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A family of simple amide-derived air-stable P,O-ligands for Suzuki cross-coupling of unactivated aryl chlorides

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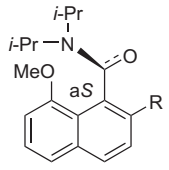
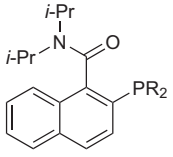
Abstract—A family of air-stable amide-derived phosphine (Aphos) ligands engineered on simple *N*,*N*-dialkyl aryl amide scaffolds has been designed and prepared by one-pot synthesis from the amides in high yields. The Aphos ligands have been used, in analogous to their atropisomeric variations, as hemilabile bidentate P,O-ligands in various Pd-catalyzed C–N and C–C bond forming reactions. We present here our results on the highly efficient Suzuki cross-coupling reactions of unactivated and/or sterically hindered aryl chlorides with arylboronic acids and a relationship of Aphos structures with catalytic efficacy.

In connection with our research program in design, synthesis, and application of atropisomeric amides in asymmetric catalysis and synthesis,[1–9] we have prepared a number of atropisomeric amide-derived P,O-ligands, such as (a*S*)-(−)-**1**–**3** and their antipodes, and have demonstrated that these non-biaryl chiral P,O-ligands are capable of inducing high enantioselectivity of >90% ee in the Pd-catalyzed asymmetric allylic alkylation,[3] asymmetric Heck reaction,[4,5] and asymmetric Suzuki cross-coupling.[5] A related atropisomeric 2-hydroxy-1-naphthamide (a*R*)-(+)-**4** has been prepared for enantioselective reactions.[6] Inspired by the performance of the atropisomeric P,O-ligands (a*S*)-(−)-**1**–**3**, we prepared and screened a family of simple amide-derived phosphines (Aphos) **5**–**9** possessing various *N*,*N*-dialkyl aromatic amide scaffolds as P,O-ligands for Pd-catalyzed C–N and C–C bond forming reactions. We discovered that these P,O-ligands afforded excellent results in the Pd-catalyzed amination of activated aryl chlorides[7] and the Suzuki cross-coupling reactions of unactivated aryl chlorides.[8] We have reported the Suzuki cross-coupling of aryl bromides at low catalyst loading of 0.01% Pd by using the Cy-Aphos ligands **6b** and **8b**.[9] We disclose here our results on the Suzuki cross-coupling of unactivated aryl chlorides in the presence of the Aphos ligands **5**–**9**.[10]

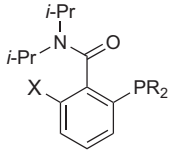
Table 1 summarizes our initial screening results of the effect of the Aphos ligands **5**–**9** on the Suzuki cross-coupling of 4-chlorobenzene with phenylboronic acid. All these Aphos ligands were conveniently prepared in high



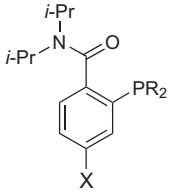
(a*S*)-(-)-**1**: R = PPh_2
(a*S*)-(-)-**2**: R = PCy_2
(a*S*)-(-)-**3**: R = $P(t\text{-Bu})_2$
(a*S*)-(+)-**4**: R = OH



5a: R = Ph
5b: R = Cy
5c: R = *t*-Bu



6a: X = H, R = Ph
6b: X = H, R = Cy
6c: X = H, R = *t*-Bu
7a: X = Ph, R = Ph
7b: X = Ph, R = Cy
7c: X = Ph, R = *t*-Bu



8a: X = Ph, R = Ph
8b: X = Ph, R = Cy
8c: X = Ph, R = *t*-Bu
9a: X = Cy, R = Ph
9b: X = Cy, R = Cy
9c: X = Cy, R = *t*-Bu

Keywords: Amides; Phosphines; Suzuki reaction; Aryl chlorides.
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yields from the amides of commercially available materials via directed *ortho* lithiation[11] followed by quenching with chlorodiphenylphosphine, chlorodicyclohexylphosphine, and di-*tert*-butylchlorophosphine, respectively.[3] Our design and selection of the amide scaffolds were based on the following four criteria: (a) the *N*,*N*-dialkyl amide moiety enhances the stability of electron-rich phosphines toward air oxidation as it was observed for our atropisomeric P,O-ligands **1**–**3**;[3] (b) the *N*,*N*-dialkyl amide moiety provides the necessary bulkiness with flexibility for steric tuning to suppress formation of bisphosphine–metal complexes;[12a] (c) the *N*,*N*-dialkyl amide moiety facilitates directed *ortho* lithiation on the amide scaffolds,[11] providing a simple and convenient method of preparation of Aphos ligands; and, more importantly, (d) the amide carbonyl oxygen acts as a coordinating atom to transition metals such as Pd,[3b,13] therefore, Aphos ligands function as hemilabile bidentate ligands.[12,14] It is well known that activation of arylboronic acid by OH^- or F^- is required for transmetallation in the catalytic cycle of Suzuki cross-coupling.[15] We selected 4-chlorobenzene as the unactivated aryl chloride[16] to react with phenylboronic acid for examining efficacy of the Aphos ligands. Among the bases screened, we obtained the following promoting order of *t*-BuONa > CsF ≈ $KF{\cdot}2H_2O$ > K_3PO_4 ≈ Cs_2CO_3 ≫ $Ba(OH)_2$ > Et_3N > Na_2CO_3 > CaH_2 according to isolated product yields. Control experiments also revealed that high yields of the biaryl products were obtained with Aphos:Pd ratio being >1.5. Therefore, we first compared the Aphos ligands **5**–**9** in the Suzuki cross-coupling in the presence of 1 mol % Pd, 2 mol % Aphos, and 3 equiv of *t*-BuONa in toluene at 110 °C for 1.5 h. A commercial monophosphine ligand, dicyclohexylphenylphosphine (**10**), was used as the reference ligand. The results listed in Table 1 can be concluded as follows: (a) Ph-Aphos ligands **5a**, **6a**, **7a**, **8a**, and **9a** are poor ligands; (b) Cy-Aphos and *t*-Bu-Aphos ligands **5b**,**c**, **6b**,**c**, **7b**,**c**, **8b**,**c**, and **9b**,**c** are excellent ligands with Cy-Aphos ligands being the best performers; (c) 1-naphthamide scaffold (entries 2 and 3) is less preferable than benzamide skeleton; (d) substituted benzamides (entries 8, 11, 12, 14, and 15) are much more efficient than the parent nucleus (entries 5 and 6); (e) an aryl substituent on the benzamide ring (entries 11 and 12) is much more beneficial than an alkyl group (entries 14 and 15); and (f) severe steric congestion on the amide scaffold (entry 9) results in almost complete incapability of coordination with metals.

We then used a mild base K_3PO_4 to evaluate the Aphos ligands **5**–**9** under similar reaction conditions with extended reaction time. The results are summarized in Table 1, indicating a parallel reactivity order. Except for Ph-Aphos ligands **5a**, **6a**, **7a**, **8a**, and **9a**, other Aphos ligands afforded the biaryl product in ⩾90% yields with reaction time of 3.5–11 h. It is interesting to note that the bulky *t*-Bu-Aphos **7c** also produced the product in 68% yield after reacting for 10 h. In contrast to these Aphos ligands, the non-amide phosphine **10** only provided a yield of 48% after 36 h of reaction. It becomes apparent that the *N*,*N*-dialkyl amide moiety is critically important for the function of the Aphos ligands. On the other hand, aryl substituent effect was observed for the Ph-Aphos **7a**, which gave 28% yield of the product (entry 7), being significantly higher than other Ph-Aphos ligands (3–7%). The best-performing ligand within the family is the Cy-Aphos **8b** possessing the 4-phenylbenzamide scaffold. It gave 95% yield of the biaryl product within 3.5 h in toluene at 110 °C in the presence of 1 mol % Pd.

We investigated the Suzuki cross-coupling of a number of structurally unique aryl chlorides with arylboronic acids using our Aphos ligands. Some results are shown in Table 2. In general, both electron-rich and sterically hindered aryl chlorides and arylboronic acids underwent smooth cross-couplings to furnish the biaryls in nearly quantitative yields (92–99%) in very short reaction time (50 min–5 h). We obtained high yield for the tri-*ortho*-substituted biaryl using a stronger base *t*-BuONa (Table 2, entry 3).

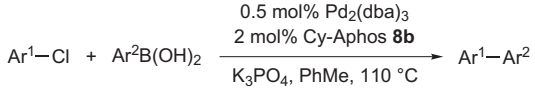
Table 1. Effect of Aphos ligand structures on Suzuki cross-coupling of 4-chlorotoluene with phenylboronic acid[a]

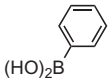
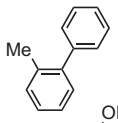
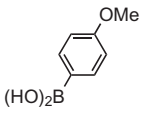
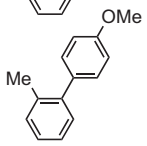
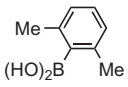
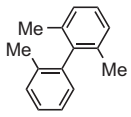
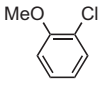
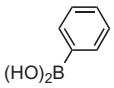
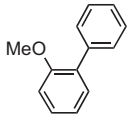
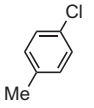
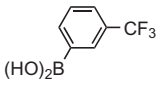
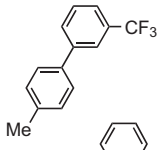
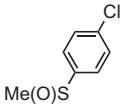
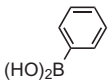
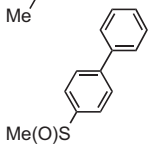
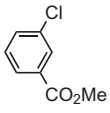
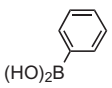
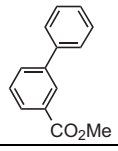
Entry	Aphos, amide scaffold	Base, time (h)	Yield[b] (%)	Base, Time (h)	Yield[b] (%)
1	**5a**: Ph-Aphos, 1-naphthamide	*t*-BuONa, 1.5	1	K_3PO_4, 20	4
2	**5b**: Cy-Aphos, 1-naphthamide	*t*-BuONa, 1.5	23	K_3PO_4, 4	92
3	**5c**: *t*-Bu-Aphos, 1-naphthamide	*t*-BuONa, 1.5	22	K_3PO_4, 10	89
4	**6a**: Ph-Aphos, benzamide	*t*-BuONa, 1.5	2	K_3PO_4, 16	3
5	**6b**: Cy-Aphos, benzamide	*t*-BuONa, 1.5	48	K_3PO_4, 4	91
6	**6c**: *t*-Bu-Aphos, benzamide	*t*-BuONa, 1.5	26	K_3PO_4, 11	93
7	**7a**: Ph-Aphos, 6-phenylbenzamide	*t*-BuONa, 1.5	2	K_3PO_4, 20	28
8	**7b**: Cy-Aphos, 6-phenylbenzamide	*t*-BuONa, 1.5	67	K_3PO_4, 6	93
9	**7c**: *t*-Bu-Aphos, 6-phenylbenzamide	*t*-BuONa, 1.5	1	K_3PO_4, 10	68
10	**8a**: Ph-Aphos, 4-phenylbenzamide	*t*-BuONa, 1.5	1	K_3PO_4, 14	4
11	**8b**: Cy-Aphos, 4-phenylbenzamide	*t*-BuONa, 1.5	90	K_3PO_4, 3.5	95
12	**8c**: *t*-Bu-Aphos, 4-phenylbenzamide	*t*-BuONa, 1.5	80	K_3PO_4, 5	91
13	**9a**: Ph-Aphos, 4-cyclohexylbenzamide	*t*-BuONa, 1.5	1	K_3PO_4, 14.5	7
14	**9b**: Cy-Aphos, 4-cyclohexylbenzamide	*t*-BuONa, 1.5	79	K_3PO_4, 5	89
15	**9c**: *t*-Bu-Aphos, 4-cyclohexylbenzamide	*t*-BuONa, 1.5	52	K_3PO_4, 11	95
16	**10**: $PhPCy_2$	*t*-BuONa, 1.5	1	K_3PO_4, 36	48

[a] Reactions were carried out with 0.5 mol % $Pd_2(dba)_3$, 2 mol % of Aphos, 1.0 equiv of 4-chlorotoluene, 1.5 equiv of phenylboronic acid, and 3.0 equiv of base in toluene (110 °C, oil bath temperature).

[b] Isolated yield.

Table 2. Suzuki cross-coupling of aryl chlorides using Cy-Aphos **8b**[a]

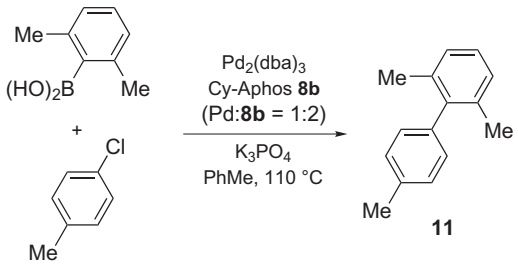


Entry	Ar–Cl[1]	$Ar^2B(OH)_2$	Ar^1–Ar^2	*t*; Yield[b] (%)
1				3 h; 93
2				70 min; 97
3[c]				2.5 h; 92
4				80 min; >99
5				5 h; >99
6				1.5 h; >99
7				1 h; >99

[a] Reaction conditions were not optimized.
[b] Isolated yield.
[c] A stronger base *t*-BuONa was used in place of K_3PO_4.

Table 3 shows some results of the Suzuki cross-coupling of aryl chlorides with phenylboronic acid at low temperature (THF, 65 °C) using Cy-Aphos **8b** as the P,O-ligand. The reaction of electron-rich 2-chloroanisole gave 77% yield (entry 1, Table 3) while methyl 4-chlorobenzoate and 4′-chloroacetophenone afforded the biaryls in 95–99% yields (Table 3, entries 2 and 3) within 3–4 h.

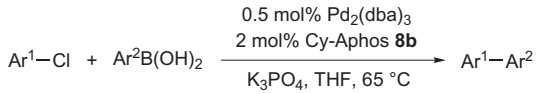
We have reported that the Suzuki cross-coupling of aryl bromides at low catalyst loading of 0.01 mol % Pd in the presence of Cy-Aphos **6b** at 60–80 °C.[9] We now have extended the reaction conditions to aryl chlorides. As illustrated in Scheme 1, we used 4-chlorotoluene to react with the sterically hindered 2,6-dimethylphenylboronic acid at different catalyst loadings with a fixed 1:2 ratio of Pd:Cy-Aphos **8b**. The biaryl product **11** was obtained in excellent yields of 98% and 96% within 3.5–7.5 h with 1 mol % and 0.1 mol % of Pd, respectively. The cross-coupling still took place with Pd loadings down to 0.01–0.03 mol % albeit significant longer reaction times were required and the product yields were reduced considerably. For laboratory application purpose, the

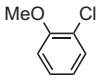
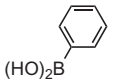
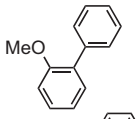
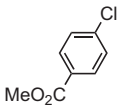
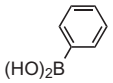
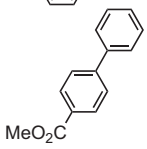
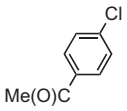
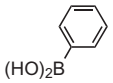
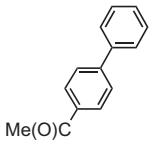


Pd (mol%)	Time (h)	Yield (%)
1	3.5	98
0.1	7.5	96
0.03	35	60
0.02	48	45
0.01	33	28

Scheme 1. Suzuki cross-coupling of aryl chlorides at low catalyst loading.

Table 3. Low temperature Suzuki cross-coupling of aryl chlorides[a]



Entry	Ar–Cl[1]	$Ar^2B(OH)_2$	Ar^1–Ar^2	*t* (h); Yield[b] (%)
1				9; 77
2				3; 95
3				4; >99

[a] Reaction conditions were not optimized.
[b] Isolated yield.

catalyst system consisting of 0.1 mol % Pd and 0.2 mol % Aphos can be conveniently used to prepare biaryls in excellent yields within acceptable reaction time of less than 10 h.

In summary, we have designed and synthesized a family of simple *N*,*N*-dialkyl aryl amide-based Aphos ligands possessing various aromatic amide scaffolds. The Aphos ligands are readily accessible and exhibit good stability toward air oxidation, allowing simple handling procedures, such as extraction and purification in open air, commonly used in organic synthesis laboratories. We have demonstrated useful application of Aphos ligands as the hemilabile P,O-ligands in the Pd-catalyzed Suzuki cross-coupling reactions of both aryl bromides and chlorides at low catalyst loading. The unique characteristic benefit of Aphos ligands originates from the *N*,*N*-alkyl amide moiety that significantly improves air oxidation stability of the electron-rich phosphines and maintains high efficacy in catalysis. We have used these Aphos ligands in multi-step synthetic reactions with excellent results,[17] that could not be obtained using commonly used catalyst system. The results will be disclosed elsewhere.

Acknowledgements

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