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Pd-Catalyzed One-Pot Multicomponent Coupling Reaction for the Highly Regioselective Synthesis of Polysubstituted Benzenes

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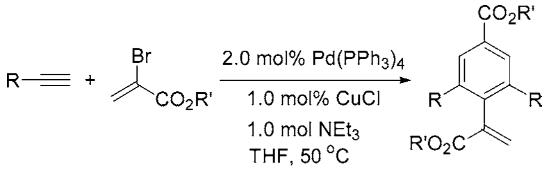
ABSTRACT



Tetrasubstituted benzenes can be efficiently synthesized in a regioselective manner from alkynes and 2-bromoacrylates by palladium-catalyzed cascade Sonogashira coupling–benzannulation reaction.

Polysubstituted benzenes are known useful compounds that are widely used in industry as well as in the laboratory. Thus, development of new multicomponent coupling reactions that allow assembly of polysubstituted benzenes in a highly regioselective manner is in high demand. Although substantial progress has been made in the synthesis of polysubstituted benzene,[1−4] the development of transition-metal-catalyzed multicomponent coupling processes remains a challenge.

Among the most frequently employed methods for accessing polysubstituted benzenes is transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes, which provides a powerful approach for the synthesis of polysubstituted benzene.[2−4] However, it suffers from serious chemo- and regioselectivity problems that normally lead to a complex mixture of products. In this context, intramolecular approaches utilizing diynes or triynes have been explored as a promising tool to selectively afford polycyclic arenes.[5−7] However, additional synthetic operations are required if the resultant polycyclic framework is not desirable.

The [4 + 2] approach for the regioselective construction of polysubstituted benzene is realized by the transition-metal-catalyzed coupling reaction of conjugated enyne with

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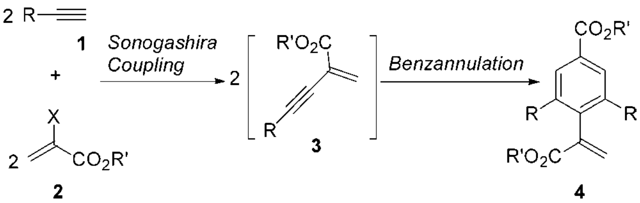
alkyne.[8,9] This reaction could be more regioselective than the [2 + 2+ 2] mode of cycloaddition since only the regioselectivity of the formation of two carbon−carbon bonds remains questionable. In other words, one of the C−C bonds in the benzene skelton (from enyne) is formed in a separate step.

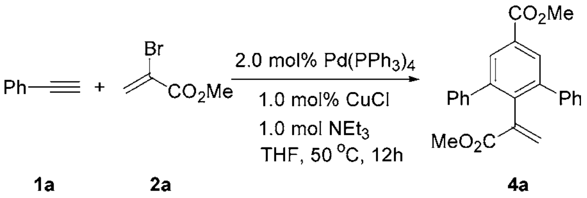
From the synthetic chemist's point of view, ideal strategies for preparing chemo- and regioselective benzene skelton would involve sequences in which regioselective formation of substituted benzene occurs in a one-pot procedure starting with simple, readily available substrates. As a part of our continuing program on the application of 2-haloacrylates in organic synthesis,[10] we report a one-pot, multicomponent coupling method for the highly regioselective synthesis of polysubstituted benzene. The underpinning strategy is based on the palladium-catalyzed intermolecular cascade process involving sequential Sonogashira coupling[11] and homobenzannulation reaction[7] between 2-haloacrylate and alkyne partners (Scheme 1). This protocol is rarely reported for highly regioselective synthesis of polysubstituted benzene in an intermolecular manner.[12]

Scheme 1



We initially examined reaction of methyl bromoacrylate and ethynyl-benzene in the presence of catalytic amounts of $Pd(PPh_3)_4$ and copper(I) chloride in a mixture of triethylamine and THF (1:2) as a solvent. Strangely, the corresponding enyne **3** was not obtained, but benzene derivative **4a** was isolated in 35% yield. At the same time, the homocoupling of ethynyl-benzene to the corresponding symmetrical diyne was also isolated in 10% yield. To increase the formation of benzene and reduce the homocoupling of diyne, we varied the reaction conditions and found that the benzene derivative **4a** was formed with excellent yield when the reaction was carried out in THF as the only solvent (Scheme 2).[13] 2′-(1-Methoxycarbonyl-vinyl)-[1,1′;3′,1″]terphenyl-5′-carboxylic acid methyl ester **4a** was obtained in 85% isolated yield with excellent regioselectivity.

Scheme 2



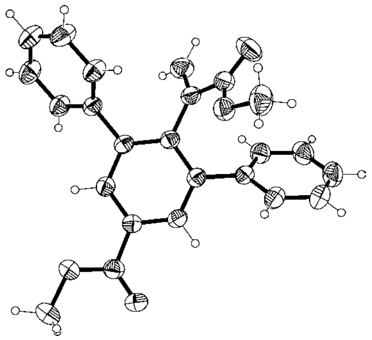
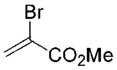
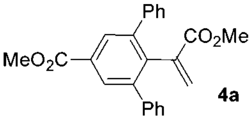
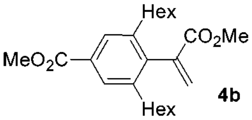
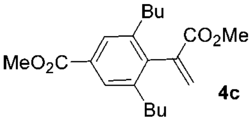
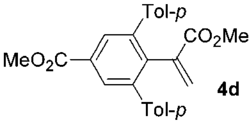
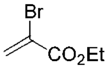
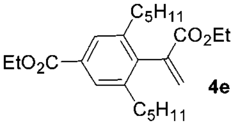
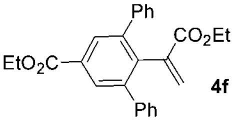
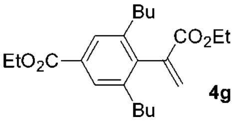


Figure 1. Structure of **4a**.

To confirm the structure of product **4a**, white crystals of **4a** suitable for X-ray analysis were obtained.[14] The structure of **4a** is shown in Figure 1. It was worth noting that in this procedure only a trace of diyne was detected by GC-MS.

We next employed a series of other alkynes bearing alkyl- and aryl-substituted groups. Table 1 summarizes results of

Table 1. Formation of Benzenes from Alkynes and 2-Bromoacrylates by Sequential Sonogashira Coupling−Benzannulation Reaction

alkyne	2-bromoacrylate	product	isolated yield (%)
Ph—≡ 1a	 **2a**	 **4a**	85
Hex—≡ **1b**	**2a**	 **4b**	68
Bu—≡ **1c**	**2a**	 **4c**	72
p-Tol—≡ **1d**	**2a**	 **4d**	81
C_5H_{11}—≡ **1e**	 **2b**	 **4e**	78
Ph—≡ **1a**	**2b**	 **4f**	79
Bu—≡ **1c**	**2b**	 **4g**	66

various alkynes reacting with 2-haloacrylates in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuCl. In all cases, the corresponding products were formed in high to excellent yields. Reactions of alkynes **1e**, **1a**, and **1c**, with ethyl 2-bromoacrylate **2b**,[15] gave similar products **4e**, **4f**, and **4g**, respectively.

In summary, a completely new, one-pot, multicomponent coupling reaction that allows facile access into polysubstituted benzene in a highly regioselective manner has been reported by using a palladium-catalyzed cascade of Sonogashira coupling−benzannulation reactions. The reaction provides an efficient method for the highly regioselective synthesis of functionalized, polysubstituted benzene under relatively mild conditions. Further investigations using other 2-halo-acrylic acid derivatives are in progress.

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Supporting Information Available: Experimental procedures and full characterization for compounds **4a−g**, ^{1}H NMR and ^{13}C NMR spectra for compounds **4a**,**b**,**d−g**, and X-ray data of **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Representative procedure was as follows: to a stirred mixture of 220 μL (2.0 mmol) of methyl 2-bromoacrylate **2a**, 1.0 mg (0.01 mmol) of CuCl, 23 mg (0.02 mmol) of $Pd(PPh_3)_4$, and 280 μL (2.0 mmol) of triethylamine in 5 mL of THF was added 240 μL (2.2 mmol) of ethynylbenzene **1a**. The reaction mixture was stirred for 12 h at 50 °C, quenched with 2 N HCl, and extracted with ether. Purification of crude product was carried out by column chromatography on silica gel (dichloromethane/petroleum ether = 1/2).

(14) Crystallographic data **4a**: colorless block, triclinic, space group $P\bar{1}$ (No. 2), $a = 9.0452(12)$, $b = 10.6117(18)$, $c = 11.2674(18)$ Å, $\alpha = 67.639(12)°$, $\beta = 79.657(13)°$, $\gamma = 84.959(13)°$, $Z = 2$, $R_1 = 0.0574$, $wR_2 = 0.0893$, GOF = 1.034.

(15) Ethyl 2-bromoacrylate was prepared according to the literature. Dachon, J. Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **1989**, *54*, 1006−1012.