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Diarylmethanes through an Unprecedented Palladium-Catalyzed C–C Cross-Coupling of 1-(Aryl)methoxy-1*H*-Benzotriazoles with Arylboronic Acids

Manish K. Singh and Mahesh K. Lakshman*[a]

1-(Aryl)methoxy-1*H*-benzotriazoles ($ArCH_2OBt$) are bench-stable reagents that are prepared readily from 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate and benzylic alcohols. These compounds, which contain a N–O–C bond, undergo cross-coupling with arylboronic acids by C–O bond scission with catalysts that comprise $Pd(OAc)_2$ and biarylphosphine ligands. Such reactivity of $ArCH_2OBt$ derivatives, which lead to diarylmethanes, has not been described previously and constitutes a new activation of benzylic alcohols. With regard to the various ligand-metal complexes that support catalytic activity, it appears that those with smaller *"percent buried volumes"* ($\%V_{bur}$) provide better outcomes. This factor has been evaluated in the initial optimization studies and in further reactions with difficult coupling partners. Ligand electronics of the biaryl moiety seem to play a lesser role in this type of reaction. The biscoordinating bis[(2-diphenylphosphino)phenyl] ether appears to be suitable to improve the yields of low-yielding reactions.

Introduction

Diarylmethanes are a structural unit encountered commonly in many pharmaceuticals, supramolecules, and in natural products. Some interesting examples are shown in Figure 1.[1–6] Classical methods to diarylmethanes include Friedel–Crafts alkylation,[7a,b] the reduction of diarylketones[7c–e] and diarylcarbinols,[7f] and the deoxygenation of secondary or tertiary benzylic alcohols[7g,h] but all of these methods have certain disadvantages.

Transition-metal-catalyzed cross-coupling reactions present straightforward access to the diarylmethane moiety. In this context, cross-coupling reactions of benzylic electrophiles with a range of organometallics as well as the coupling of benzylic nucleophiles with aryl electrophiles can be accomplished by catalysis methodologies. Among these various methods, Pd-catalyzed C–C cross-coupling with boronic acids as the nucleophilic component[8] has manifold advantages, such as the commercial availability of a wide range of boronic acids, their insensitivity to moisture, ease of handling, high functional group compatibility, and benign reaction byproducts, to name a few.

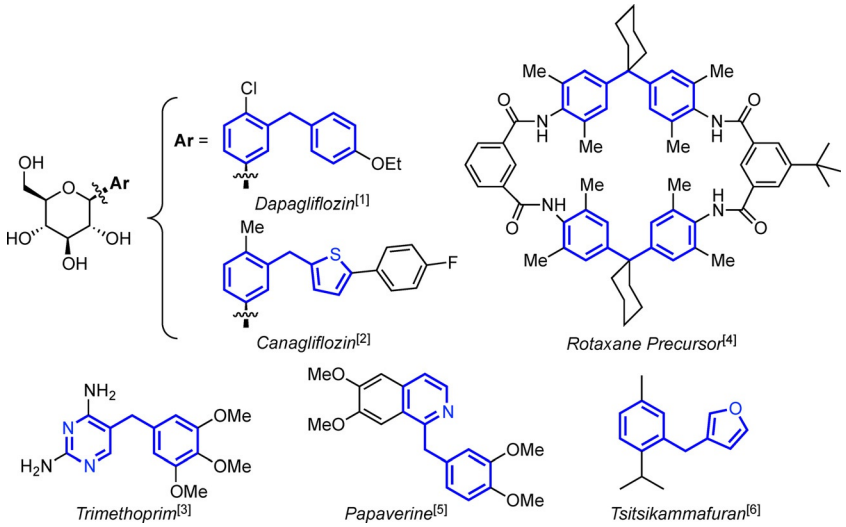

Figure 1. Structures of various diarylmethane-containing molecules.

Diarylmethanes are accessible through the reactions of arylboronic acids or aryltrifluoroborates with the easily accessed benzylic halides (bromides and chlorides, and to some extent iodides).[9–12] In most cases, reactions typically exemplify the reactivity of new catalytic systems.[10,11] Benzylic boronates, which can either be obtained by Pd-catalyzed reactions of benzylic halides with bis(pinacolato)diboron or pinacolborane[13] or produced in situ by reactions of aryl halides with diborylmethane,[14] and chiral secondary benzylic boro-

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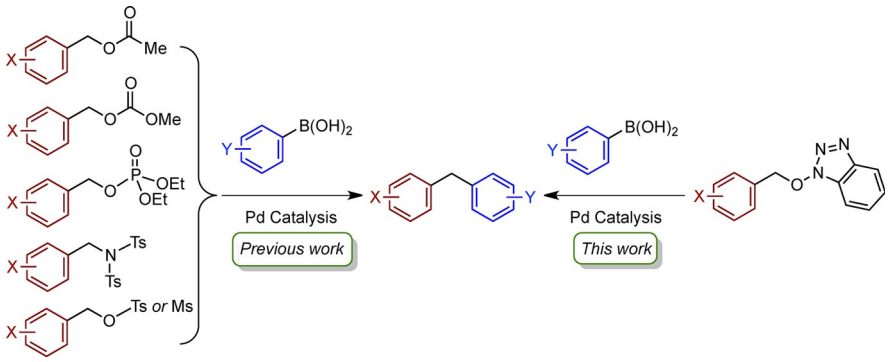
nates obtained by hydroboration are suitable precursors to diarylmethanes as well.[15]

Alternatives to reactive and moisture-sensitive benzylic halides have been investigated as the electrophilic coupling partners. Benzylic acetates,[16] carbonates,[17] phosphates,[18] and more recently *N*,*N*-ditosylbenzylamines[19] as well as benzylic tosylates and mesylates[20] have been employed successfully in Pd-mediated cross-couplings with arylboronic acids (Scheme 1). Benzylic pivalates and benzylic alcohols, respectively, undergo Ni- and Pd-catalyzed C–C cross-coupling with arylboroxines.[21,22] However, arylboroxines are not commercially available and have to be prepared from the corresponding boronic acids.[23]

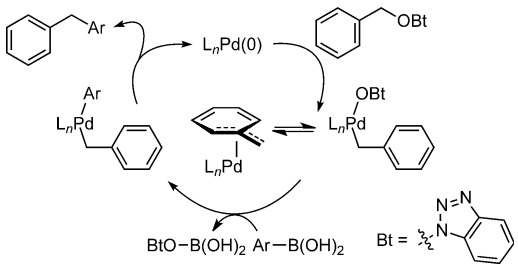


Scheme 1. Alternate substrates for C–C cross-coupling reactions with arylboronic acids.

We have investigated benzotriazole-based peptide coupling agents for nucleoside functionalization and other synthetic applications.[24] In this context, we showed that 1-alkoxy-1*H*-benzotriazoles (RCH(R′)OBt) are formed readily in reactions of alcohols with 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (BtOTs)[25] and (1*H*-benzotriazol-1-yloxy)tris(dimethylaminophosphonium) hexafluorophosphate (BOP).[26] Herein, we disclose the previously unknown reactivity of 1-(aryl)methoxy-1*H*-benzotriazoles in which a benzylic benzotriazolyloxy group acts as a nucleofuge in Pd-mediated C_{sp^3}–C_{sp^2} cross-couplings (Scheme 1).

Results and Discussion

To our knowledge, there are only two known Pd-mediated reactions of HOBt derivatives. One is an attempted decarboxylative Heck reaction of the benzoate ester of HOBt with styrene, which gave a 25% yield of 1,2 and 1,1 Heck arylation products.[27] The other is a Pd-mediated α-allylation of ketones using the cinnamyl ether of BtOH (PhCH=CHCH$_2$OBt).[26] The latter indicated the plausible formation of π-allyl Pd complexes, which led us to consider Pd-mediated C–C bond-forming reactions of 1-(aryl)methoxy-1*H*-benzotriazoles. Our proposal is based on the mechanistic rationale shown in Scheme 2, in which a σ complex that arises from the oxidative addition of ArCH$_2$OBt to a Pd catalyst could coexist with an η^3 complex.



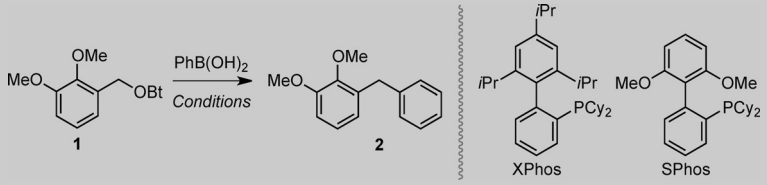
Scheme 2. Plausible mechanism for the C–C bond formation.

We selected $Pd(PPh_3)_4$, $Pd_2(dba)_3$,(dba = dibenzylideneacetone) and $Pd(OAc)_2$ as the metal sources and chose to evaluate the biarylphosphines 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) as ligands because they have been well documented to effect C–C reactions with boronic acids. Metal complexes from these bulky ligands have relatively high stability, with the likely formation of L_1Pd species, both of which are critical to catalytic efficiency. Of the two ligands, SPhos is superior for C–C bond formation.[28] With this background, initial reactions were conducted with 1-[(2,3-dimethoxybenzyl)oxy]-1*H*-benzotriazole (**1**), as a representative 1-(aryl)methoxy-1*H*-benzotriazole, and $PhB(OH)_2$, and the results are shown in Table 1.

The key observations from Table 1 are as follows. As hypothesized, both XPhos and SPhos give catalytic systems that provide high product formation in PhMe at 100 °C, and SPhos gave a faster reaction (entry 3 vs. 5). Cs_2CO_3 was effective but Ag_2O, which is known to accelerate boronic acid cross-coupling,[29] and the commonly useful CsF[30] were not (entries 3–7). Both K_3PO_4 and its hydrate gave incomplete reactions (entries 8 and 9), but K_3PO_4 with two equivalents of water gave a fast reaction and a high yield (entry 10). A decrease of the amount of ligand or the amount of $PhB(OH)_2$ decreased the product yield (entries 11 and 12). Boronic acid homocoupling,[31,32] which occurs in the presence of dissolved oxygen, may be one reason for the decrease in yield. No efforts were made to deoxygenate the reaction mixtures rigorously. MeCN in place of PhMe as the solvent was inferior (entry 13). Evidence that the reaction is not an uncatalyzed process comes from entry 14, in which $Pd(OAc)_2$ was omitted. Most notably, the reaction also proceeded with simple $Pd(PPh_3)_4$, which gave a good yield in a slightly longer reaction time compared to the reaction with SPhos (entry 15 vs. 10). The use of aqueous Na_2CO_3 resulted in a much slower reaction and a poorer yield (entry 16). $Ni(cod)_2$ (COD = cyclooctadiene) was ineffective (entries 17–19).

Based on these results, other biarylphosphine ligands were assessed for the reaction of **1** with $PhB(OH)_2$ under the condi-

Table 1. Conditions tested for the reaction of **1** and $PhB(OH)_2$.[a]



Entry	Catalyst	Ligand [mol%]	Base, additive	Time [h]	T [°C]	Result[b] [%]
1	$Pd_2(dba)_3$	XPhos (20)	Cs_2CO_3	14.5	RT	no reaction
2	$Pd(OAc)_2$	XPhos (20)	Cs_2CO_3	24	RT to 50	54
3	$Pd(OAc)_2$	XPhos (20)	Cs_2CO_3	18	100	**90**
4	$Pd(OAc)_2$	XPhos (20)	Ag_2O	22	100	no reaction
5	$Pd(OAc)_2$	SPhos (20)	Cs_2CO_3	5	100	**84**
6	$Pd(OAc)_2$	SPhos (20)	Ag_2O	22	100	no reaction
7	$Pd(OAc)_2$	SPhos (20)	CsF	18	100	incomplete[c]
8	$Pd(OAc)_2$	SPhos (20)	K_3PO_4	24	100	incomplete[c]
9	$Pd(OAc)_2$	SPhos (20)	$K_3PO_4 \cdot H_2O$	22	100	incomplete[c]
10	$Pd(OAc)_2$	SPhos (20)	K_3PO_4+2 equiv. H_2O	1	100	**88**
11	$Pd(OAc)_2$	SPhos (10)	K_3PO_4+2 equiv. H_2O	4	100	78
12	$Pd(OAc)_2$	SPhos (20)	K_3PO_4+2 equiv. H_2O	26	100	incomplete[c,d]
13	$Pd(OAc)_2$	SPhos (20)	K_3PO_4+2 equiv. H_2O	24	100	incomplete[c,e]
14	none	SPhos (20)	K_3PO_4+2 equiv. H_2O	26	100	no reaction
15	$Pd(PPh_3)_4$	none	K_3PO_4+2 equiv. H_2O	2	100	**83**
16	$Pd(PPh_3)_4$	none	0.2 M aq Na_2CO_3	26	100	57[f]
17	$Ni(cod)_2$	PPh_3 (30)	K_3PO_4+2 equiv. H_2O	16	100	no reaction
18	$Ni(cod)_2$	PCy_3 (30)	K_3PO_4+2 equiv. H_2O	26	100	no reaction
19	$Ni(cod)_2$	SPhos (20)	K_3PO_4+2 equiv. H_2O	16	100	no reaction

[a] Reactions were conducted with a 0.14 M solution of **1** in PhMe with 10 mol% of the Pd or Ni catalyst, 2 equiv. of $PhB(OH)_2$, and 2 equiv. of base. [b] If reported, the yield is of isolated and purified product. [c] Product formation was observed by TLC but unreacted **1** was present. [d] Reaction was conducted with 1.2 equiv. of $PhB(OH)_2$. [e] Reaction was conducted in MeCN. [f] Aqueous Na_2CO_3 was degassed.

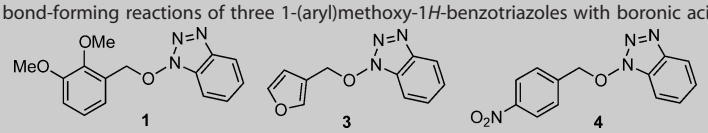
tions identified in entry 10 of Table 1. For this purpose, XPhos, SPhos, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos), 2-(dicyclohexylphosphino)biphenyl (CyJohnPhos), (2-biphenyl)di-*tert*-butylphosphine (JohnPhos), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), as well as 2-dicyclohexylphosphino-4′-(*N*,*N*-dimethylamino)biphenyl (Ligand 1) were selected for the second stage of the analysis. We have shown that Ligand 1, an isomer of DavePhos, has a different reactivity profile as well as interactions with $Pd(OAc)_2$ as compared to DavePhos.[33] The outcomes from the use of these related biaryl ligands are represented graphically in Scheme 3. In this analysis, catalysts supported by RuPhos and JohnPhos were less effective than those from XPhos and SPhos. DavePhos was comparable to XPhos, but CyJohnPhos and Ligand 1 performed comparably and were superior.

As all the biarylphosphine ligands tested yielded product with some notable differences, we wanted to rationalize their effectiveness in light of their relative bulk. The Tolman cone angle (θ)[34] is a classical measure of ligand sterics and, more recently, *percent buried volume* ($\%V_{bur}$) has been evaluated for a series of ligands, which includes the biarylphosphine ligands.[35] $\%V_{bur}$ indicates the spatial occupancy of a coordinated ligand, that is, the overall steric influence, around a metal center. As a result of the available data, we chose to compare the $\%V_{bur}$ for the ligands in a series of similar AuCl complexes (data for a uniform series of Pd complexes are unavailable). For this, the $\%V_{bur}$ values of the substituted biarylphosphines were compared with that of CyJohnPhos, which has the smallest $\%V_{bur}$ in the series (51.0% at 2.00 Å and 46.7% at 2.28 Å).[35] In this comparison, the $\%V_{bur}$ increased in the order XPhos > JohnPhos > SPhos (by ~13, ~9, and ~6%, respectively, over CyJohnPhos). DavePhos will likely have a smaller $\%V_{bur}$ than XPhos, but like the *i*Pr group in XPhos, DavePhos has a NMe_2 group in a similar location. Also, the amino group could pose other interactions with the metal center. In contrast to DavePhos, Ligand 1, which has a *para*-dimethylamino group, is expected to be sterically similar to CyJohnPhos but with a more electron-rich upper ring. Thus, it appears that a smaller $\%V_{bur}$ of the monocoordinating biarylphosphines may be more favorable for the reactions considered here, but the electron density in the upper ring appears to have less consequence, as seen from the comparable reactions of CyJohnPhos and Ligand 1. From this analysis, CyJohnPhos appeared to be suitable for further analysis combined with cost considerations (CyJohnPhos = $11.2 per mmol, SPhos = $20.3 per mmol, and Ligand 1 has only become available commercially recently at $56.40 per mmol).

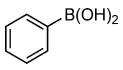
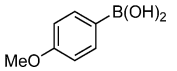
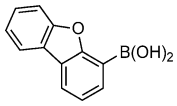
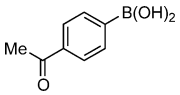
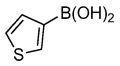
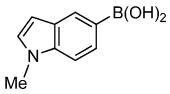
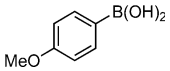
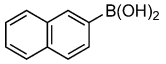
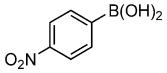
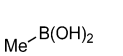
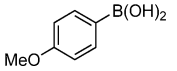
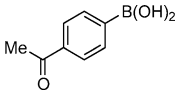
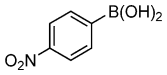
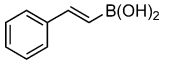
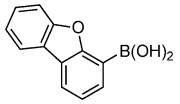
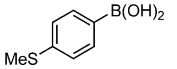
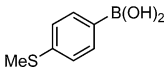
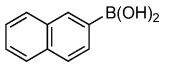
Next, a series of C–C bond-forming reactions were evaluated with three benzyloxy benzotriazoles; substrate **1** with an electron-rich aryl ring, substrate **2** with a heterocyclic ring, and substrate **3** with an electron-deficient aryl ring. The study also includes results from reduced catalyst loadings, and these data are summarized in Table 2.

Good to modest yields were obtained in most of these reactions and some reactions progressed respectably at lower Pd loadings as well (entries 7–10, 14–16). Yields of <40% were obtained in the reactions of **1** and **3** with *N*-methylindole-5-boronic acid and in the reaction of **3** with [(*E*)-2-phenylvinyl]-boronic acid (entries 6, 14, and 21). However, the desired products were obtained in these cases. Reactions of *p*-nitrophenylboronic acid were incomplete; with substrate **1** at a 2% Pd loading (entry 9) and with substrate **4** at a 10% Pd loading (entry 22) ≈30% yields were obtained. With furanyl substrate **3**, a 54% product yield was obtained despite an incomplete reaction (entry 13). Methylboronic acid underwent reaction with substrate **1** at a 5% Pd loading (entry 10) to give the ethyl derivative **12** in a respectable yield. This is a rare example of the cross-coupling of an alkylboronic acid with benzylic electro-

Table 2. C–C bond-forming reactions of three 1-(aryl)methoxy-1*H*-benzotriazoles with boronic acids.[a]



1 3 4

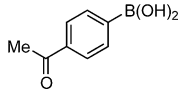
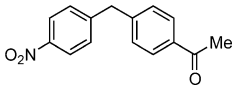
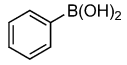
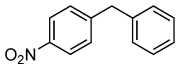
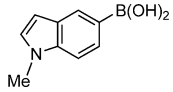
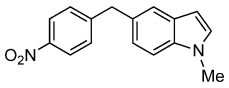
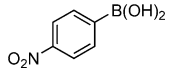
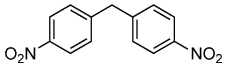
Entry	Boronic Acid	$ArCH_2OBt$	$Pd(OAc)_2$ [mol%]	Product	Time [h]	Yield[b] [%]
1[c]		**1**	10	**2**[36]	0.83	92
2[c]		**1**	10	**5**	0.83	90
3[c]		**1**	10	**6**	1.7	92
4[d]		**1**	10	**7**	14	57
5[e]		**1**	10	**8**	16	44[f]
6[c]		**1**	10	**9**	16	25
7[c]		**1**	2	**5**	4.5	93
8[c]		**1**	2	**10**	2	64
9[g]		**1**	2	**11**	16	29[f]
10[h]		**1**	5	**12**[37]	14	44
11[e]		**3**	10	**13**[38]	0.83	95
12[i]		**3**	10	**14**	12	64
13[e]		**3**	10	**15**[39]	19	54[f]
14[c]		**3**	2	**16**	3.5	36
15[c]		**3**	2	**17**	3.5	89
16[c]		**3**	2	**18**	5	80
17[e]		**4**	10	**19**[40]	1	91
18[e]		**4**	10	**20**[41]	1.5	88

philes. However, the reaction of 2-phenylethaneboronic acid with **1** did not provide a product, possibly because of β-hydride elimination problems. In the reaction of 1-(1-phenylethoxy)-1*H*-benzotriazole ($PhCH(CH_3)OBt$), which contains a 2° reactive center, the formation of styrene was observed by TLC. Such an outcome was noted previously in the reaction of 1-bromoethylbenzene with potassium (*p*-methoxyphenyl)trifluoroborate[12b] and in the reaction of the corresponding phosphate with phenylboronic acid.[18] The use of XPhos or SPhos did not ameliorate this problem.

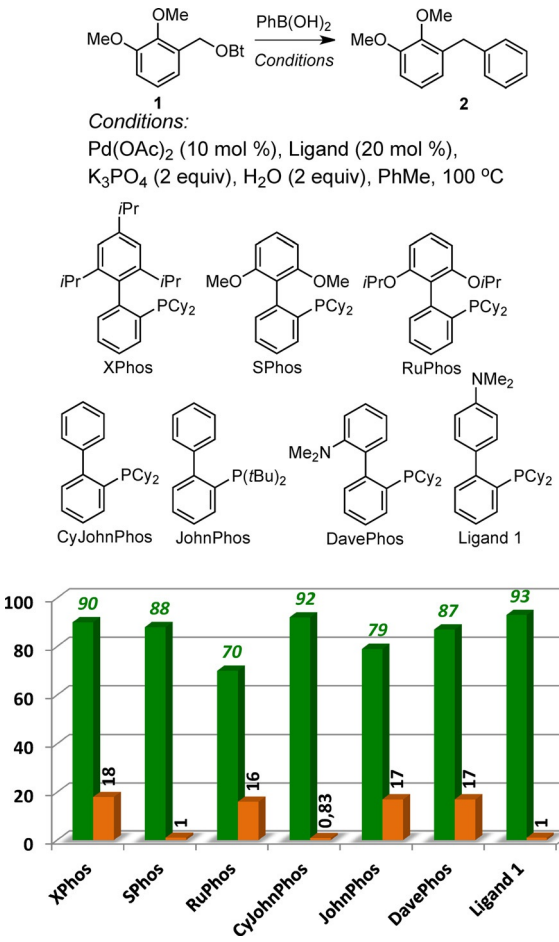
One other observation during these experiments was the formation of palladium black in the reactions of *p*-nitrophenylboronic acid, which did not reach completion. This also occurred to varying extents in other reactions although they reached completion. The use of the electron-rich 2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl (BrettPhos), decreased reaction temperatures, and other solvents did not produce a major change in the outcome. Thus, we decided to test a biscoordinating ligand and chose bis[(2-diphenylphosphino)phenyl] ether (DPEPhos), which has been useful for the cross-coupling of arylboronic acids with two different electrophilic coupling partners; benzylic acetates and *N*,*N*-ditosylbenzylamines.[16,19] To evaluate the utility of this bidentate ligand, two low-yielding reactions of *p*-nitrophenylboronic acid were chosen for further analysis (Scheme 4).

The combination of $Pd(OAc)_2$ and DPEPhos gave twofold yield improvements in both reactions that involve a boronic acid, which is expected to undergo slow transmetalation (isolated yields of purified products were >65%). In the reaction of substrate **1**, the formation of some 2,3-dimethoxybenzaldehyde was observed

Table 2. (Continued)

Entry	Boronic Acid	$ArCH_2OBt$	$Pd(OAc)_2$ [mol%]	Product	Time [h]	Yield[b] [%]
19[d]		**4**	10	 **21**[42]	14	51
20[c]		**4**	10	 **22**[43]	0.83	40
21[d]		**4**	10	 **23**	5	35
22[e]		**4**	10	 **24**[44]	24	30[f]

[a] Reactions were conducted with a 1:2 ratio of $Pd(OAc)_2$/CyJohnPhos, 2 equiv. of the boronic acid (except in entries 4 and 19 where 3.3 equiv. were used), 2 equiv. K_3PO_4, and 2 equiv. H_2O, in PhMe at 100 °C. [b] Yields shown are of isolated and purified products. [c] Reaction was performed with 0.7 mmol of the $ArCH_2OBt$. [d] Reaction was performed with 0.25 mmol of the $ArCH_2OBt$. [e] Reaction was performed with 0.07 mmol of the $ArCH_2OBt$. [f] Reaction was incomplete and the $ArCH_2OBt$ was still present. [g] Reaction was performed with 0.4 mmol of the $ArCH_2OBt$. [h] Reaction was performed with 0.5 mmol of the $ArCH_2OBt$. [i] Reaction was performed with 0.2 mmol of the $ArCH_2OBt$.



Scheme 3. Comparison of the cross-coupling of **1** and $PhB(OH)_2$ using several biarylphosphine ligands. The green bars represent the yields of isolated, purified products [%], and the orange bars show the reaction times [h].

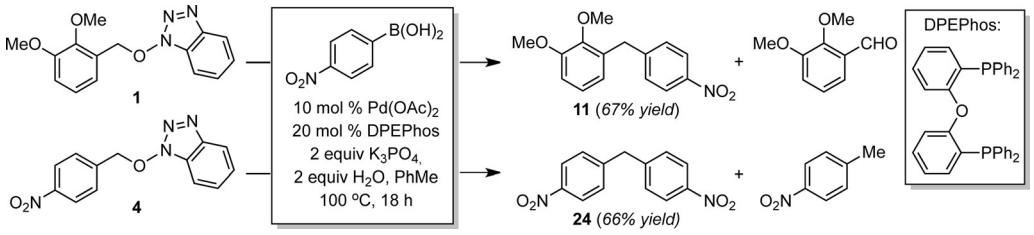
by TLC and ^1H NMR spectroscopy. This product may arise from the oxidative addition of the N–O bond in the $ArCH_2OBt$ to Pd followed by β-hydride elimination. In the reaction of substrate **4**, one fraction that contained the product and *p*-nitrotoluene was isolated separately, which indicates a process apparently similar to protio-dehalogenation observed in the cross-coupling of aryl halides.

In the consideration of previously reported C–C bond-forming reactions of benzylic acetates, carbonates, phosphates, and *N*,*N*-ditosylbenzylamines reported previously, the most effective catalytic systems involved complexes of Pd with DPEPhos, 1,5-bis(diphenylphosphino)pentane (DPPpent), and PPh_3, and DPEPhos, respectively.[16–19] Here again, the $\%V_{bur}$ of the ligands in AuCl complexes are known. For DPEPhos it is 45.3% (at 2.00 Å) and 41.3% (at 2.28 Å), for DPPpent it is 33.3% (at 2.00 Å) and 28.4% (at 2.28 Å), and for PPh_3 it is 34.8% (at 2.00 Å) and 29.9% (at 2.28 Å).[35] From these data and our present results with the biarylphosphines, it appears that in addition to various reaction parameters such as solvent, base, temperature, etc., these types of benzylic C–C cross-coupling reactions may benefit from the use of Pd catalysts in which the ligands have a relatively small $\%V_{bur}$, from ≈50% for CyJohnPhos to even smaller values with DPPpent and PPh_3 (determined from the corresponding AuCl complexes). We note, however, the correlation with $\%V_{bur}$ is only a proposal, which we hope will assist catalyst selection. Bidentate ligands, such as DPEPhos, may offer additional advantages.

Atom economy (AE) considerations offer an interesting comparison of these types of C–C reactions. The AEs were evaluated for the cross-couplings of $PhB(OH)_2$ with various benzyl electrophiles, which lead to diphenylmethane. Benzyl chloride and benzyl acetate have the highest AEs of 68 and 62%, respectively. This is followed by benzyl carbonate and benzyl bromide, with comparable values of 58 and 57%, respectively. Next in this comparison are benzyl iodide and 1-benzyloxy-1*H*-benzotriazole, which have comparable AEs of 49 and 48%, respectively. The AEs for benzyl phosphate and benzyl tosylate are similar at 46 and 45%, respectively, and finally that of *N*,*N*-ditosylbenzylamine is 33%.

Conclusions

We have shown the reactivity of 1-(aryl)methoxy-1*H*-benzotriazoles ($ArCH_2OBt$) in Pd-catalyzed C–C bond-forming reactions with arylboronic acids that was unknown previously. The C–O bond in these compounds undergoes bond scission under the



Scheme 4. Reactions of two 1-(aryl)methoxy-1*H*-benzotriazoles with *p*-nitrophenylboronic acid catalyzed by $Pd(OAc)_2$/DPEPhos.

conditions, and the benzotriazolyloxy unit acts as the leaving group. Biarylphosphine ligands provide catalysts with varying reactivities. In the reactions of 1-[(2,3-dimethoxybenzyl)oxy]-1*H*-benzotriazole (**1**) with $PhB(OH)_2$, 2-(dicyclohexylphosphino)-biphenyl, and 2-dicyclohexylphosphino-4′-(*N*,*N*-dimethylamino)biphenyl provided fast reactions with high yields. Thus, 2-(dicyclohexylphosphino)biphenyl was tested in a broader range of reactions. Several reactions proceeded well with a reduced catalyst loading. If the steric properties of the biarylphosphine ligands are considered, it appears that those with smaller *percent buried volumes* ($\%V_{bur}$) may be more suitable for such reactions. This seems to correlate with other Pd-catalyzed reactions of benzylic acetates, carbonates, phosphates, and *N*,*N*-ditosylbenzylamines, in which bis[(2-diphenylphosphino)phenyl] ether, 1,5-bis(diphenylphosphino)pentane, and PPh_3 supported effective catalysts. These preliminary results on the Pd-catalyzed reactions of 1-(aryl)methoxy-1*H*-benzotriazoles could open new investigational avenues; for example, in reactions with other boron derivatives, in other types of cross-coupling reactions, and in the evaluation of new catalytic systems. Finally, the facile methylation of a benzotriazole N atom has recently proven to be important for nucleophilic substitution reactions of a α-(benzotriazolyloxy)ketone, whereas no progress was observed without such activation.[45] Therefore, further activation of 1-(aryl)methoxy-1*H*-benzotriazoles for cross-coupling, which could possibly lead to reactions at lower temperatures and/or with lowered catalyst loading, appear to be possible. Results from such investigations can be anticipated in our future work.

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