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An efficient palladium-catalyzed protocol was demonstrated for the chemoselective cross-coupling of functionalized benzylic bromides with triarylbismuth reagents. Under the established conditions, catalyzed by palladium in the presence of  $K_3PO_4$  base in DMA at 90 °C for 1 h, the threefold arylations using triarylbismuth reagents proceeded smoothly with electronically diverse benzylic bromides. All the coupling reactions furnished the corresponding functionalized diarylmethanes in high yields.

Cross-coupling studies with further development in terms of new reagents and/or protocol conditions are vital to realize hitherto unknown capabilities of reactivity and selectivity of these reactions in organic synthesis. Recent developments in the utilization of new reagents, such as organotrifluoroborates1 and organosilicon,2 are a step forward in this direction. Diarylmethanes are ubiquitous in nature with a range of biological and pharmacological properties. Typically, diarylmethanes are constructed either through the coupling of benzylic metal reagents and aryl electrophiles or aryl metal reagents and benzylic electrophiles.<sup>3-10</sup> The methods involving benzylic derivatives in combination with aryl metal reagents demonstrated a varied reactivity under different metal catalyzed protocol conditions. Usually, cross-coupling reactions are dominated by reagents which deliver one organic group at the expense of one equivalent organometallic reagent for each C-C coupling. Development of new organometallic reagents which can serve more than one organic group for example, such as triarylindium<sup>11</sup> and triarylbismuth reagents,<sup>12,13</sup> would add more value to the coupling with sub-stoichiometric loadings of organometallic reagents. Importantly, triarylbismuths<sup>14</sup> are compatible with three C-C couplings without losing stoichiometry in a facile manner.<sup>12</sup>

Interestingly, the cross-coupling study of triarylbismuth reagents with benzylic systems has not been described in the literature. In addition, the diarylmethane core is one of the most

# Pd-catalyzed chemoselective threefold cross-coupling of triarylbismuths with benzylic bromides<sup>†</sup>

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frequently found skeletons entering Phase I clinical trials and beyond.<sup>15</sup> This encouraged us to explore the synthesis of diarylmethane skeletons through the hitherto unexplored coupling reactivity of triarylbismuths with benzylic systems.<sup>13</sup> This was done with the aim to develop a viable threefold arylation strategy for the synthesis of functionalized diarylmethanes (Fig. 1).

As described herein, these efforts led to the development of an efficient chemoselective palladium-catalyzed protocol for the threefold coupling of triarylbismuths with benzylic bromides in a one-pot operation.

Triarylbismuth compounds usually give homo-coupled biaryls under palladium catalytic conditions.<sup>14</sup> To develop an efficient cross-coupling protocol with benzylic bromides a suitable combination of reagents is necessary. Hence, this investigation was carried out under various conditions (Table 1).

The cross-coupling of 4-acetylbenzyl bromide with BiPh<sub>3</sub> was initially investigated in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and K<sub>3</sub>PO<sub>4</sub> base (6 equiv.) in DMF solvent. This reaction afforded the cross-coupled 4-acetyldiphenylmethane, 2.1, in 54% yield (entry 1). However, N-methyl-2-pyrrolidone these couplings in (NMP), N,N-dimethylacetamide (DMA), acetonitrile and 1,2-dimethoxyethane (DME) solvents furnished 53-71% yields (entries 2-5). From these, DMA was found to be suitable with high product yield (entry 3). Further screening was carried out with K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> bases. This attempt using different bases delivered moderate product yields (entries 6-8). Additionally, increase of the reaction time to 2 h furnished 71% yield (entry 9), whereas coupling with 4 equiv. of benzyl bromide furnished 74% yield (entry 10). Lowering the reaction temperature did not show any positive effect (entry 11). Optimization with lowering the base equivalents (entries 12-15) and the amount of catalyst (entries 16 and 17) also lowered the yields. Thus, this investigation using





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 $<sup>\</sup>dagger$  Electronic supplementary information (ESI) available: Detailed cross-coupling representative procedure along with characterization data of all the products (including <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectra). See DOI: 10.1039/c3ra40413g

#### Table 1 Screening conditions<sup>a,b,c</sup>

Ac	Br + Ph (3.5 equiv) (1	Ph Bi <sub>Ph</sub> [Pd] Ac	2.1
			(3 equiv)
Entry	Base	Solvent	Yield (%)
1	K <sub>3</sub> PO <sub>4</sub>	DMF	54
2	$K_3PO_4$	NMP	54
3	$K_3PO_4$	DMA	71
4	$K_3PO_4$	MeCN	53
5	$K_3PO_4$	DME	63
6	$K_2CO_3$	DMA	49
7	$Na_2CO_3$	DMA	55
8	$Cs_2CO_3$	DMA	50
9	$K_3PO_4$	DMA	$71^d$
10	$K_3PO_4$	DMA	$74^e$
11	$K_3PO_4$	DMA	$64^{f}$
12	$K_3PO_4$	DMA	$64^g$
13	$K_3PO_4$	DMA	$54^h$
14	$K_3PO_4$	DMA	$40^i$
15	No base	DMA	42
16	$K_3PO_4$	DMA	$58^{j}$
17	$K_3PO_4$	DMA	$0^k$

<sup>*a*</sup> Reaction conditions: 4-acetylbenzyl bromide (0.875 mmol, 3.5 equiv.), BiPh<sub>3</sub> (0.25 mmol, 1 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.0225 mmol, 0.09 equiv.), base (1.5 mmol, 6 equiv.), solvent (3 mL), 90 °C, 1 h. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> Homo-coupled biphenyl formed in minor amounts. <sup>*d*</sup> For 2 h. <sup>*e*</sup> With 4 equiv. of bromide. <sup>*f*</sup> Reaction at 60 °C. <sup>*g*</sup> With 4 equiv. of base. <sup>*i*</sup> With 2 equiv. of base. <sup>*i*</sup> With 1 equiv. of base. <sup>*j*</sup> With 0.06 equiv. of catalyst. <sup>*k*</sup> Without catalyst.

various bases, solvents, temperature and time conditions, delivered the combination of  $Pd(PPh_3)_4$  (0.09 equiv.) and  $K_3PO_4$  (6 equiv.) in DMA at 90 °C for 1 h as the optimum protocol to obtain high yields of cross-coupling products, involving the threefold coupling of triphenylbismuth reagent in a one-pot operation. This catalytic protocol is more efficient as three phenyl couplings occurred in 1 h reaction time. This is more advantageous from a synthetic point of view in comparison to similar couplings known for boron and other reagents.<sup>10a</sup>

At this stage, the study was further extended to different triarylbismuth reagents. These results are given in Table 2. In summary, the cross-coupling ability of various triarylbismuths was tested with 4-acetylbenzyl bromide under the established conditions. This study revealed the atom-economic threefold arylation of 3 equivalents of benzylic bromide with various triarylbismuths to afford high yields. The reactivity of various electronically different BiAr<sub>3</sub> reagents in coupling with 4-acetylbenzyl bromide was found to be very facile in a one-pot operation.

Further coupling of different benzylic bromides were tested with triarylbismuth reagents and these results are given in Table 3. In this study, electronically different, functionalized benzylic bromides with substituents such as benzoyl, cyano, methyl, methoxy and carboxylic ester groups were coupled elegantly to afford high product yields. The simple unsubstitued benzyl bromide also reacted smoothly with high yields. It is noteworthy that the protocol is very efficient in furnishing uninterrupted Table 2 Couplings with BiAr<sub>3</sub> reagents<sup>a,b</sup>

Ac	Br Bi	Pd(PPh <sub>3</sub> ) <sub>4</sub> (0.09 equiv) K <sub>3</sub> PO <sub>4</sub> (6 equiv) Ac	R	
(3.5 equiv) (1 equiv) (3.5 equiv) (3.5 equiv)				
Entry	BiAr <sub>3</sub>	Diarylmethanes	Yield (%)	
1	ві	Ac 2.1	71	
2	Bi-OMe)_3	Ac 2.2 OMe	75	
3	Bi-Me)_3	Ac 2.3 Me	65	
4	Bi-OEt)	Ac 2.4 OEt	70	
5	Bi	Ac 2.5	63	
6	Bi	Ac 2.6	69	
7	Bi-(F)3	Ac 2.7 F	63	
8	Bi-CI)3	Ac 2.8 CI	60	
9	ві	Ac 2.9	61	
10	Bi	Ac 2.10 CF3	53	

<sup>*a*</sup> Reaction conditions: 4-acetylbenzyl bromide (0.875 mmol, 3.5 equiv.), BiAr<sub>3</sub> (0.25 mmol, 1 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.0225 mmol, 0.09 equiv.), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol, 6 equiv.), DMA (3 mL), 90 °C, 1 h. Isolated yields based on three aryl couplings from BiAr<sub>3</sub> with 0.75 mmol of product as 100% yield. <sup>*b*</sup> Homo-coupled biaryls from the BiAr<sub>3</sub> reagents formed in minor amounts.

threefold aryl couplings from triarylbismuths with both functionalized or unfunctionalized benzylic bromides. Electronically diverse triarylbismuths containing electron-rich or -deficient aryl groups reacted with equal ease in high yields. The reactivity of sterically congested tri(2-methoxyphenyl)bismuth reagent also furnished moderate coupling yields. The observed variation in the relative reactivity in some cases is well known with

#### Table 3 Couplings with different benzylic bromides<sup>a,b</sup>



<sup>*a*</sup> Reaction conditions: benzylic bromide (0.875 mmol, 3.5 equiv.), BiAr<sub>3</sub> (0.25 mmol, 1 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.0225 mmol, 0.09 equiv.), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol, 6 equiv.), DMA (3 mL), 90 °C, 1 h. Isolated yields based on three aryl couplings from BiAr<sub>3</sub> with 0.75 mmol of product as 100% yield. <sup>*b*</sup> Homo-coupled biaryls formed in minor amounts.

electronically different organometallic reagents in such couplings.  $^{\rm 16,17}$ 

This made us look into chemoselective couplings with benzylic substrates. The optional challenge was to check the competitive reactivity of aryl halide *versus* benzylic bromide embedded in the same molecular skeleton. Importantly, the coupling reactivity of aryl halides was well studied and nurtured under the Suzuki and other coupling conditions.<sup>18</sup> Again, the proposed chemoselective coupling is substrate dependent and often problematic.<sup>19</sup> Hence, examples of such chemoselective couplings are scarce in the literature. Expectedly, these chemoselective couplings are advantageous as this allows further core functionalization in a desired manner. So, we tested these chemoselective benzylic couplings despite the known facile reactivity of aryl halides under palladium conditions<sup>20</sup> (Table 4).

It was heartening to see that the present palladium protocol was chemoselective and led to the desired site-selective benzylic coupling, leaving the aryl halide terminus intact. Encouragingly, investigations using various *o*-, *m*- and *p*-bromo substituted benzylic bromides revealed a smooth site-selectivity with a





chemoselective coupling at the benzylic terminus, thus furnishing regio-isomeric bromo-substituted diarylmethanes in high yields. The coupling of *o*-chloro benzylic bromide also proved to be chemoselective affording high yields.

The chemoselective benzylic coupling made us curious to check the cross-coupling of bromo substituted diarylmethanes under the known aryl bromide palladium coupling conditions.<sup>20</sup> This was to explore the viability of core expansion of *o*-, *m*- and *p*-bromo diarylmethanes through sequential couplings. This brief study amply demonstrated this feasibility and led to the corresponding aryl–aryl coupling in good yields (Table 5). This study thus unequivocally established the wide synthetic utility and the facile coupling ability of triarylbismuths in both benzylic and aryl coupling under palladium coupling conditions.

It is well known that the diarylmethane core was subjected to a variety of medicinal studies as reported in the literature.<sup>21</sup> In addition to various methods given in the introduction,<sup>3–10</sup> these skeletons can also be synthesized through the coupling of benzylic manganese halide,<sup>22</sup> organo-indium<sup>23</sup> and -magnesium,<sup>24</sup> and aryltrifluoroborate<sup>17</sup> reagents in addition to other methods.<sup>25</sup> Close examination of these coupling methods for the synthesis of diarylmethanes clearly indicated that the present method is more advantageous in terms of (a) higher reactivity of triarylbismuths in threefold arylations with benzylic bromides (b) chemoselective compatibility (c) atom-economic couplings with high yields (d) threefold couplings in a one-pot operation in 1 h reaction time. In this way, the threefold reaction using triarylbismuths with



<sup>*a*</sup> Reaction conditions: benzylic bromide (0.875 mmol, 3.5 equiv.), BiAr<sub>3</sub> (0.25 mmol, 1 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.0225 mmol, 0.09 equiv.), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol, 6 equiv.), DMA (3 mL), 90  $^{\circ}$ C, 1 h. Isolated yields based on three aryl couplings from BiAr<sub>3</sub> with 0.75 mmol of product as 100% yield. <sup>*b*</sup> Homo-coupled biaryls formed in minor amounts.

<sup>*a*</sup> Reaction conditions: 4-bromo diarylmethane (3.3 equiv.), BiAr<sub>3</sub> (1 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (4 equiv.), PdCl<sub>2</sub> (0.09 equiv.), PPh<sub>3</sub> (0.18 equiv.) DMA, 90 °C, 2 h. <sup>*b*</sup> Isolated yields based on three aryl couplings from BiAr<sub>3</sub>.

additional chemoselectivity is an advantageous process and not many reagents match this reactivity coupled with high synthetic utility and yields.

In summary, the hitherto unexplored reactivity of triarylbismuths as threefold arylating agents for benzylic coupling was demonstrated under palladium conditions. Additional chemoselective coupling studies of *o*-, *m*- and *p*-bromo or *o*-chloro benzylic bromides also afforded high product yields involving benzylic couplings. Further arylations at the aryl bromide terminus of diarylmethanes were also achieved using triarylbismuths under palladium coupling conditions.

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