Palladium-Catalyzed Three-Component Coupling Reaction of Aryl Halides, Norbornadiene and Alkynols. Convenient Synthesis for Their Ternary Coupling Products

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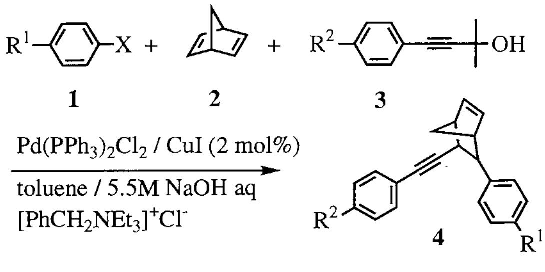
2,3-Disubstituted norbornenes were obtained by the Pd/Cu-catalyzed three-component ternary coupling reaction of aryl halides, norbornadiene, and alkynols in the presence of aqueous NaOH and a phase transfer catalyst in toluene at 100 °C in high yields.

Transition metal-catalyzed multi-component coupling reactions are of importance to construct complex molecules in a single step.[1-6] They are also potentially of importance to develop a new precision polycondensation in which more than three kinds of building blocks can be sequentially incoperated into polymer chains.[7]

In general, the reported ternary coupling systems consist of aromatic halides (or vinyl halides), nucleophiles, and unsaturated systems such as allenes, carbon monoxide, and olefins. So as to conduct the objective reaction selectively, great efforts seem to have been paid to avoid the direct cross-coupling of organic halides with nucleophiles. For example, Kosugi et al.[8-12] have reported that the reaction of aryl halides, norbornadiene (or norbornene), and organostannanes in the presence of a palladium complex provides an analogous overall transformation. Although acetylenes containing heteroatoms at their propargylic positions are also suitable to attain the ternary coupling reaction,[13-15] the use of terminal acetylenes might give rise the binary coupling products of aryl halides with acetylenes.[16] Owing to the toxicity and rather high price of organotin compounds,[17,18] it is practically of importance to explore an alternative candidate that can be employed in the ternary coupling with organic halides and norbornene. On the basis of the fact that alkynols serve as equivalence of terminal acetylenes,[19] we report herein a convenient route for the equivalent three-component coupling of aromatic halides and norbornadiene by use of alkynols as one component (Scheme 1).

The three-component coupling reaction of bromobenzene (**1A**), 4-methoxyphenyl-2-methyl-3-butyn-2-ol (**3a**), and norbornadiene (**2**) was carried out at 100 °C for 2 days in toluene/5.5M aq NaOH in the presence of benzyltriethylammonium chloride and $Pd(PPh_3)_2Cl_2$/CuI catalyst (2 mol%) to obtain a 2,3-disubstituted norbornene (**4Aa**) in 94% isolated yield (Table 1, run 1). The structure of **4Aa** was confirmed by ^1H-NMR, ^{13}C-NMR, IR spectra, and elemental analysis.[20,21] The ternary coupling reaction of aryl bromides, norbornadiene, and alkynols gives excellent yields of corresponding ternary coupling products (**4**) which are best compared to the previous strategy of Kosugi et al (Table 1, runs 6-8).



Scheme 1.

Table 1. Palladium-catalyzed ternary coupling reaction of **1A** - **1F**, **2**, and **3a** - **3c**[a]

Run	Aryl Halide	Alkynol	Yield/%[b]
1	R^1= H, X= Br (**1A**)	R^2= OMe (**3a**)	94
2	R^1= H, X= I (**1B**)	R^2= OMe (**3a**)	73
3	R^1= H, X= OTf (**1C**)	R^2= OMe (**3a**)	41
4	R^1= H, X= Br (**1A**)	R^2= CN (**3b**)	65
5	R^1= H, X= Br (**1A**)	R^2= H (**3c**)	93
6	R^1= C(O)CH_3, X= Br (**1D**)	R^2= H (**3c**)	73
7	R^1= CH_3, X= Br (**1E**)	R^2= H (**3c**)	99
8	R^1= OCH_3, X= Br (**1F**)	R^2= H (**3c**)	98

[a]Reaction conditions: **1A** - **1F**(0.5 mmol), **2** (10 mmol), **3a** - **3c** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.01 mmol), CuI (0.01 mmol), 5.5M aq NaOH (0.2 mL), benzyltriethylammonium chloride (0.015 mmol), toluene (2 mL), at 100 °C for 2 days. [b]Isolated yields by column chromatography (SiO_2, *n*-hexane : ethyl acetate = 4:1).

From both aromatic iodide and triflate (**1B** and **1C**), the products were obtained in good yields. Both aryl halides and alkynols bearing electron donating substituents are particulary suitable (runs 2 and 7-8) compared to those having electron withdrawing groups (runs 4 and 6), giving higher yield of the product.

The present tin-free three-component coupling reaction of aryl halides, norbornadiene, and alkynols are practically useful to provide the desired 2,3-disubstituted norbornene in high yields.

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16 In fact, when the reaction of bromobenzene and 4-methoxyphenylacetylene was carried out under the conditions employed for the present study, the binary coupling product (a tolane derivative) was obtained in 32% yield besides the ternary coupling product (64%).

17 Both bis(tributylstannyl)acetylene and 2,5-dimethyl-3-hexyn-2,5-diol are available from Aldrich Co., Inc, whose prices are $8,500/mole and $31/mole, respectively derived from the largest sized bottles listed in the 1996-97 catalog.

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20. [2-Phenyl-3-(4-methoxyphenylethynyl)bicyclo[2.2.1] heptene (**4Aa**)]: ^{1}H-NMR (400 MHz, in CDCl$_3$) δ = 1.68 (d, *J* = 8.8 Hz, 1H), 2.17 (d, *J* = 8.8 Hz, 1H), 2.94 (d, *J* =8.8 Hz, 1H), 3.03 (d, *J* = 8.8 Hz, 1H), 3.14 (s, 2H), 3.75 (s, 3H), 6.24 (s, 1H), 6.39 (s, 1H), 6.67 - 6.80 (m, 4H), 7.23 - 7.35 (m, 5H); ^{13}C-NMR (100 MHz, in CDCl$_3$) δ = 37.2, 45.9, 46.3, 48.3, 49.8, 55.2, 84.0, 90.7, 113.5, 116.1, 125.7, 127.7, 128.7, 132.6, 136.6, 139.8, 143.0, 158.8; IR (KBr) 2222 (-C≡C-), 1568 (norbornene) cm^{-1}; MS (EI) *m/z* 300.1414 (M+); Found: C, 87.52; H, 6.72%. Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71; O, 5.33%.

21 The ternary coupling reaction of **1A**, **2**, and **3a** was carried out in the presence of NaOH, KOH, K_2CO_3, CH_3CO_2K, and CH_3CO_2Na, from which the ternary coupling product was obtained in 94%, 91%, 62%, 14%, and 5% yields, respectively. Thus, NaOH was used for the present study.