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Pd-catalyzed atom-efficient cross-coupling of triarylbismuth reagents with protecting group-free iodophenylmethanols: Synthesis of biarylmethanols

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ABSTRACT

An atom-efficient procedure for the synthesis of functionalized biarylmethanols *via* the Pd-catalyzed cross-coupling reactions of differently functionalized iodophenylmethanols and triarylbismuth reagents is described. This protecting group-free direct couplings of 2-, 3- or 4-iodophenylmethanols with triarylbismuth reagents afforded biarylmethanols in good to high yields.

Functionalized biaryls are significant scaffolds prevalent in several pharmaceuticals and natural products leading to the development of several new approaches for their synthesis [1,2]. In particular, the alcohol functionality in these skeletons allows easy modification to other desired functional groups. It also serves as an alternative electrophile for C—C bond formations [3]. Importantly, limited synthetic methods, including cross-coupling approaches, have been reported for the synthesis of biarylmethanols [4]. The development of atom-economic cross-coupling methods using triarylbismuth reagents as threefold organometallic coupling partners is an ongoing interest [5–7]. It led to the present study of utilising protecting group-free cross-couplings of iodophenylmethanols with triarylbismuth reagents under Pd-catalyzed conditions for the synthesis of biarylmethanols. This effort is in continuation of our interest in developing atom-economic cross-coupling methods using triarylbismuth reagents under Pd-catalyzed conditions [5,6].

Our investigation to develop an efficient method for the synthesis of substituted biarylmethanols was carried out using protecting group-free 2-iodophenylmethanol **1a** in the cross-coupling reaction with Bi(p-tolyl)$_3$ under Pd-catalyzed conditions. These results are summarized in Table 1. The proposed cross-coupling reaction was initially screened with different Pd-catalytic systems using KOAc in NMP (Table 1, entries 1–4). This resulted in the development of Pd(OAc)$_2$/P(o-tolyl)$_3$ as a more efficient system to deliver the desired biarylmethanol **2a** in 74% yield (Table 1, entry 4).

Other catalytic systems including Pd(OAc)$_2$/PPh$_3$, PdCl$_2$(PPh$_3$)$_2$, and Pd(PPh$_3$)$_4$ gave **2a** in 64–68% yield (Table 1, entries 1–3). The desired coupling reaction was further screened in different solvents including DMA, DMF, and DMSO (Table 1, entries 5–7). These solvents provided product **2a** in 60–71% yield. Hence, further screening was carried out in NMP with different bases (Table 1, entries 8–10). However, the use of different bases did not provide higher yields in comparison to the yield obtained with KOAc (Table 1, entry 4). At this stage, we screened the coupling with 4 equiv. of KOAc which gave **2a** in 44% yield (Table 1, entry 11). The control reaction carried out without catalyst and base resulted in no cross-coupling product (Table 1, entry 12). The above screening thus provided the standard protocol with Pd(OAc)$_2$ (0.1 equiv.), P(o-tolyl)$_3$ (0.4 equiv.), KOAc (6 equiv.), TBAB (3 equiv.), NMP (3 mL) at 110 °C for 4 h (Table 1, entry 4) to deliver biarylmethanol **2a** in high yield.

Under these established conditions, the threefold coupling of various triarylbismuth reagents was tested with 2-iodophenylmethanol **1a** and the results are given in Table 2. The cross-couplings with Bi(p-tolyl)$_3$ and Bi(m-tolyl)$_3$ reagents proceeded efficiently to give the corresponding biarylmethanols **2a** and **2d** in 74% and 85% yield, respectively. Similarly, triphenylbismuth also reacted well to give biphenylmethanol **2b** in 84% yield. Further cross-couplings with Bi(p-anisyl)$_3$ and Bi(m-anisyl)$_3$ gave biarylmethanols **2c** and **2e** in 82% and 84% yield, respectively. Other

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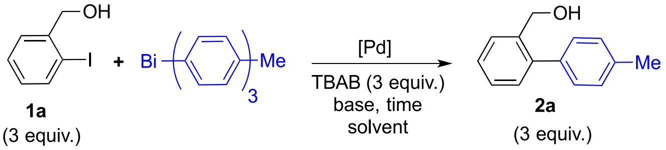
Table 1
Screening with 2-iodophenylmethanol (**1a**).[a,b,c,d]

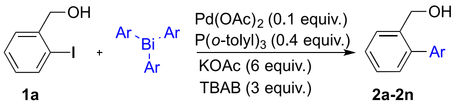


1a
(3 equiv.)
2a
(3 equiv.)

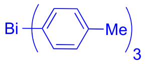
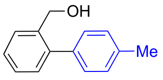
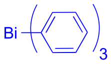
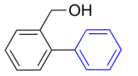
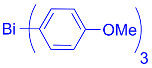
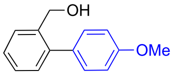
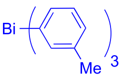
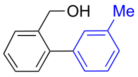
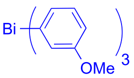
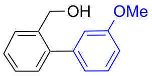
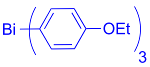
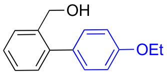
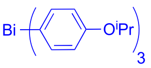
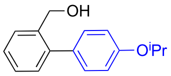
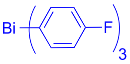
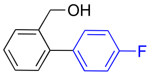
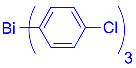
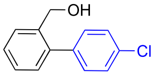
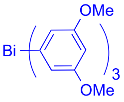
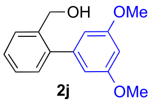
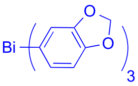
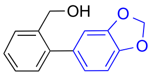
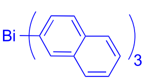
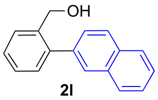
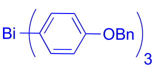
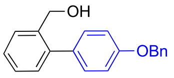
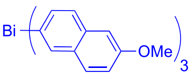
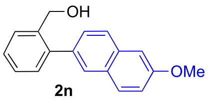
Entry	Catalyst/Ligand	Base	Solvent	Yield **2a** (%)
1	$Pd(OAc)_2/PPh_3$	KOAc	NMP	64
2	$PdCl_2(PPh_3)_2$	KOAc	NMP	66
3	$Pd(PPh_3)_4$	KOAc	NMP	68
4	$Pd(OAc)_2/P(o\text{-tolyl})_3$	KOAc	NMP	74
5	$Pd(OAc)_2/P(o\text{-tolyl})_3$	KOAc	DMA	60
6	$Pd(OAc)_2/P(o\text{-tolyl})_3$	KOAc	DMF	71
7	$Pd(OAc)_2/P(o\text{-tolyl})_3$	KOAc	DMSO	63
8	$Pd(OAc)_2/P(o\text{-tolyl})_3$	K_3PO_4	NMP	61
9	$Pd(OAc)_2/P(o\text{-tolyl})_3$	K_2CO_3	NMP	52
10	$Pd(OAc)_2/P(o\text{-tolyl})_3$	Cs_2CO_3	NMP	65
11	$Pd(OAc)_2/P(o\text{-tolyl})_3$	KOAc	NMP	44[d]
12	–	–	NMP	–

[a] Reagents and conditions: **1a** (0.75 mmol, 3 equiv.), Bi(*p*-tolyl)$_3$ (0.25 mmol, 1 equiv.), Pd catalyst (0.025 mmol, 0.1 equiv.), ligand (0.1 mmol, 0.4 equiv.), base (6 equiv.), TBAB (3 equiv.), 110 °C, 4 h, solvent (3 mL).
[b] Isolated yield.
[c] Homo-coupled bitolyl from Bi(*p*-tolyl)$_3$ was obtained in minor amounts.
[d] KOAc (4 equiv.).

Table 2
Couplings of 2-iodophenylmethanol (**1a**) with BiAr$_3$ reagents.[a,b,c]



1a
(3 equiv.)
2a-2n
(3 equiv.)

Entry	Triarylbismuths	Products	Yield (%)[b]
1		 **2a**	74%
2		 **2b**	84%
3		 **2c**	82%
4		 **2d**	85%
5		 **2e**	84%
6		 **2f**	88%
7		 **2g**	85%
8		 **2h**	63%
9		 **2i**	59%
10		 **2j**	85%
11		 **2k**	75%
12		 **2l**	72%
13		 **2m**	75%
14		 **2n**	70%

[a] Reagents and conditions: **1a** (0.75 mmol, 3 equiv.), BiAr$_3$ (0.25 mmol, 1 equiv.), Pd(OAc)$_2$ (0.025 mmol, 0.1 equiv.), P(*o*-tolyl)$_3$ (0.1 mmol, 0.4 equiv.), KOAc (1.5 mmol, 6 equiv.), TBAB (0.75 mmol, 3 equiv.), NMP, 110 °C, 4 h.
[b] Isolated yields.
[c] Homo-coupled biaryls from BiAr$_3$ were obtained in minor amounts.

triarylbismuth reagents with different aryl and alkoxy substituents gave the corresponding biarylmethanols **2f**, **2g**, **2j**, **2k-2n** in 70–88% yield. Further study of triarylbismuth reagents with 4-fluoro and 4-chloro functionality afforded the corresponding biarylmethanols **2h** and **2i** in 63% and 59% yield, respectively. Thus, the threefold cross-coupling of 1 equiv. of triarylbismuth reagents with 3 equiv. of **1a** gave different functionalized biarylmethanols in good to high yields.

We further explored the protecting group-free cross-coupling of 3-iodophenylmethanol **1b** with different triarylbismuth reagents under the above Pd-catalyzed conditions (Table 3). The initial coupling of 3-iodophenylmethanol **1b** with triphenylbismuth gave the corresponding biarylmethanol **3a** in 81% yield. Other cross-couplings performed using electron-rich triarylbismuth reagents with 4-methyl, 4-methoxy, 3-methoxy, and 4-benzyloxy groups afforded differently functionalized biarylmethanols **3b-3e** in 74–84% yield. The cross-coupling carried out with a 4-fluoro functionalized triarylbismuth reagent gave biarylmethanol **3f** in 77% yield. Also, the cross-couplings of trinaphthalen-2-ylbismuth and tris(benzo[*d*][1,3]dioxol-5-yl)bismuthane furnished biarylmethanols **3g** and **3h** in 85% and 74% yield, respectively.

Next, we studied the protecting group-free cross-coupling of 4-iodophenyl-methanol (**1c**) with different triarylbismuth reagents under the above Pd-catalyzed conditions (Table 4). The cross-coupling of 4-iodophenylmethanol **1c** with triphenylbismuth afforded biarylmethanol **4a** in 85% yield. Subsequent couplings of 4-iodophenylmethanol with electron-rich triarylbismuth reagents functionalized with 4-methyl, 4-methoxy, 3-methoxy, 4-ethoxy, 4-isoproxy, and 3,5-dimethoxy groups gave the corresponding biarylmethanols **4b-4g** in 78–91% yield. Similarly, the coupling reaction of tri(naphthalen-2-yl)bismuth also proved to be efficient giving the corresponding biarylmethanol **4h** in 75% yield.

To further expand the general synthetic scope, a few reactions were carried out with differently functionalized iodophenylmethanols such as 2-iodo-3,4,5-trimethoxyphenylmethanol (**1d**), 5-iodo-2-methoxyphenyl-methanol (**1e**) and

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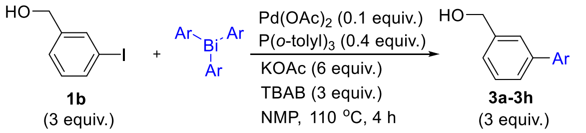
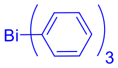
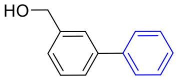
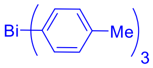
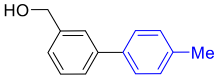
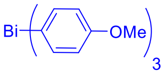
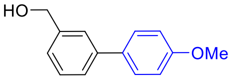
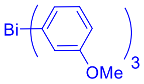
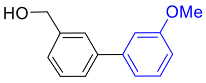
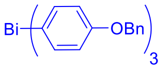
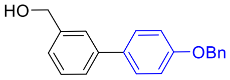
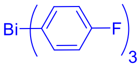
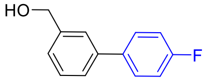
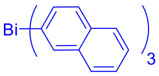
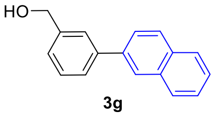
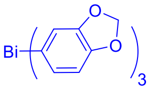
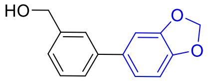
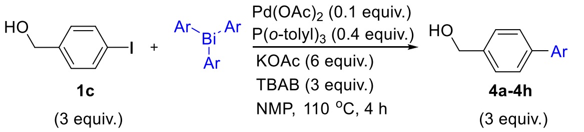
Table 3
Couplings of 3-iodophenylmethanol **1b** with $BiAr_3$ reagents.[a,b,c]

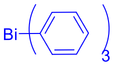
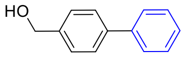
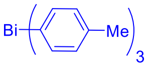
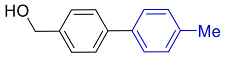
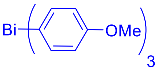
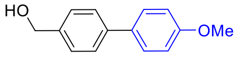
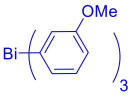
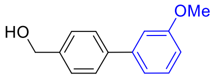
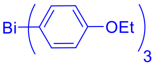
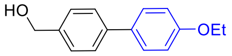
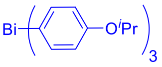
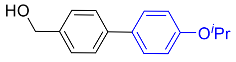
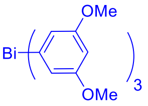
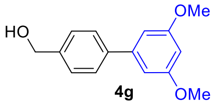
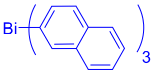
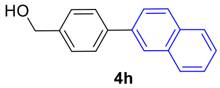


Entry	Triarylbismuths	Products	Yield (%)[b]
1		 **3a**	81%
2		 **3b**	83%
3		 **3c**	84%
4		 **3d**	82%
5		 **3e**	74%
6		 **3f**	77%
7		 **3g**	85%
8		 **3h**	74%

[a] Reagents and conditions: **1b** (0.75 mmol, 3 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv.), P(o-tolyl)$_3$ (0.1 mmol, 0.4 equiv.), KOAc (1.5 mmol, 6 equiv.), TBAB (0.75 mmol, 3 equiv.), NMP, 110 °C, 4 h.
[b] Isolated yields.
[c] Homo-coupled biaryls from $BiAr_3$ were obtained in minor amounts.

Table 4
Couplings of 4-iodophenylmethanol **1c** with $BiAr_3$ reagents.[a,b,c]



Entry	Triarylbismuths	Products	Yield (%)[b]
1		 **4a**	85%
2		 **4b**	78%
3		 **4c**	87%
4		 **4d**	84%
5		 **4e**	85%
6		 **4f**	91%
7		 **4g**	85%
8		 **4h**	75%

[a] Reagents and conditions: **1c** (0.75 mmol, 3 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv.), P(o-tolyl)$_3$ (0.1 mmol, 0.4 equiv.), KOAc (1.5 mmol, 6 equiv.), TBAB (0.75 mmol, 3 equiv.), NMP, 110 °C, 4 h.
[b] Isolated yields.
[c] Homo-coupled biaryls from $BiAr_3$ were obtained in minor amounts.

3-iodo-4-methoxyphenylmethanol (**1f**) and different triarylbismuth reagents under the above Pd-catalyzed conditions (Table 5).

These studies afforded the corresponding functionalized biarylmethanols **5a-5d** in good to excellent yields. It is important to note that product **5b** is a well-known precursor for the synthesis of eupomatilone [8].

This study thus established the general cross-coupling ability of protecting group-free 2-iodo, 3-iodo and 4-iodophenyl-methanols in threefold coupling reactions with different triarylbismuth reagents under Pd-coupling conditions. The established conditions proved to be very efficient as demonstrated by the generalized cross-couplings with differently substituted iodophenylmethanols [4].

In summary, a convenient method was established for the atom-efficient synthesis of differently functionalized biarylmethanols *via* the cross-couplings of different iodophenylmethanols and triarylbismuth reagents. These reactions involving threefold couplings from triarylbismuth reagents afforded functionalized biarylmethanols in good to high yields [9]. The direct cross-couplings carried out with iodophenylmethanols without invoking alcoholic group protection/deprotection protocols for the synthesis of biarylmethanols under palladium coupling conditions is noteworthy and is expected to be highly useful in organic synthesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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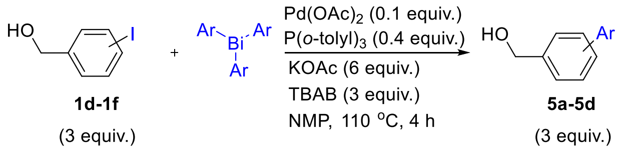
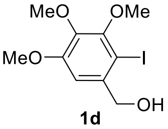
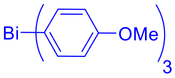
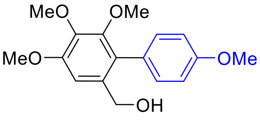
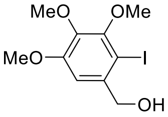
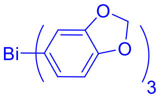
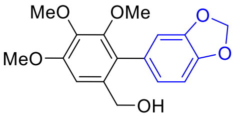
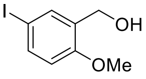
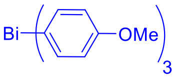
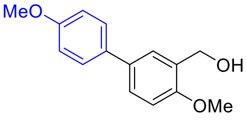
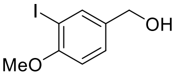
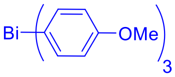
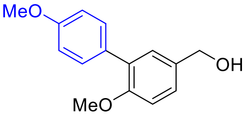
Table 5
Couplings of substituted iodophenylmethanols with $BiAr_3$ reagents.[a,b,c]


1d-1f (3 equiv.)

5a-5d (3 equiv.)

Entry	Substrate	Triarylbismuths	Products	Yield (%)[b]
1	 **1d**		 **5a**	83%
2	 **1d**		 **5b**	76%
3	 **1e**		 **5c**	71%
4	 **1f**		 **5d**	75%

[a] Reagents and conditions: **1d/1e/1f** (0.75 mmol, 3 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv.), P(o-tolyl)$_3$ (0.1 mmol, 0.4 equiv.), KOAc (1.5 mmol, 6 equiv.), TBAB (0.75 mmol, 3 equiv.), NMP, 110 °C, 4 h.

[b] Isolated yields.

[c] Homo-coupled biaryls from $BiAr_3$ were obtained in minor amounts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151676.

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[9] Representative cross-coupling procedure: Cross-coupling of **1a** with Bi(p-tolyl)$_3$: An oven-dried Schlenk tube was charged with (2-iodophenyl) methanol (**1a**) (0.75 mmol, 3 equiv.), Bi(*p*-tolyl)$_3$ (0.25 mmol, 1 equiv.), Pd (OAc)$_2$ (0.025 mmol, 0.1 equiv.), P(*o*-tolyl)$_3$ (0.1 mmol, 0.4 equiv.), KOAc (1.5 mmol, 6 equiv.), TBAB (0.75 mmol, 3 equiv.) and NMP (3 mL) under a N_2 atmosphere. The mixture was stirred in an oil bath at 110 °C for 4 h. The contents were quenched with water (10 mL) at rt and extracted with ethyl acetate (30 mL). The organic extract was washed with brine and dried using $MgSO_4$. The organic solvent was removed under reduced pressure to obtain the crude product. It was purified by silica gel chromatography using hexane/ethyl acetate as eluent. The product **2a** was obtained in 74% yield. The spectral characterization data for all the products is given in the Supporting information.

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