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Pd-Catalyzed Domino Synthesis of Internal Alkynes Using Triarylbismuths as Multicoupling Organometallic Nucleophiles

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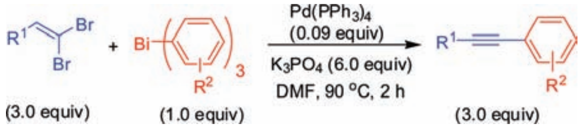
ABSTRACT



The domino coupling reaction of 1,1-dibromo-1-alkenes with triarylbismuth nucleophiles has been demonstrated to furnish disubstituted alkynes directly under catalytic palladium conditions. The couplings of triarylbismuths as multicoupling nucleophiles with 3 equiv of 1,1-dibromo-1-alkenes are very fast, affording high yields of alkynes in a short reaction time. Thus, an efficient domino process has been accomplished using 1,1-dibromo-1-alkenes as surrogates for internal alkyne synthesis in couplings with triarylbismuths in a one-pot operation.

Alkynes as novel scaffolds have a wide range of applications in organic synthesis and in material applications.[1−3] For this reason, the Sonogashira reaction is considered as a premium tool for the synthesis of disubstituted alkynes.[2] However, the preparation of internal alkynes using a domino process through in situ generation of alkyne in addition to cross-coupling would invariably endow the process a high scope and utility. This also obviates the direct use of alkyne as starting material for the synthesis of internal alkynes.

There is a growing interest in the utilization of bismuth reagents due to their nontoxicity and facile reactivity.[4,5] The awesome ability of triarylbismuths as multicoupling nucleophiles has an additional advantage in coupling reactions.[6,7] Recently, we have reported an efficient palladium-catalyzed cross-coupling of vinylic iodides with triarylbismuth compounds.[7b] These studies prompted us to study the reactivity of 1,1-dibromo-1-alkenes as they are very useful bifunctional electrophilic organic synthons in coupling reactions.[8] Reactions of $C_{(sp2)}-C_{(sp2)}$ and $C_{(sp2)}-C_{(sp)}$ couplings have immense potential for the construction of novel functional molecules.[9,10]

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Earlier couplings of 1,1-dibromo-1-alkenes reported with organometallic reagents provided di- or trisubstituted alkenes and internal alkynes under different conditions.[11−13] For example, reactions under the Stille coupling conditions needed longer reaction time,[12a] whereas Suzuki-type couplings needed a two-step protocol for alkyne formation.[11c] This variance in reactivity prompted us to explore and expand the potential of these synthons with triarylbismuths to develop a domino multicoupling protocol for the synthesis of internal alkynes (Figure 1). This novel protocol was expected to deliver 3 equiv of internal alkynes in a multicoupling one-pot domino operation.

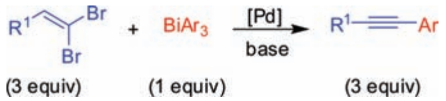
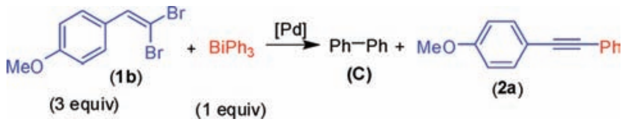


Figure 1. Domino coupling with triarylbismuths.

The envisioned domino coupling process is quite challenging because of: (i) the high propensity of triarylbismuths to give biaryls under palladium catalysis,[7a] (ii) homocoupling or elimination reactions of 1,1-dibromo-1-alkenes,[14] and (iii) the combined reactivity of both triarylbismuths and 1,1-dibromo-1-alkenes in a domino one-pot operation under palladium-catalyzed conditions.

Therefore, the initial focus was to drive the reaction toward the desired domino cross-coupling using 1,1-dibromo-1-alkene, **1b**, with BiPh$_3$ to obtain disubstituted alkyne, **2a** (Table 1). The reaction with a Pd(PPh$_3$)$_4$ catalyst using different solvents and bases furnished mixed results (entries 1−9).

Table 1. Screening Conditions[a−c]



entry	catalysts	base	solvent	C (%)	**2a** (%)
1	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	1,4-dioxane	36	9
2	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	MeCN	36	47
3	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	THF	4	<1
4	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DME	22	14
5	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	NMP	38	62
6	Pd(PPh$_3$)$_4$	K$_2$CO$_3$	DMF	20	67
7	Pd(PPh$_3$)$_4$	KOAc	DMF	5	75
8	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMF	5	95 (88)
9	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMA	4	91 (82)
10	PdCl$_2$(PPh$_3$)$_2$	K$_3$PO$_4$	DMF	19	70 (65)
11	PdCl$_2$(MeCN)$_2$	K$_3$PO$_4$	DMF	25	63[d]
12	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMF	12	88 (80)[e]
13	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMF	23	67[f]
14	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMF	6	34[g]
15	Pd(PPh$_3$)$_4$	K$_3$PO$_4$	DMF	3	62 (53)[h]
16	Pd(PPh$_3$)$_4$	none	DMF	35	19
17	none	K$_3$PO$_4$	DMF	3	3[i]

[a] Reaction conditions: 1,1-dibromo-1-alkene, **1b** (0.75 mmol, 3 equiv), BiPh$_3$ (0.25 mmol, 1 equiv), Pd catalyst (0.0225 mmol, 0.09 equiv), base (1.5 mmol, 6 equiv), solvent (3 mL), 90 °C, 2 h. [b] Products based on GC analysis of crude reaction mixtures. [c] Isolated yields are given in parentheses. [d] With PPh$_3$ (0.18 equiv). [e] 4 equiv of base. [f] 2 equiv of base. [g] At 60 °C. [h] At 80 °C. [i] 75% of 1-bromo-2-(4-methoxyphenyl)acetylene was formed.

The GC analysis of the crude product mixtures revealed the formation of cross-coupled alkyne (**2a**) and homocoupling biphenyl (**C**) from BiPh$_3$ along with unreacted 1,1-dibromo-1-alkene and triphenylbismuth in minor amounts in some cases. This study revealed that the domino process is more effective with K$_3$PO$_4$ base in *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) solvents with 88% and 82% yield of alkyne, **2a** (entries 8 and 9). With the additional study using different catalyst precursors (entries 10 and 11), it was clear that Pd(PPh$_3$)$_4$ provided better product yield. Further, different amounts of base and temperature conditions showed that lowering base equivalents or temperature is detrimental to alkyne formation (entries 12−16). A control reaction without palladium catalyst delivered a large amount of elimination product, 1-bromo-2-(4-methoxyphenyl)acetylene, in 75% yield from 1,1-dibromo-1-alkene (entry 17). Similarly, formation of 1-bromoalkyne has also been observed at lower temperature conditions in 39% and 23% amounts (entries 14 and 15). Overall, this investigation revealed that the protocol using Pd(PPh$_3$)$_4$ catalyst in combination with K$_3$PO$_4$ base and DMF solvent at 90 °C was optimal (entry 8). Gratifyingly, these conditions delivered the disubstituted alkyne with high yield and in short reaction time in a facile manner. It is to be noted that the reaction involves three C−C domino cross-couplings involving the bismuth reagent. In this domino process, triphenylbismuth was also involved as a multicoupling nucleophile for coupling with 3 equiv of 1,1-dibromo-1-alkene effectively. It is also to be mentioned that the homocoupling product biphenyl from BiPh$_3$ invariably formed in minor amounts depending on the degree of cross-coupling conversion.

With the optimized condition in hand, we further examined the scope of this reaction. The generalization of the reaction performed with divergently functionalized 1,1-dibromo-1-alkenes and BiAr$_3$ is summarized in Tables 2 and 3. In general, the domino coupling process afforded a variety of unsymmetrical internal alkynes in high yields. Thus, a series of divergent 2-aryl-1,1-dibromo-1-alkenes reacted with triarylbismuths very efficiently. Further couplings carried out with 2-heteroaryl-1,1-dibromo-1-alkenes also furnished high yields of heteroaryl-substituted alkynes in a facile manner

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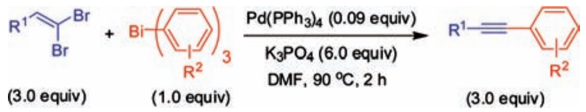
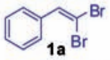
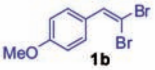
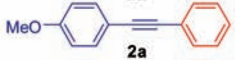
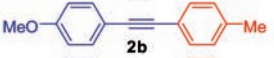
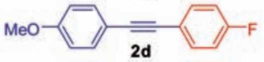
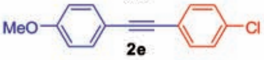
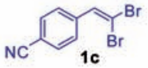
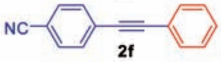
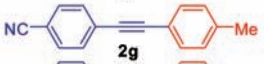
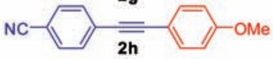
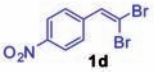
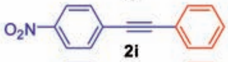
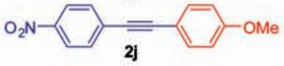
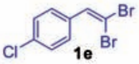
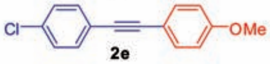
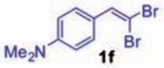
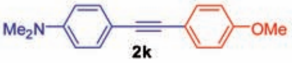
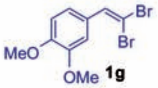
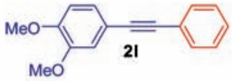
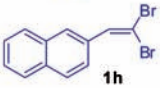
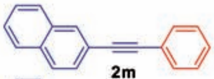
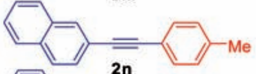
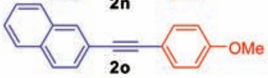
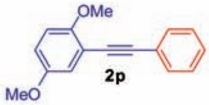
Table 2. Domino Couplings with 1,1-Dibromo-1-alkenes[a−c]



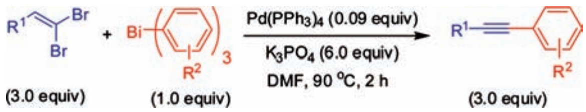
entry	1,1-dibromoalkene	alkyne	yield (%)
1	 **1a**	 **2a**	85
2	 **1b**	 **2a**	88
3	"	 **2b**	82
4	"	 **2c**	80
5	"	 **2d**	83
6	"	 **2e**	70
7	 **1c**	 **2f**	79
8	"	 **2g**	81
9	"	 **2h**	76
10	 **1d**	 **2i**	60
11	"	 **2j**	76
12	 **1e**	 **2e**	64
13	 **1f**	 **2k**	63
14	 **1g**	 **2l**	79
15	 **1h**	 **2m**	80
16	"	 **2n**	82
17	"	 **2o**	78
18	 **1i**	 **2p**	74

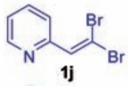
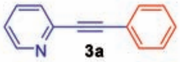
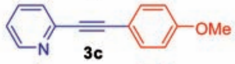
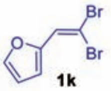
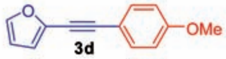
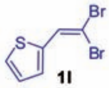
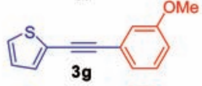
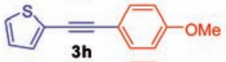
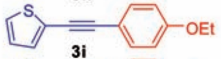
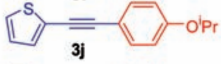
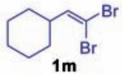
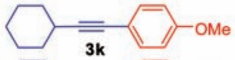
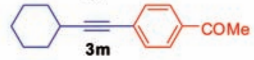
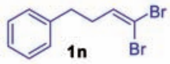
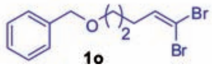
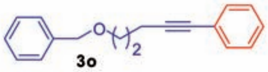
[a] Condition: Triarylbismuth (0.25 mmol, 1 equiv), 1, 1-dibromo-1-alkene (0.75 mmol, 3 equiv), Pd catalyst (0.0225 mmol, 0.09 equiv), K_3PO_4 (1.5 mmol, 6 equiv), DMF (3 mL), 90 °C, 2 h. [b] Isolated yields. [c] Minor amounts of biaryls are also formed.

(Table 3). The couplings with aliphatic 1,1-dibromo-1-alkenes also furnished the corresponding mixed alkynes efficiently.

The versatility of this reaction was additionally demonstrated in multicoupling processes using both 1,1-dibromides and triarylbismuth compounds in bis- and tris-couplings. As given in Scheme 1, bis-coupling reactions furnished high yields of the corresponding diynes with 1,3- and 1,4-disubstituted dibromoalkenes in high yields (Scheme 1, **4a**−**4d**). Additional tris-couplings are demonstrated to be effective with triarylamine derived 1,1-dibromides, furnishing the corresponding tris-alkynes in good yields (Scheme 1, **4e** and **4f**). In these couplings we have employed triarylbismuths in slight excess for effective coupling. These preliminary bis- and tris-couplings also showed promising results with high yields of multicoupled products under the conditions studied.

Table 3. Heteroaryl and Aliphatic Domino Cross-Couplings[a−c]

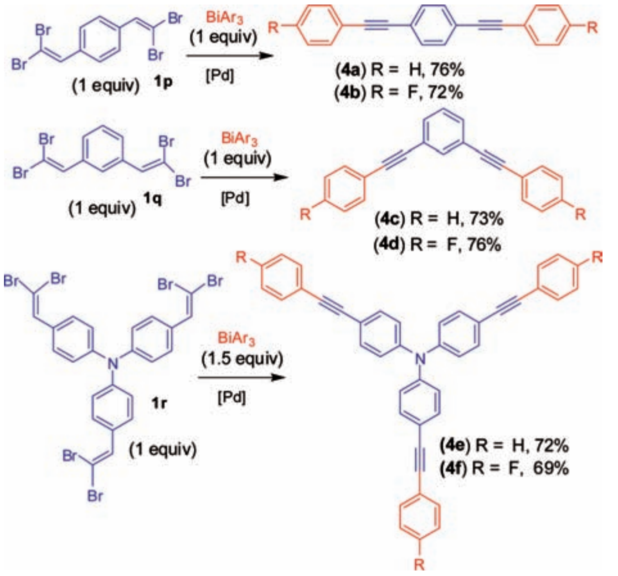


entry	1,1-dibromoalkene	alkyne	yield (%)
1	 **1j**	 **3a**	81
2	"	 **3b**	74
3	"	 **3c**	82
4	 **1k**	 **3d**	73
5	"	 **3e**	71
6	"	 **3f**	82
7	 **1l**	 **3g**	81
8	"	 **3h**	84
9	"	 **3i**	82
10	"	 **3j**	84
11	 **1m**	 **3k**	74
12	"	 **3l**	69
13	"	 **3m**	60
14	 **1n**	 **3n**	70
15	 **1o**	 **3o**	73

[a] Condition: Triarylbismuth (0.25 mmol, 1 equiv), 1,1-dibromo-1-alkene (0.75 mmol, 3 equiv), Pd catalyst (0.0225 mmol, 0.09 equiv), K_3PO_4 (1.5 mmol, 6 equiv), DMF (3 mL), 90 °C, 2 h. [b] Isolated yields. [c] Minor amounts of biaryls are also formed.

To understand the mechanism, several control reactions have been carried out (see details in Supporting Information).

Scheme 1. Bis- and Tris-Domino Couplings[a,b]



[a] Conditions. For bis-couplings: dibromide (0.375 mmol, 1 equiv), $BiAr_3$ (0.375 mmol, 1 equiv), Pd catalyst (0.0225 mmol, 0.06 equiv), K_3PO_4 (1.5 mmol, 4 equiv), DMF (3 mL), 90 °C, 3 h. [b] Conditions. For tris-couplings: dibromide (0.25 mmol, 1 equiv), $BiAr_3$ (0.375 mmol, 1.5 equiv), Pd catalyst (0.0225 mmol, 0.09 equiv), K_3PO_4 (1.5 mmol, 6 equiv), DMF (3 mL), 90 °C, 3 h.

These reactions revealed the formation of 1-bromoalkyne and 1,3-diyne in some cases.

Formation of 1-bromoalkyne in the presence of base from 1,1-dibromo-1-alkene is a known transformation.[14] The proposed mechanistic cycles (Figure 2) for the formation of an internal alkyne in a domino process are based on our control reactions and earlier similar studies.[12a] The domino coupling is most likely going through either path A or path B involving an alkyne−Pd intermediate (**R**). Participation of this intermediate in subsequent transmetalation followed by reductive elimination would deliver the alkyne product. Alternately, dehydrobromination of (*Z*)-bromo-1-alkene product from the cross-coupling reaction of 1,1-dibromo-1-alkene and triarylbismuth is also expected to deliver the disubstituted alkyne product.[11b,c] However, a control reaction involving a two-step protocol demonstrated the facile formation of 1-bromoalkyne from 1,1-dibromo-1-alkene via dehydrobromination and its effective coupling with $BiPh_3$, furnishing an internal alkyne in high yield (see details in Supporting Information). This outcome is in favor of reaction path A, although it is difficult to discount either path B or other possibilities[12a] at this stage. Importantly, during transmetalation, the Ar_2BiBr or $ArBiBr_2$ species can participate in subsequent catalytic cycles. Alternate disproportionative regeneration of $BiAr_3$ from mono- and diarylbismuths would also facilitate the transfer of three aryls during transmetalation.[7a,b]

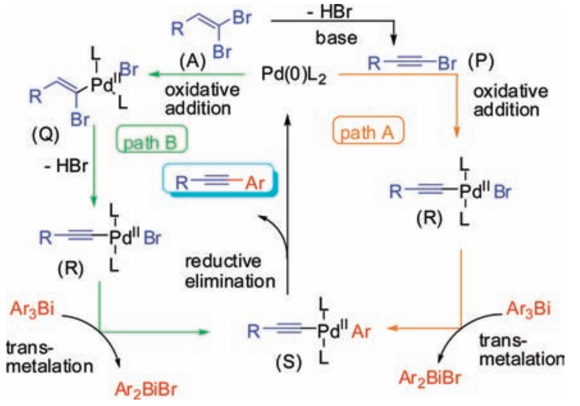


Figure 2. Proposed mechanism.

In summary, the highlight of the present domino coupling process is that triarylbismuths have been demonstrated as highly reactive organometallic reagents along with an additional feature of multicoupling ability to furnish disubstituted alkynes in a novel one-pot operation. The couplings described here are noteworthy for reasons such as: (i) the domino sequence encompasses three C−C couplings from triarylbismuths; (ii) reactions are fast, completed in 2 h; (iii) 3 equiv of disubstituted alkyne is obtained from 1 equiv of triarylbismuths in a one-pot operation; and (iv) triarylbismuths serve as nontoxic atom-efficient multicoupling reagents. In conclusion, an efficient domino process has been accomplished using 1,1-dibromo-1-alkenes as surrogates for internal alkyne synthesis in the couplings with triarylbismuths under palladium catalysis.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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