Palladium-Catalyzed Coupling of Two Alkynes and an Alkenyl Iodide: Formation of Pentasubstituted Fulvenes
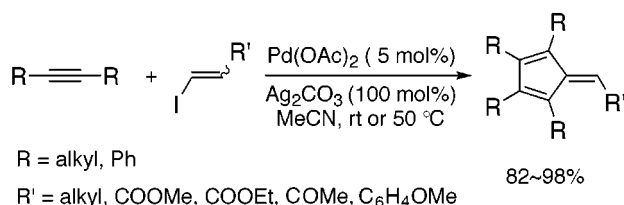
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ABSTRACT

Disubstituted alkynes reacted with alkenyl iodide in the presence of a catalytic amount of $Pd(OAc)_2$ and Ag_2CO_3 to give pentasubstituted fulvene derivatives in excellent yields. Other Ag salts such as $AgNO_3$, $AgBF_4$, and $AgOTf$ are not effective, whereas a combination of $AgNO_3$ and K_2CO_3 has a remarkable effect on the formation of fulvene.

Transition metal catalyzed [2 + 2 + 1] cycloaddition of alkene–alkene, alkene–alkyne, or alkyne–alkynes with carbenoids (CO, RNC) is well-known and eventually results in the formation of five-membered ring ketones or their derivatives.[1] On the other hand, [2 + 2 + 1] cycloaddition of alkynes with some other unsaturated compound to cyclopentadienes[2–5] or fulvenes[6–10] has so far received only marginal attention (eq 1). Although several Pd-catalyzed
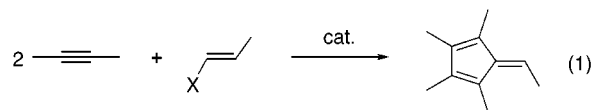
reactions of vinyl halides with alkynes have been reported to give fulvenes, there are some limitations, such as (i) reaction conditions requiring elevated temperatures (100

(1) (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (b) Dell, C. P. *J. Chem Soc., Perkin Trans. 1* **1998**, 3873. (c) Fruhauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (d) Schore, N. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press Ltd: Oxford, 1991; Vol. 5, p 1037. (e) Negishi, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press Ltd: Oxford, 1991; Vol. 5, p 1163.

(2) Pd-catalyzed preparation of hexasubstituted cyclopentadienes: (a) Reinheimer, H.; Moffat, J., Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2285. (b) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93. (c) Kong, K.-C.; Cheung, C.-H. *Organometallics* **1992**, *11*, 1972.

(3) Ni-catalyzed preparation of hexasubstituted cyclopentadienes: (a) Inoue, Y.; Itoh, Y.; Hashimoto, H. *Chem. Lett.* **1978**, 633. (b) Inoue, Y.; Itoh, Y.; Kazama, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329. (c) See ref 2.

(4) For reactions of alkynes or carbenes with a stoichiometric amount of Co or Ir-metallacycles to afford cyclopentadienes coordinated to the transition metal, see: (a) O'Connor, J. M.; Pu, L.; Uhrhammer, R.; Jonhson, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1889. (b) O'Connor, J. M.; Fong, B. S.;

Ji. H.-L.; Hiibner, K. *J. Am. Chem. Soc.* **1995**, *117*, 8029. (c) O'Connor, J. M.; Hiibner, K.; Merwin, R.; Gantzel, P. K.; Fong, B. S.; Adams, M.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 3631. For reactions of alkynes with a stoichiometric amount of a Rh complex, see also: (d) Moran, G.; Green, M.; Orpen, A. G. *J. Organomet. Chem.* **1983**, *250*, C15.

(5) For a stoichiometric reaction between a Ru π-allyl complexes with alkynes, see: Older, C. M.; Stryker, J. M. *Organometallics* **1998**, *17*, 5596.

(6) Ti-catalyzed trimerization of *tert*-butylacetylene: Johnson, E. S.; Balaich, G. J.; Fanwick, P. E.; Rothwell, I. *J. Am. Chem. Soc.* **1997**, *119*, 11086.
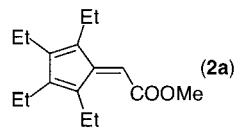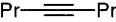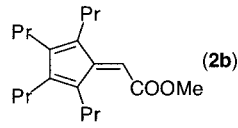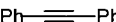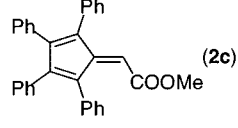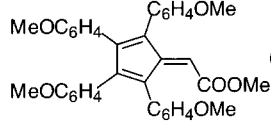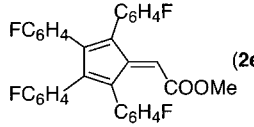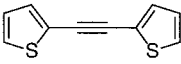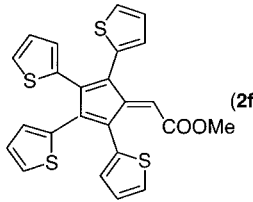
(7) Pd-catalyzed trimerization of alkynes: Radhakrishnan, U.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 1971.

(8) (a) Wu, G.; Rheigold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Silverberg, L. J.; Wu, G.; Rheigold, A. L.; Heck, R. F. *J. Organomet. Chem.* **1991**, *409*, 411.

(9) Lee, G. C. M.; Tobias, B.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 9330.

(10) Dyker, G.; Siemsen, P.; Sostmann, S.; Wiegand, A.; Dix, I.; Jones, P. G. *Chem. Ber.* **1997**, *130*, 261.

Table 1. Pd-Catalyzed Reaction of (Z)-3-Iodopropenoate **1a** with Alkynes to Give Fulvenes **2a−f**

Entry	Alkyne	Conditions[a]	Fulvene	Yield (%)[c]
1	Et———Et	20 °C, 6h	(2a)	98 (85)
2	Pr———Pr	20 °C, 18h	(2b)	98 (73)
3	Ph———Ph	50 °C, 12h[b]	(2c)	98 (81)
4	MeOC₆H₄———C₆H₄OMe	50 °C, 24h[b]	(2d)	96 (90)
5	FC₆H₄———C₆H₄F	50 °C, 24h[b]	(2e)	93 (76)
6		50 °C, 24h	(2f)	82 (73)

[a] MeCN was used as a solvent unless otherwise noted. [b] MeCN/benzene, 1/1. [c] ^{1}H NMR yields. Isolated yields are in parentheses.

°C),[8,10] (ii) the reaction being specific to a certain alkyne,[9] (iii) a migration of double bonds in the products,[8] and (iv) moderate yields.[8−10] This prompted us to investigate the palladium cation system using Ag salts[11] for the catalytic formation of fulvenes. In this paper we would like to report novel catalytic coupling reaction of two alkynes with one alkenyl halide using the combination of cat. Pd(OAc)₂ and 1 equiv of Ag₂CO₃, giving highly substituted fulvene derivatives in excellent yields.

Recently, we have concentrated our efforts on the study of [2 + 2 + 1] cycloadditions of alkynes with unsaturated compounds with the aim of synthesizing cyclopentadiene derivatives by the means of both stoichiometric and catalytic protocols. This resulted in the development of new procedures for the preparation of pentasubstituted cyclopentadienes by the reaction of zirconacyclopentadienes with pro- pynoates[12] or 3-halopropenoates[13] in the presence of a stoichiometric amount of CuCl. Our further studies in this area resulted in the development of the first catalytic procedure for the preparation of pentasubstituted cyclopen- tadienes by the reaction of alkynes with 3-bromopropenoates in the presence of NiBr₂(cat.)/Zn.[14] Surprisingly, the use of palladium salts (e.g., PdCl₂) under the identical conditions
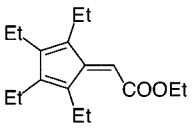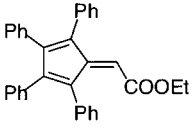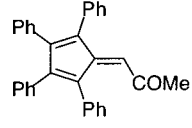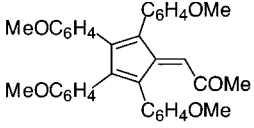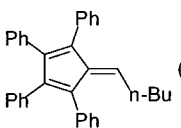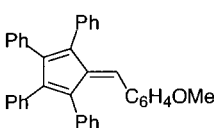
(11) For the coupling of alkenyl halides with the carbon−carbon double bond or triple bond moieties, see: (a) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131−3132. (b) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896−3900. (c) Abelman, M. M.; Overman, T. O. L. E. *J. Org. Chem.* **1987**, *52*, 4133−4135. (d) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909−4919. (e) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953−1954. (f) Meyer, F. E.; Parsons, P. J.; Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487−6488. (g) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *18*, 2589− 2592. (h) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965−4968. (i) Meyer, F. E.; Ang, K. H.; Steinig, A. G.; Meijere, A. *Synlett* **1994**, 191. (j) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737−11748. (k) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371−382. (l) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; Meijere, A. *Tetrahedron* **1996**, *52*, 11545. (m) Bengoa, E. G.; Cuerva, J. M.; Echavarren, A. M.; Martorell, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 767. (n) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970−975.

(12) Takahashi, T.; Sun, W.-H.; Xi, C.; Kotora, M. *Chem. Commun.* **1997**, 2069.
(13) Kotora, M.; Xi, C.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 4321.
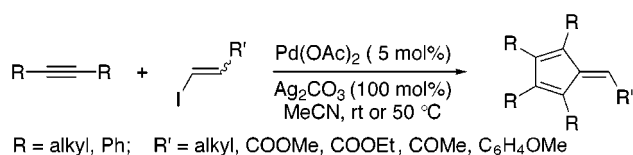(14) Kotora, M.; Ishikawa, M.; Tsai, F.-Y.; Takahashi, T. *Tetrahedron* **1999**, *55*, 4969.

| Entry	1	Alkyne	Conditions[a]	Fulvene	Yield (%)[c]
1	**1e**	Et—≡—Et	20°C, 3h	(2g)	97 (87)
2	**1e**	Ph—≡—Ph	50°C, 24h[b]	(2h)	85 (85)
3	**1b**	Ph—≡—Ph	50°C, 24h[b]	(2i)	95 (81)
4	**1b**	MeOC₆H₄—≡—C₆H₄OMe	50°C, 24h[b]	(2j)	95 (88)
5	**1f**	Ph—≡—Ph	50°C, 24h[b]	(2k)	- (50)
6	**1g**	Ph—≡—Ph	50°C, 48h[b]	(2l)	- (66)

[a] MeCN was used as a solvent unless otherwise noted. [b] MeCN/benzene, 1/1. [c] ^{1}H NMR yields. Isolated yields are in parentheses.

did not result in the formation of any major products. However, after considerable experimentation we found that alkynes and alkenyl iodides **1a–g**[15,16] could react in the presence of a catalytic amount of Pd(OAc)$_2$ (5 mol %) and 1 equiv of Ag$_2$CO$_3$ in MeCN to give fulvenes as shown in Scheme 1.

Scheme 1

R—≡—R + (vinyl iodide with R') → [Pd(OAc)$_2$ (5 mol%) / Ag$_2$CO$_3$ (100 mol%) / MeCN, rt or 50 °C] → fulvene

R = alkyl, Ph; R' = alkyl, COOMe, COOEt, COMe, C$_6$H$_4$OMe

Our initial interest focused on the reactions with 3-iodo-propenoates. Reaction of methyl (Z)-iodopropenoate **1a** with

various disubstituted alkynes proceeded very cleanly with full conversion of the starting material under mild reaction conditions (Table 1). The reaction of 3-hexyne with **1a** afforded the desired product **2a** in 98% NMR yield (isolated yield 85%). The reaction with diphenylacetylene required using a mixture of MeCN/benzene (1/1) as solvent and heating of the reaction mixture to 50 °C. In pure MeCN the product precipitated from the reaction mixture and caused the reaction to stop at about 50% conversion of the starting material. However, in a mixture of MeCN and benzene, the corresponding product **2c** was obtained in an excellent yield. The reaction proceeded well with *para*-substituted diphenyl-acetylenes with both electron-donating as well as electron-withdrawing groups (mixture of MeCN/benzene was used

1a, R = COOMe
1b, R = COMe
1c, R = CONHMe
1d, R = CONMe$_2$
1e, R = COOEt
1f, R = n-Bu
1g, R = C$_6$H$_4$OMe
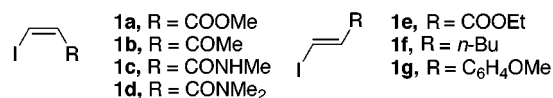
Figure 1.

(15) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816. See also: (a) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709. (b) Marek, I.; Alexakis, A.; Normat, J.-F. *Tetrahedron Lett.* **1991**, *32*, 5329–5332. (c) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643.
(16) Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2753–2755.

as a solvent). Thus the reaction of **1a** with bis(4-methoxy-phenyl)- or bis(4-fluorophenyl)acetylene afforded **2d** and **2e** in 96%, and 93% yields, respectively. The use of bis(thienyl)acetylene gave fulvene **2f** in good yield (82%).

To investigate the scope of the reaction various vinyl iodides were checked. The use of (*E*)-iodopropenoate **1e** instead of *Z*-isomer in the reaction with 3-hexyne and diphenylacetylene furnished **2g** and **2h** in 97% and 85% yields, respectively. Reactions of (*Z*)-4-iodo-2-butenone **1b** with diphenylacetylene and bis(4-methoxyphenyl)acetylene gave fulvenes **2i** and **2j** in high yields (95% and 95%). On the other hand, reaction of methyl and dimethyl (*Z*)-iodopropenamide **1c** and **1d** was disappointing.

The reaction conditions were also suitable for utilization of nonactivated vinyl iodides. The reaction of **1f** with diphenylacetylene afforded **2k** in 50% isolated yield after 24 h at 50 °C. Less reactive vinyl iodide such as **1g** reacted with diphenylacetylene and gave fulvene **2l** in 66% isolated yield.

As far as choice of solvent was concerned, the best yields were obtained in MeCN (for alkyl-substituted alkynes) or a mixture of MeCN/benzene (for phenyl-substituted alkynes). Nonetheless, the reaction of **1a** with 3-hexyne also proceeded in other solvents: DMF (6 h, 98%), DMSO (24 h, 88%), THF (24 h, 81%), benzene (24 h, 84%). The use of AgOAc has an effect similar to that of Ag_2CO_3. The product **2a** was formed in 99% yield. It is interesting to note that the other silver salts such as $AgBF_4$, AgOTf, and $AgNO_3$ did not give **2a** under the same conditions. As for carbonates, the use of Na_2CO_3, K_2CO_3, and Cs_2CO_3 did not give **2a** at all. However, surprisingly, the combination of the silver salts and carbonates such as $AgBF_4 + K_2CO_3$, $AgNO_3 + K_2CO_3$, and $AgNO_3 + Na_2CO_3$ had a remarkable effect, and **2a** was obtained in 86%, 94%, and 82% yields, respectively. The combination of $AgNO_3 + Et_3N$ also gave **2a** in 67% yield. In the case of acetates, the same phenomena were observed. The use of NaOAc instead of AgOAc did not give the product **2a**, whereas the combination of $AgNO_3$ and NaOAc gave **2a** in 75% yield. These results clearly indicated that both Ag^+ and CO_3^{2-} (or OAc^-) have an important role in the catalytic reaction. Silver carbonate is a mild base (halide scavenger), and it is widely accepted as an agent for the abstraction of

halide from a halopalladium species to generate palladium cationic species that are more reactive.[11m] The counteranion CO_3^{2-} plays an role of removal of the acid generated in the reaction. The higher reactivity enables one to conduct the reaction at low temperature,[11m] which is essential for the successful course of the reaction.

As far as the reaction mechanism of this process is concerned, it is reasonable to assume that it proceeds, after initial oxidative addition of vinyl iodide to Pd to give **5**, via 2-fold carbopalladation (**5** → **6** → **7**) followed by intramolecular Heck reaction (**7** → **8** → **2**) as is outlined in Scheme 2.

Scheme 2
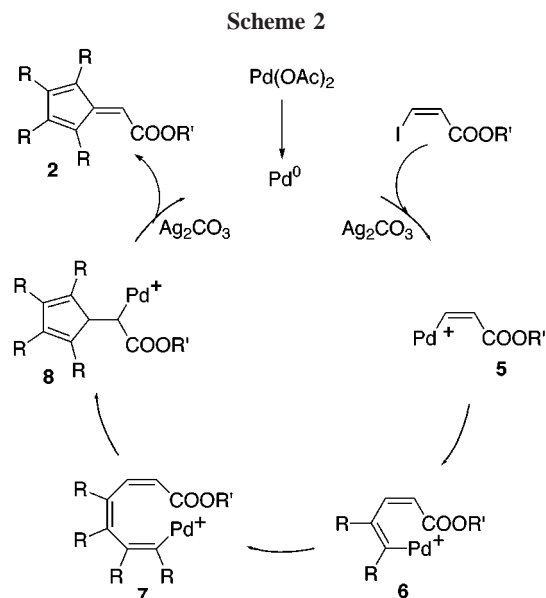
Further investigations to clarify the reaction mechanism are now in progress.

Supporting Information Available: Experimental details and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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