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

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Abstract

1-(Aryl)methoxy-1*H*-benzotriazoles (ArCH₂OBt) are bench-stable reagents that are prepared readily from 1*H*-benzotriazol-1-yl-4-methylbenzenesulfonate (BtOTs) 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 ArCH₂OBt derivatives, leading to diarylmethanes, has not been described previously and constitutes a new activation of benzylic alcohols. With regard to the various ligands-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 bis-coordinating bis[(2-diphenylphosphino)phenyl]ether appears to be suitable to improve the yields of low-yielding reactions.

Keywords

Pd catalysis; phosphine ligands; boronic acid; benzotriazole; C_{sp}³–C_{sp}² cross-coupling

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] reduction of diarylketones^[7c–e] as well as diaryl carbinols,^[7f] and 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

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methods, Pd-catalyzed C–C cross coupling with boronic acids as the nucleophilic component^[8] has manifold advantages, such as 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.

Diarylmethanes are accessible through 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 boronates 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 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]

We have been investigating 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-yl-4-methoxy)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=CHCH₂OBt).^[26] The latter indicated the plausible formation of π -allyl Pd complexes, which lead 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 ArCH₂OBt to a Pd catalyst could coexist with an η^3 complex.

We selected Pd(PPh₃)₄, Pd₂(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 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 $PhB(OH)_2$. These results are shown in Table 1.

The key observations from Table 1 are as follows. As hypothesized, both XPhos and SPhos gave catalytic systems that provide high product formation in PhMe at 100 °C, and SPhos gave a faster reaction (entry 3 vs. entry 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 (see 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 as compared to the reaction with SPhos (entry 15 vs. entry 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 conditions 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 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 appeared 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 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 among a series of similar AuCl complexes (data for a uniform series of Pd complexes are unavailable). For this, the % V_{bur} 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 iPr group in XPhos, Davephos has a NMe₂ 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, Ligand 1 has only recently become available commercially 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 of these reactions progressed respectably at lowered Pd loadings as well (see 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) *ca.* 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 electrophiles. However, 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(CH₃)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] 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. Use of the electron-rich 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6',-trimethoxy (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 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**, formation of some 2,3-dimethoxybenzaldehyde was observed by TLC and ¹H NMR spectroscopy. This product may arise from the oxidative-addition of the N–O bond in the ArCH₂OBt 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, indicating a process apparently similar to protio-dehalogenation observed in the cross coupling of aryl halides.

In the consideration of 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), PPh₃, 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 PPh₃ 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 use of Pd catalysts in which the ligands have a relatively small % V_{bur} , from *ca.* 50% for CyJohnPhos to even smaller values with DPPent and PPh₃ (determined from the corresponding AuCl complexes). We note, however, that 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) consideration 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 benzylic 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, with 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 (ArCH₂OBt) 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 conditions, with the benzotriazolyl unit acting 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 as well as 2-dicyclohexylphosphino-4'-(*N,N*-dimethylamino)biphenyl provided fast, high-yielding reactions. 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 where bis[(2-diphenylphosphino)phenyl]ether, 1,5-bis(diphenylphosphinopentane), and PPh₃ supported effective catalysts. These preliminary results on the Pd catalyzed reactions of 1-(aryl)methoxy-1*H*-benzotriazoles can possibly 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, it is interesting to note that facile methylation of a benzotriazole nitrogen atom has recently proven important for nucleophilic substitution reactions of a α -(benzotriazolyl)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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of various diarylmethane-containing molecules.

Scheme 1.

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

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

Scheme 3.

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

Scheme 4.

Reactions of two 1-(aryl)methoxy-1*H*-benzotriazoles with *p*-nitrophenylboronic acid catalyzed by Pd(OAc)₂/DPEPhos.

Table 1

Conditions tested for the reaction of **1** and PhB(OH)₂.^[a]

Entry	Catalyst	Ligand (mol %)	Base, additive	Time, T °C	Result ^[b]
1	Pd ₂ (dba) ₃	XPhos (20)	Cs ₂ CO ₃	14.5 h, rt	No reaction
2	Pd(OAc) ₂	XPhos (20)	Cs ₂ CO ₃	24 h, rt to 50 °C	54%
3	Pd(OAc) ₂	XPhos (20)	Cs ₂ CO ₃	18 h, 100 °C	90%
4	Pd(OAc) ₂	XPhos (20)	Ag ₂ O	22 h, 100 °C	No reaction
5	Pd(OAc) ₂	SPhos (20)	Cs ₂ CO ₃	5 h, 100 °C	84%
6	Pd(OAc) ₂	SPhos (20)	Ag ₂ O	22 h, 100 °C	No reaction
7	Pd(OAc) ₂	SPhos (20)	CsF	18 h, 100 °C	Incomplete ^[c]
8	Pd(OAc) ₂	SPhos (20)	K ₃ PO ₄	24 h, 100 °C	Incomplete ^[c]
9	Pd(OAc) ₂	SPhos (20)	K ₃ PO ₄ •H ₂ O	22 h, 100 °C	Incomplete ^[c]
10	Pd(OAc) ₂	SPhos (20)	K ₃ PO ₄ + 2 eq H ₂ O	1 h, 100 °C	88%
11	Pd(OAc) ₂	SPhos (10)	K ₃ PO ₄ + 2 eq H ₂ O	4 h, 100 °C	78%
12	Pd(OAc) ₂	SPhos (20)	K ₃ PO ₄ + 2 eq H ₂ O	26 h, 100 °C	Incomplete ^[c,d]
13	Pd(OAc) ₂	SPhos (20)	K ₃ PO ₄ + 2 eq H ₂ O	24 h, 100 °C	Incomplete ^[c,e]
14	None	SPhos (20)	K ₃ PO ₄ + 2 eq H ₂ O	26 h, 100 °C	No reaction
15	Pd(PPh ₃) ₄	None	K ₃ PO ₄ + 2 eq H ₂ O	2.5 h, 100 °C	83%
16	Pd(PPh ₃) ₄	None	0.2 M aq Na ₂ CO ₃	26 h, 100 °C	57% ^[f]
17	Ni(COD) ₂	PPh ₃ (30)	K ₃ PO ₄ + 2 eq H ₂ O	16 h, 100 °C	No reaction
18	Ni(COD) ₂	PCy ₃ (30)	K ₃ PO ₄ + 2 eq H ₂ O	26 h, 100 °C	No reaction
19	Ni(COD) ₂	SPhos (20)	K ₃ PO ₄ + 2 eq H ₂ O	16 h, 100 °C	No reaction

^[a]Reactions were conducted with a 0.14 M solution of compound **1** in PhMe with 10 mol % of the Pd or Ni catalyst, 2 equiv of PhB(OH)₂, and 2 equiv of base.

^[b]Where reported, 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 Na₂CO₃ was degassed.

Table 2

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

Entry	Boronic Acid	ArCH ₂ OBt	Pd(OAc) ₂	Product	Time, yield ^[b]
1 ^[c]			10 mol %		0.83 h 2 ^[36] : 92%
2 ^[c]			10 mol %		0.83 h 5: 90%
3 ^[c]			10 mol %		1.7 h 6: 92%
4 ^[d]			10 mol %		14 h 7: 57%
5 ^[e]			10 mol %		16 h 8: 44% ^[f]

Entry	Boronic Acid	ArCH ₂ OBt	Pd(OAc) ₂	Product	Time, yield ^[b]
6 ^[c]			10 mol %		16 h 9 : 25%
7 ^[c]		1	2 mol %		4.5 h 5 : 93%
8 ^[c]		1	2 mol %		2 h 10 : 64%
9 ^[g]		1	2 mol %		16 h 11 : 29% ^[f]
10 ^[h]		1	5 mol %		14 h 12 ^[37] : 44%
11 ^[c]		3	10 mol %		0.83 h 13 ^[38] : 95%
12 ^[f]		3	10 mol %		12 h 14 : 64%

Entry	Boronic Acid	Ar-CH ₂ OBt	Pd(OAc) ₂	Product	Time, yield ^{d/b/}
13 ^[c]			10 mol %		19 h 15 ^[39] ; 54% ^[f]
14 ^[c]			2 mol %		3.5 h 16 ; 36%
15 ^[c]			2 mol %		3.5 h 17 ; 89%
16 ^[c]			2 mol %		5 h 18 ; 80%
17 ^[e]			10 mol %		1 h 19 ^[40] ; 91%
18 ^[c]			10 mol %		1.5 h 20 ^[41] ; 88%
19 ^[d]			10 mol %		14 h 21 ^[42] ; 51%
20 ^[c]			10 mol %		0.83 h 22 ^[43] ; 40%

Entry	Boronic Acid	ArCH ₂ OBt	Pd(OAc) ₂	Product	Time, yield ^[b]
21 ^[d]		4	10 mol %		5 h 23 : 35%
22 ^[e]		4	10 mol %		24 h 24 ^[44] : 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. K₃PO₄, and 2 equiv. H₂O, in PhMe at 100 °C.

^[b] Yields shown are of isolated and purified products.

^[c] Reaction was performed with 0.7 mmol of the ArCH₂OBt.

^[d] Reaction was performed with 0.25 mmol of the ArCH₂OBt.

^[e] Reaction was performed with 0.07 mmol of the ArCH₂OBt.

^[f] Reaction was incomplete and the ArCH₂OBt was still present.

^[g] Reaction was performed with 0.4 mmol of the ArCH₂OBt.

^[h] Reaction was performed with 0.5 mmol of the ArCH₂OBt.

^[i] Reaction was performed with 0.2 mmol of the ArCH₂OBt.