thank Thomas Staigers, Jeff Haase, Bob Buckingham, and Billy Buzon for assistance in the original scale up of Bippyphos at Pfizer. We thank Scott Laneman for his help in the commercial production of Bippyphos at Digital Specialty Chemicals.

Received for review December 12, 2007.

OP7002858