Synthetic Methods

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Expedient Synthesis of Functionalized Conjugated Enynes: Palladium-Catalyzed Bromoalkynylation of Alkynes**

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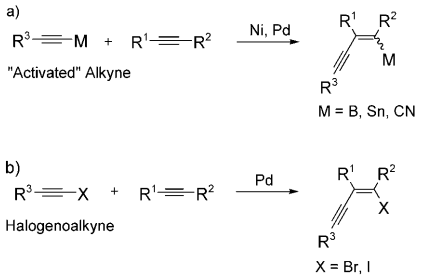
The construction of C(sp)–C(sp^2) bonds is an important method for the synthesis of various conjugated structures and biologically active compounds.[1] Among different protocols for achieving this goal, the coupling between substituted alkenes and terminal alkynes stands as the most widely used method.[2] However, the synthesis of functionalized alkenynes is problematic because of the potential of the desired functional group to react with the catalytic system. In this context, a more expedient and favored, although still underdeveloped, route to form this structure is the direct addition of an "activated" alkyne to other alkynes. To this end, several groups have reported novel catalytic systems for alkynylcyanation, alkynylstannylation, and alkynylboranation reactions,[3] which simplified the original strategies (Scheme 1a). Therefore, the importance of the search for more direct alkynylation modes is evident.

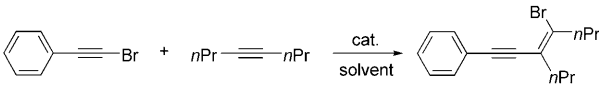


Scheme 1. a) Reported methods for the alkynylation and b) the method presented herein.

During the pursuit for more catalytic possibilities in palladium catalysis, other groups[4] as well as ours[5] have disclosed a new mode of selective intermolecular cross-coupling between internal alkynes (Scheme 1b). Additional research on this subject revealed another version of the alkyne–alkyne cross-coupling reaction: direct bromoalkynylation of internal alkynes, which are important for the aforementioned direct alkynylation strategy. Herein, we describe our preliminary results in for the bromoalkynylation process.

Our initial attempts were aimed at studying the effect of the solvent on the bromoalkynylation reaction (Table 1). In the presence of the $Pd(OAc)_2$ catalyst (5 mol%), the reaction of phenylethynyl bromide (**1a**, 1.2 mmol) and 4-octyne (**2a**, 1 mmol) in THF at 30°C afforded **3aa** in a 30% yield (entry 1). The screening of various solvents revealed that the solvent played a very important role in this reaction (entries 1–6). Only trace amounts of the desired product **3aa** was obtained when DMSO was used (entry 2), and unsatisfactory results were obtained using toluene (entry 4). The best results were obtained when the reaction was carried out with $Pd(OAc)_2$ in CH_3CN at 30°C. Under these conditions **3aa** was formed in 91% yield, in an exclusively *cis* fashion (entry 6). We next tested the bromoalkynylation reaction in the presence of different catalysts and additives. $Pd(OAc)_2$ and $PdBr_2$ were superior to any other palladium catalysts so far tested (entries 8–12). Notably, the reaction was sluggish when Pd/C or $[Pd(PPh_3)_4]$ was employed (entries 11 and 12). Additionally, reductive additives such as nBu$_3$P

Table 1: Optimization of the reaction conditions for the bromoalkynylation process.[a]



1a **2a** **3aa**

Entry	Catalyst	Solvent	Additive	Yield [%][b]
1	$Pd(OAc)_2$	THF	–	30
2	$Pd(OAc)_2$	DMSO	–	trace
3	$Pd(OAc)_2$	CH_2Cl_2	–	77
4	$Pd(OAc)_2$	toluene	–	32
5	$Pd(OAc)_2$	$MeNO_2$	–	83
6	$Pd(OAc)_2$	MeCN	–	91
7[c]	$Pd(OAc)_2$	MeCN	–	55
8	$PdBr_2$	MeCN	–	89
9	$PdCl_2$	MeCN	–	83
10[d]	$[Pd_2(dba)_3]$	MeCN	–	81
11	5% Pd/C	MeCN	–	trace
12	$[Pd(PPh_3)_4]$	MeCN	–	0
13	$Pd(OAc)_2$	MeCN	nBu$_3$P	60
14	$Pd(OAc)_2$	MeCN	CuI/Na_2CO_3 (1:1)	65
15	$Pd(OAc)_2$	MeCN	NEt_3	trace
16	$Pd(OAc)_2$	MeCN	benzoquinone	85

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), catalyst (5 mol%) in 2 mL of solvent at 30°C for 8 h. [b] Yields of isolated product are based on **2a**. [c] Reaction was carried out at 20°C for 12 h. [d] Reaction was carried out in air for 24 h. dba = dibenzylideneacetone, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

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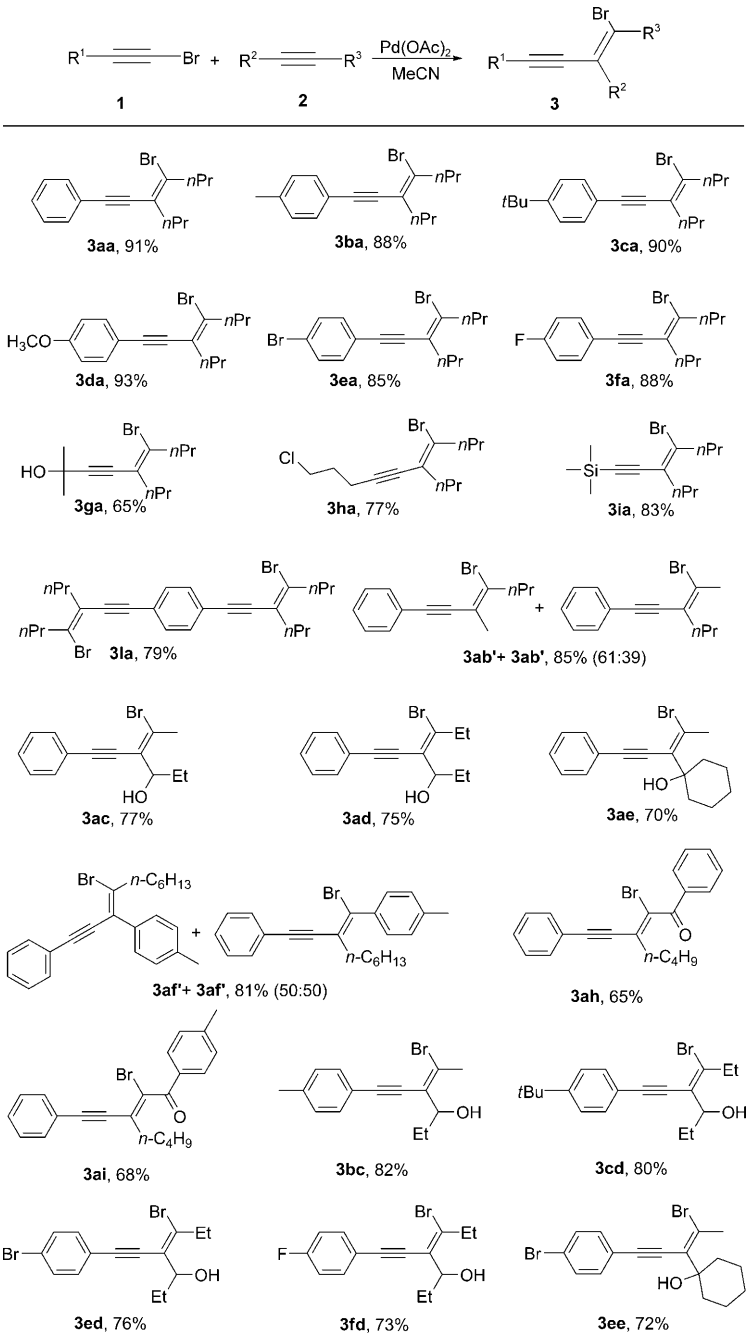
and NEt_3, as well as an inorganic base slow down the bromoalkynylation reaction (entries 13–15). An organic oxidant or air does not disturb the reaction (entries 10 and 16).

With the optimized reaction conditions in hand, we turned our attention to the bromoalkynylation reaction by varying bromoalkyne and alkyne components. Gratifyingly, both symmetrical and unsymmetrical internal alkynes exclusively gave the *cis*-addition products in the presence of palladium catalysts. As shown in Scheme 2, aromatic alkynyl bromides with either an electron-donating or electron-withdrawing group on the benzene ring, were able to undergo bromoalkynylation with 4-octyne to generate the corresponding products in excellent yields (**3aa**–**3fa**). The reaction conditions were compatible with alkyl, bromide, fluorine, and methoxy groups. The bromoaryl group was tolerated in this transformation and therefore available for additional functionalization of the product at the C–Br bond (**3ea**). It was also mechanistically interesting, because it is well-known that the $C(sp^2)$–Br bond is susceptible to reaction in a $Pd^0/^{II}$ catalytic cycle. Alkynyl bromides such as 3-hydroxy-3-methylbutynyl bromide, 5-chloropentynyl bromide, and trimethylsilylethynyl bromide can also undergo the same transformation in good yields (**3ga**, **3ha**, **3ia**). Importantly, silylethynyl bromides have proven to be useful starting materials for the construction of conjugated enynes.[6] To our surprise, the use of 1,4-bis(2-bromoethynyl)benzene resulted in the formation of the corresponding product **3la** in 79% yield in one step.

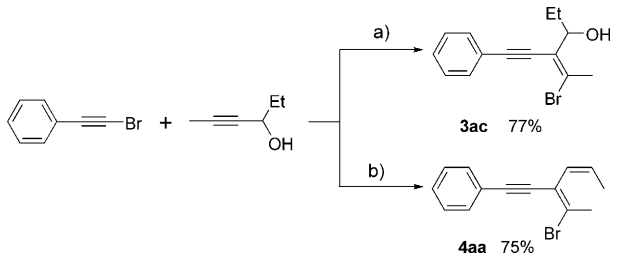


Scheme 2. Palladium-catalyzed bromoalkynylation of bromoalkynes with alkynes.

The addition of symmetrical internal alkynes gave the single *cis*-isomer products in the present palladium catalysts. Unsymmetrical disubstituted acetylenes were also investigated as substrates. Pleasingly, the functional groups in the unsymmetrical internal alkynes play a very important role in the regioselectivity. When either 2-hexyne or 1-methyl-4-(oct-1-ynyl)benzene was treated with 1.5 equivalents of alkynyl bromide, a pair of corresponding regioisomers were furnished without significant influence from the phenyl or alkyl substituents upon the stereoselectivity of the reaction (**3ab**, **3af**). However, introducing the electron-donating group OH into the internal alkynes led to the formation of single *cis*-isomer products in good yields (**3ac**–**3ae**, **3bc**–**3ee**). Interestingly, the reaction of electron-withdrawing alkynyl ketones under similar conditions afforded single *cis* products with opposite regioselectivity (**3ah**, **3ai**). Unfortunately terminal alkynes, such as phenylacetylene, only afforded a mixture of products, and diarylacetylene gave a very low yield of the product.

Additionally, when a propargyl alcohol was employed as the substrate, the expected product **3ac** was obtained in 77% yield when a mixed solvent system, CH_2Cl_2/CH_3CN (1:1), was used, whereas the bromoalkynylation in neat CH_3CN gave **4aa**, a dehydration product of **3ac**, in 75% yield (Scheme 3).[7] Therefore, we attempted the reaction of propargyl alcohols with 1.5 equivalents of bromoalkyne in the mixed solvent system, and multifunctional allylic alcohols were obtained as single isomers in good yields (Scheme 2, **3ac**–**3ee**).[8]

The regio- and stereochemistry of the products were confirmed by using NMR methods. In a typical example, NOE enhancements were observed between the methylene and methine protons of alcohol **3ad** (Figure 1), indicating a *cis* relationship between these substituents. The regioselectivity of **3ah** and **4aa** was confirmed by HMBC, HSQC, ROESY methods.[9]



Scheme 3. Solvent-involved dehydration. Reaction conditions: a) alkynes (1 mmol), bromoalkynes (1.5 mmol), $Pd(OAc)_2$ (5 mol%), CH_3CN (1 mL), CH_2Cl_2 (1 mL), 30°C, 12 h; yields of isolated products. Reaction conditions: b) alkynes (1 mmol), bromoalkynes (1.5 mmol), $Pd(OAc)_2$ (5 mol%), CH_3CN (2 mL), 80°C, 8 h; yields of isolated products.

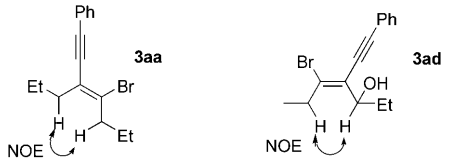
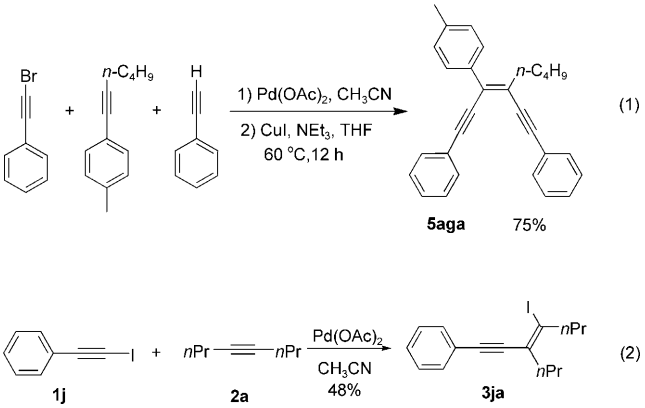


Figure 1. NOE interactions were used to confirm the configuration of the products (see the Supporting Information).

During the course of these studies, we discovered that the Pd/Cu-catalyzed one-pot coupling of **3aa** with phenylacetylene gave enediyne **5aga** in 75% yield, which when prepared by the current method is potentially useful for materials science [Eq. (1)].[10]

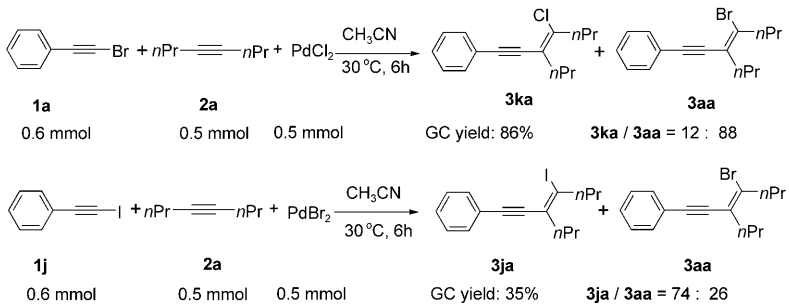
We also extended this reaction to phenylethynyl iodide as a substrate and found that the iodoalkynylation took place to give **3ja** in reasonable yield [Eq. (2)].[11]



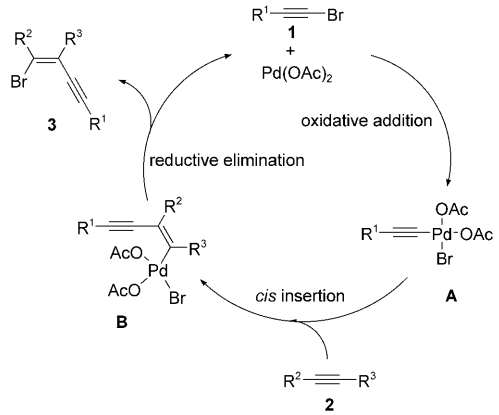
The direct halogenation of the electron-deficient alkynes by palladium(II) salts selectively afforded β-carbon halogenated products.[12] To our surprise, palladium(II)-catalyzed bromoalkynylation of alkynyl ketones afforded only the α-carbon brominated products, indicating a different pathway relative to the direct palladation process (Scheme 2, **3ah**, **3ai**).

To gain insight into the reaction, the stoichiometric PdX_2 experiments were carried out, and they showed the major halogenated products were originated from phenylethynyl halides (Scheme 4). These results provided evidence of a mechanism which proceeds through an unusual oxidative addition of PdX_2 species to phenylethynyl bromide, rather than through direct halogenopalladation of alkynes by palladium salts. Therefore, we proposed a tentative mechanism for the palladium-catalyzed bromoalkynylation in Scheme 5.[13] Different from its alkynylcyanation, alkynylstannylation, and alkynylboranation counterparts,[3] we believed that this reaction was initialized by oxidative addition of the Pd^{II} salt to bromoalkyne **1** to form a Pd^{IV} species **A**. Then the *cis*-alkynyl vinylpalladium intermediate **B** was formed by the addition of **A** to alkyne **2**. A subsequent reductive elimination of **B** regenerated the brominated product **3** and the active catalyst species Pd^{II}. Notably, the insertion of a simple palladium salt into alkynyl bromide is very rare, however, the formation of an alkynylpalladium(IV) complex was achieved with alkynyl iodide derivatives as oxidative reagents.[14]

In conclusion, we have discovered a novel type of palladium-catalyzed cross-coupling reaction between bromoalkynes and internal alkynes. This bromoalkynylation process provided a new idea for the regio- and stereoselective synthesis of conjugated *cis*-bromo alkenynes. Preliminary mechanistic experiments have provided evidence in support of a rare Pd^{II}/Pd^{IV} catalytic cycle for this transformation.



Scheme 4. Stoichiometric palladium halide experiments.



Scheme 5. Tentative mechanism for the bromoalkynylation reaction.

Current efforts are aimed at elucidating the detailed reaction mechanism, broadening the scope of the catalytic system, and exploring synthetic utility for advanced materials.

Experimental Section

Typical procedure for the reaction of phenylethynyl bromide and 4-octyne: A mixture of $Pd(OAc)_2$ (12 mg, 0.05 mmol), CH_3CN (2 mL), 4-octyne (110 mg, 1 mmol), phenylethynyl bromide (216 mg, 1.2 mmol) was added successively in Schlenk tube. After stirring for 8 h at 30 °C, the solution was filtered though a small amount of silica gel. The residue was then purified by silica gel preparative TLC (*n*-hexane), which furnished **3aa** (264 mg, 91 %) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.46$–7.48 (m, 2H, Ph), 7.28–7.31 (m, 3H, Ph), 2.58 (t, $J = 7.2$ Hz, 2H, $=CBrCH_2$), 2.27 (t, $J = 7.2$ Hz, 2H, $=CCH_2$), 1.60–1.67 (m, 4H, $-CH_2Me$), 0.96 ppm (q, $J = 7.8$ Hz, 6H, Et-CH_3); ^{13}C NMR ($CDCl_3$, 100 Hz): $\delta = 132.8$, 131.5, 131.5, 128.2, 128.2, 128.1, 124.3, 123.4 (C=C), 93.1, 90.3 (s, C≡C), 39.0 (s, $=CBrCH_2$), 35.2 (s, $=CCH_2$), 22.0 (s, CH_2), 21.9 (s, CH_2), 13.7, 13.2 ppm (s, CH_3); HRMS (EI) (*m*/*z*): calcd for $C_{16}H_{19}Br$ 290.0670; found 290.0664.

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