Tetrahedron Letters 50 (2009) 5757–5761

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Arylations of allylic acetates with triarylbismuths as atom-efficient multi-coupling reagents under palladium catalysis

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ARTICLE INFO

Article history:
Received 1 June 2009
Revised 27 July 2009
Accepted 30 July 2009
Available online 3 August 2009

Keywords:
Arylation
Triarylbismuths
Palladium-catalysis
Allylic acetates
Multi-coupling

ABSTRACT

Arylation of allylic acetates employing triarylbismuths as multi-coupling reagents under palladium-catalyzed conditions was reported. Triarylbismuths as nucleophilic coupling partners were used in sub-stoichiometric amounts with respect to allylic acetates and thus served as atom-efficient multi-coupling reagents. A variety of allylic acetates were cross-coupled with triarylbismuths to furnish the corresponding functionalized 1,3-disubstituted propenes in good to excellent yields in short reaction times. The reported palladium protocol also yielded chemo-selective allylic arylations in high yields.

Allylic substrates are useful for a variety of transformations in organic synthesis. In the presence of metal catalyst these substrates undergo selective transformations such as allylic alkylations, aminations, allylation of carbonyl compounds and Heck-type couplings.[1] Cross-coupling of allylic substrates with aryl halides or organometallic reagents provides an easy access to functionalized allylic scaffolds under metal catalysis. In specific, arylation of allylic substrates using organometallic reagents is a versatile route for the synthesis of 1,3-diarylpropene[2,3] skeletons which are part of some natural products[4a–d] and are useful for synthetic transformations.[4e] The high reactive nature of allylic substrates often leads to regio- and stereo-selective reactions under metal-catalyzed conditions.[1,2] In the presence of metal catalyst such as palladium(0), allylic substrates generally form π-allylpalladium(II) intermediate through oxidative addition.[3a] This intermediate further reacts with nucleophilic organometallic reagent through transmetalation followed by reductive elimination and affords coupling product.[3] However, these reactions are often sensitive to metal and ligand combinations along with the stability and reactivity of allylic and nucleophilic coupling partners.[3]

Organometallic reagents as nucleophilic coupling partners offer a plethora of opportunities under metal catalysis for applications in organic synthesis. Majority of these reagents react with stoichiometric amounts of organic electrophiles in coupling reactions.[5,6]

Ever growing environmental concerns[7] demand the development of reactions with new organometallic reagents which can perform multi-couplings with organic electrophiles. This approach would reduce loadings of organometallic reagents to a considerable extent in large-scale preparations.[8,9] Triarylbismuths[10] have attracted our attention as multi-coupling organometallic reagents for C–C bond formations in organic synthesis.[11,12] Thus, triarylbismuths with their three aryl groups were employed in sub-stoichiometric amounts with respect to organic electrophiles. Further, triarylbismuths were considered as atom-efficient as all the three aryl groups were utilized for coupling with three equivalents of organic electrophiles for C–C bond formations.[12]

Previously, coupling reactions of allylic bromides with triarylbismuths were reported under palladium catalysis. These couplings have been carried out with $Pd(PPh_3)_4$ catalyst in refluxing tetrahydrofuran for longer reaction times.[13,14] In this Letter, our focused efforts were directed to establish the reactivity of allylic acetates with triarylbismuths under palladium catalysis. This led to the development of an efficient palladium-catalyzed arylation of allylic acetates with triarylbismuths as multi-coupling reagents. Here, we wish to report a rapid and facile palladium-catalyzed chemo-selective arylation of allylic acetates with triarylbismuths in sub-stoichiometric amounts to furnish the corresponding 1,3-disubstituted propenes in high yields.

To accomplish this, at first we have carried out the arylation studies using triphenylbismuth and cinnamyl acetate under different palladium catalytic conditions as illustrated in Table 1.

In this screening, coupling reactions were carried out using $Pd(PPh_3)_4$ and in combination with bases such as sodium acetate, potassium acetate, sodium carbonate and potassium phosphate. These reactions did not furnish appreciable amount of allylic

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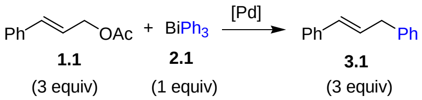
doi:10.1016/j.tetlet.2009.07.148

Table 1
Catalyst screening with cinnamyl acetate[a-c]



Entry	Catalyst	Base/additive (equiv)	Solvent	Temp (°C)	Time (h)	Conv[b] (%)
1	$Pd(PPh_3)_4$	NaOAc	DMF	90	1	15
2	$Pd(PPh_3)_4$	KOAc	DMF	90	1	21
3	$Pd(PPh_3)_4$	Na_2CO_3	DMF	90	1	22
4	$Pd(PPh_3)_4$	K_3PO_4	DMF	90	1	38
5	$Pd(PPh_3)_4$	K_3PO_4	DMA	90	1	0
6	$Pd(PPh_3)_4$	K_3PO_4	MeCN	90	1	0
7	$Pd(PPh_3)_4$	K_3PO_4	THF	90	1	7
8	$Pd(PPh_3)_4$	K_3PO_4	DME	90	1	0
9	$Pd(PPh_3)_4$	K_3PO_4	Toluene	90	1	0
10	$Pd(PPh_3)_4$	K_3PO_4	DMF	80	2	46
11	$Pd(PPh_3)_4$	K_3PO_4	DMF	60	3	40
12	$Pd(PPh_3)_4$	K_3PO_4/KBr (1)	DMF	90	1	50
13	$Pd(PPh_3)_4$	K_3PO_4/KBr (2)	DMF	90	1	55
14	$PdCl_2(PPh_3)_2$	K_3PO_4	DMF	90	1	39
15	$PdCl_2(PPh_3)_2$	K_3PO_4/KBr (2)	DMF	90	1	68
16	$PdCl_2(PPh_3)_2$	K_3PO_4/KI (2)	DMF	90	1	78 (76)
17	$PdCl_2(PPh_3)_2$	None	DMF	90	1	39
18	$PdCl_2(PPh_3)_2$	None/KI (2)	DMF	90	1	39
19	None	K_3PO_4/KI (2)	DMF	90	1	0

[a] Conditions: $BiPh_3$ (1 equiv, 0.5 mmol), cinnamyl acetate (3.5 equiv, 1.75 mmol), base (1 equiv, 0.5 mmol), palladium catalyst (0.09 equiv, 0.045 mmol), additive (0, 1 or 2 equiv) and solvent (6 mL).

[b] Conversion based on GC analysis of the crude reaction mixture. Isolated yield is given in parenthesis.

[c] Homo-coupling product biphenyl from triphenylbismuth formed as a minor side product.

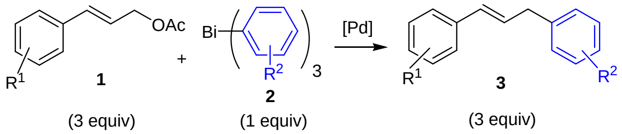
arylation product 1,3-diphenylpropene, **3.1** (Table 1, entries 1–4). The reaction with potassium phosphate base yielded 38% of the product in *N*,*N*-dimethylformamide (DMF) solvent (Table 1, entry 4). Further screening was carried out in different solvents using $Pd(PPh_3)_4$ and potassium phosphate as base. In this, polar aprotic *N*,*N*-dimethylacetamide (DMA), acetonitrile and tetrahydrofuran (THF) solvents failed to deliver good conversion (Table 1, entries 5–7). The solvents such as 1,2-dimethoxyethane (DME) and toluene (Table 1, entries 8 and 9) were also found to be equally inefficient. Then, the reaction was studied by lowering the temperature condition. This provided a slight increase in the cross-coupling product **3.1** with improved conversion of up to 46% (Table 1, entries 10 and 11). To further drive the reaction towards cross-coupling, additives have been employed to check their efficacy. Although we have not observed any dramatic change in the overall cross-coupling conversion (Table 1, entries 12 and 13), this attempt yielded a positive outcome at a later stage with the change of catalyst combination. Thus, the initial reaction with $PdCl_2(PPh_3)_2$ in DMF solvent did not show any improvement in combination with K_3PO_4 as base (Table 1, entry 14). Satisfyingly, under the same condition but with potassium bromide as additive the reaction delivered conversion up to 68% (Table 1, entry 15). The reaction was further driven towards high cross-coupling with potassium iodide as additive which afforded the conversion up to 78% with 76% isolated yield (Table 1, entry 16). The increase in conversion with salt additives may be ascribed to the expected stabilization of the η^3-palladium intermediate with the exchange of acetate for halide anion.[3] Additional control experiments were carried out without base, additive and catalyst combinations. These controls revealed a definitive role for the catalyst, base and additive to yield higher cross-coupling conversion (Table 1, entries 17–19). As known before, the formation of biphenyl as homo-coupling side product from triphenylbismuth was observed in minor amounts in these screening reactions.[15] However, the amount of biphenyl varied with respect to cross-coupling conversions.

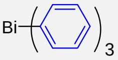
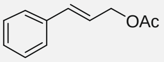
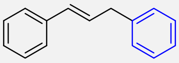
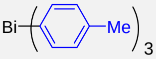
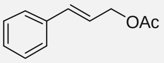
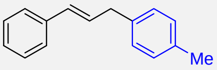
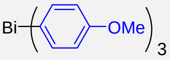
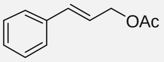
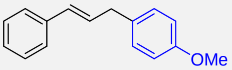
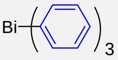
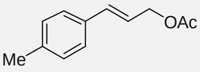
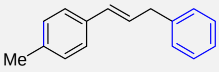
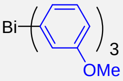
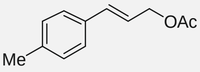
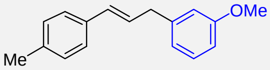
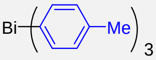
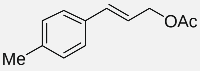
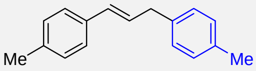
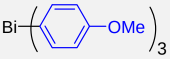
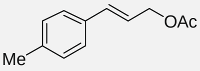
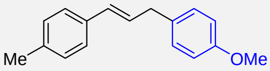
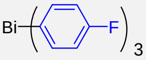
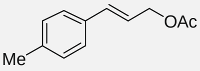
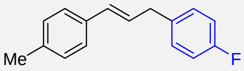
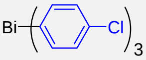
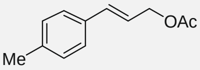
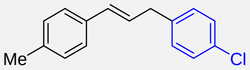
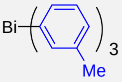
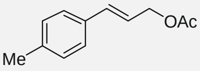
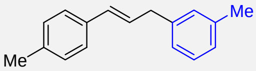
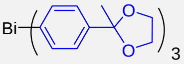
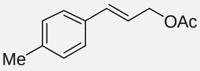
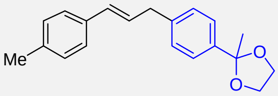
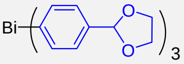
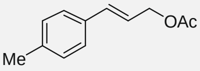
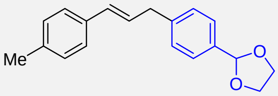
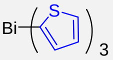
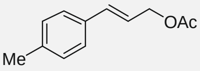
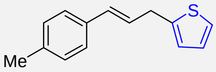
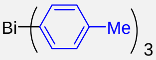
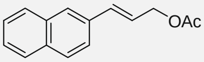
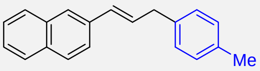
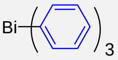
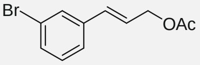
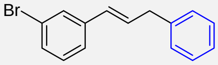
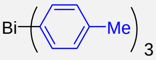
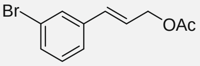
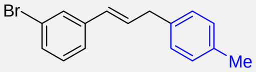
Further, we have also noted the hydrolysis of cinnamyl acetate to cinnamyl alcohol in minor amounts during the reaction. Notably, this hydrolysis was prominent in DMA, acetonitrile, THF, DME and toluene solvents and that led to no or poor conversion to cross-coupling product (Table 1, entries 5–9). Although three equiv of cinnamyl acetate is enough to react with one equivalent of triphenylbismuth theoretically, we have employed 0.5 equiv of cinnamyl acetate in excess for all the reactions to compensate the loss due to partial hydrolysis.

Our systematic study revealed the facile coupling reactivity of triphenylbismuth for arylation of cinnamyl acetate under the established palladium-catalyzed conditions (Table 1, entry 16). This prompted us to further elaborate this study with different triarylbismuths to establish the scope of allylic arylations using various allylic acetates (Table 2).

The arylation studies carried out with different triarylbismuths and a variety of functionalized allylic acetates furnished a variety of 1,3-disubstituted propenes in regio- and chemo-selective manner (Table 2).[16] In all these reactions 3.5 equiv of allylic acetate was employed with 1 equiv of triarylbismuth under the standard palladium protocol. Firstly, the arylating ability of different triarylbismuths was found to be facile with cinnamyl acetate to afford 1,3-diarylpropenes in high yield (Table 2, entries 1–3). Further arylations were carried out using divergent triarylbismuths in combination with *p*-methyl cinnamyl acetate. These reactions proved to be facile and afforded the functionalized 1,3-diarylpropenes in high yields (Table 2, entries 4–12). The coupling reaction with trithiophen-2-ylbismuth also afforded the corresponding coupling product in moderate yield (Table 2, entry 13). Reaction with 3-(naphthalene-2-yl)allylic acetate also yielded the cross-coupling product in high yield. (Table 2, entry 14). Notably, reactions of 3-bromocinnamyl acetates and 4-bromocinnamyl acetates were chemo-selective, yielding allylic arylation products in high isolated yields (Table 2, entries 15–20). Reactivity of 3-methoxycinnamyl acetate was efficient furnishing high yields of coupled products

Table 2
Arylations of allylic acetates with triarylbismuths[a-c]



Entry	Triarylbismuth	Allylic acetate	Product		Yield[b]
1				**3.1**	76
2				**3.2**	82
3				**3.3**	86
4				**3.4**	77
5				**3.5**	80
6				**3.6**	85
7				**3.7**	85
8				**3.8**	77
9				**3.9**	80
10				**3.10**	75
11				**3.11**	75
12				**3.12**	70
13				**3.13**	65
14				**3.14**	70
15				**3.15**	80
16				**3.16**	83

(*continued on next page*)

Table 2 (*continued*)

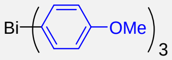
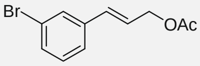
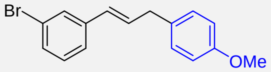
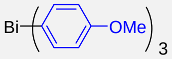
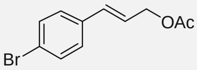
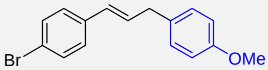
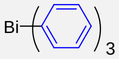
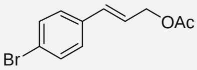
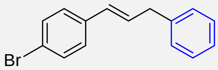
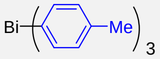
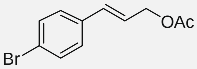
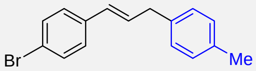
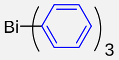
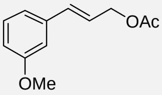
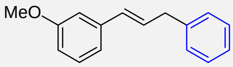
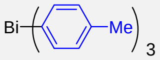
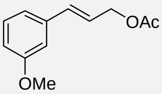
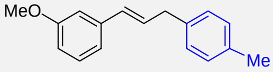
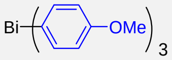
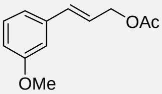
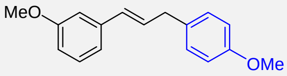
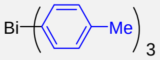
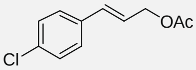
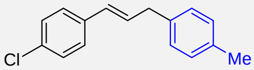
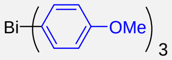
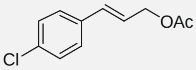
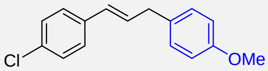
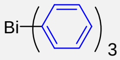
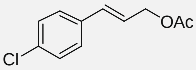
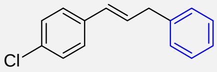
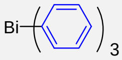
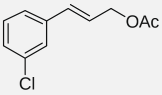
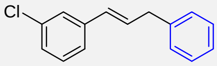
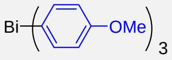
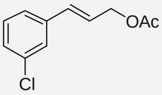
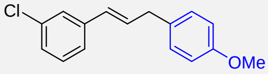
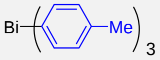
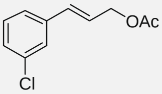
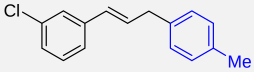
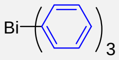
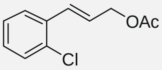
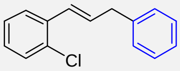
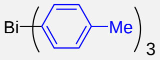
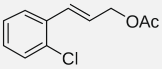
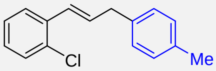
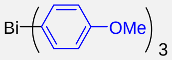
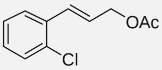
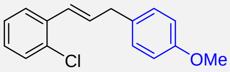
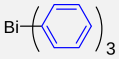
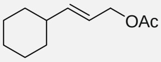
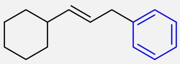
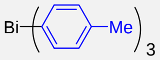
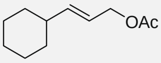
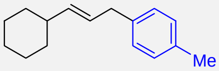
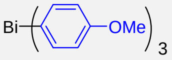
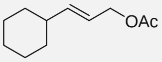
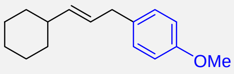
Entry	Triarylbismuth	Allylic acetate	Product	Yield[b]
17			 **3.17**	80
18			 **3.18**	90
19			 **3.19**	73
20			 **3.20**	80
21			 **3.21**	82
22			 **3.22**	86
23			 **3.23**	82
24			 **3.24**	82
25			 **3.25**	80
26			 **3.26**	82
27			 **3.27**	70
28			 **3.28**	84
29			 **3.29**	79
30			 **3.30**	83
31			 **3.31**	90
32			 **3.32**	85
33			 **3.33**	70
34			 **3.34**	70

Table 2 (*continued*)

Entry	Triarylbismuth	Allylic acetate	Product	Yield[b]
35			 **3.35**	71

[a] Reaction conditions: $BiAr_3$ (1 equiv, 0.5 mmol), allylic acetate (3.5 equiv, 1.75 mmol), $PdCl_2(PPh_3)_2$ (0.09 equiv, 0.045 mmol), K_3PO_4 (1 equiv, 0.5 mmol), KI (2 equiv, 1 mmol), DMF (6 mL), 90 °C and 1 h.

[b] Isolated yields were calculated considering all the three aryl groups for coupling from triarylbismuths. Thus, cross-coupling product 3 equiv (1.5 mmol) corresponds to 100% yield. All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and ESI-HRMS data and in comparison with the literature data.

[c] In general, homo-coupling bi-aryls from triarylbismuths were formed in all the reactions and the amount varied with respect to the degree of the cross-coupling product.

(Table 2, entries 21–23). Further, chloro-substituted allylic acetates in *para*, *meta* and *ortho* positions afforded chemo-selective arylation in allylic position (Table 2, entries 24–32). It is worth mentioning that arylation of 3-cyclohexylallylic acetate was effective under the present protocol and furnished 1,3-disubstituted propenes in good yields (Table 2, entries 33–35). Thus, the general reactivity of various electronically divergent triarylbismuths was facile for the arylation of various functionalized allylic acetates under the established coupling conditions. The present protocol also proved to be efficient for chemo-selective arylation of allylic acetates. The effectiveness of triarylbismuths to function as multi-coupling reagents was demonstrated with allylic acetates in all these coupling reactions. This established the atom-efficient transfer of three aryl groups from triarylbismuths for the purpose of allylic arylation.

The noteworthy points regarding the cross-couplings of triarylbismuths with allylic acetates (Tables 1 and 2) in comparison with the corresponding reactivity known with allylic bromides[13] are (i) the catalyst and solvent combination suitable for allylic bromides was found to be ineffective for allylic acetate couplings. Reactions of allylic bromide with triarylbismuth were reported to be facile with $Pd(PPh_3)_4$ in tetrahydrofuran, whereas this combination did not furnish effective coupling with allylic acetate in our screening conditions, (ii) the coupling reactivity was not improved either in different solvents with $Pd(PPh_3)_4$ catalyst (Table 1), (iii) allylic acetate was hydrolyzed in some solvents and led to no or poor cross-coupling conversions during our screening, (iv) allylic acetates were efficiently coupled under our coupling conditions in very short reaction time of 1 h compared to longer reaction times reported with allylic bromides and (v) in our protocol allylic acetates were employed in 3.5 equiv ratio with 1 equiv of triphenylbismuth, whereas it was higher in amounts with allylic bromides.

In summary, we have demonstrated an efficient arylation of allylic acetates with electronically different triarylbismuths under palladium-catalyzed conditions. This reaction also demonstrated triarylbismuths as sub-stoichiometric multi-coupling and atom-efficient reagents for chemo-selective allylic arylation of allylic acetates under the established palladium protocol conditions.

Acknowledgements

We thank the Department of Science and Technology (DST), New Delhi for financial support. D.B. also thanks IIT Kanpur and S.G. thanks CSIR, New Delhi for research fellowships.

References and notes

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16. *Representative procedure*: To an oven-dried Schlenk tube, cinnamyl acetate (3.5 equiv, 1.75 mmol, 309 mg) was added followed by triphenylbismuth (1 equiv, 0.5 mmol, 220 mg), K_3PO_4 (1 equiv, 0.5 mmol, 106 mg), KI (2 equiv, 1.0 mmol, 166 mg), $PdCl_2(PPh_3)_2$ (0.09 equiv, 0.045 mmol, 31.5 mg) and DMF (6 mL) under nitrogen atmosphere. The reaction mixture was stirred in an oil bath maintained at 90 °C for 1 h. After the reaction was complete, the contents in the Schlenk tube were cooled to room temperature, quenched with 10 mL water and extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with water (2 × 10 mL) followed by brine (20 mL) and dried over anhydrous $MgSO_4$. The organic extract was concentrated under reduced pressure. The crude product was purified by column chromatography using petroleum ether as eluent to afford 1,3-diphenylpropene, **3.1** (221 mg, 76%).