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Free-Radical Carboalkynylation and Carboalkenylation of Olefins

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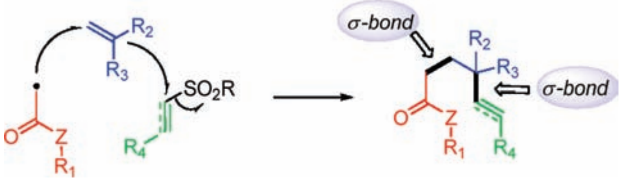
ABSTRACT



Free-radical three-component carboalkynylation and -alkenylation of olefins have been developed. These involve the addition, across the double bond of an unactivated olefin, of a radical species α- to an electron-withdrawing group and an alkenyl or alkynyl moiety, derived from the corresponding sulfones.

Intermolecular addition of two functionalized carbon fragments across an electron-rich olefinic π-system remains a challenging transformation and still the subject of intense scrutiny. Several transition metal complexes are able to mediate such a process, in a single pot, but the versatility of the method is somewhat restricted by the limited functional group tolerance on both the olefin and the added fragments.[1] Radical chemistry is potentially able to mediate such a transformation with more flexibility. Several examples of one-pot functionalization of conjugated olefins under mild radical conditions have thus been reported.[2] In contrast, little has been done on the analogous transformation involving electron-rich olefins.[3] Pioneering studies by Fuchs et al.[4] have shown that carboalkynylation using trifluoromethylsulfonylalkyne derivatives is effective, allowing the addition of CF_3 and alkyne moieties across the π-system. However, this method is limited to the introduction of a CF_3 group as the initial electrophilic component. Multicomponent reactions may offer an attractive solution, extending the nature of the fragments that may be added onto the olefinic backbone. Multicomponent processes[5] rely on the matched polarity between the different partners.[6] The free-radical addition onto an electron-rich olefin thus implies that an electrophilic radical component is added first on the olefin, affording a nucleophilic radical intermediate that should in turn be trapped by an electrophilic partner. These three-component reactions were recently defined as ADA-processes involving the intermolecular assembly between an acceptor (A), a donor (D), i.e. an olefin, and an

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[1] Carbopalladation: (a) Bräse, S.; De Meijere, A. *Palladium-catalyzed cascade carbo-palladation: Termination by nucleophilic reagents in Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons, Inc: 2002; pp 1405–1429. (b) Oda, H.; Hamataka, K.; Fugami, K.; Kosugi, M.; Migita, T. *Synlett* **1995**, 1225. Pt-catalyzed diboration: (c) Kilman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. Zr-catalyzed carboalumination: (d) Zhu, G.; Liang, B.; Negishi, E.-I. *Org. Lett.* **2008**, *10*, 1099 and references cited therein.

[2] (a) Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1996**, *118*, 1209. (b) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591. (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (d) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (e) Schaffner, A. P.; Sarkunam, K.; Renaud, P. *Helv. Chim. Acta* **2006**, *89*, 2450.

[3] (a) Ryu, I.; Sonoda, N. *Angew. Chem.* **1996**, *35*, 1050. (b) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396. (c) Kim, S.; Lee, I. Y.; Yoon, J. Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138. (d) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662.

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[5] (a) Ryu, I. Multicomponent radical reactions. In *Multicomponent Radical Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

[6] (a) DeVleeschouwer, F.; VanSpeybroeck, V.; Waroquier, M.; Geerlings, P.; DeProft, F. *Org. Lett.* **2007**, *9*, 2721. (b) Arthur, N. L.; Potzinger, P. *Organometallics* **2002**, *21*, 2874. (c) Giese, B. *Radical Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986; Chapter 2, pp 4–35.

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10.1021/ol2007633

acceptor (A).[7] Based on this concept, we describe here the development of a new free-radical carboalkenylation and -alkynylation of olefins, which result in the formation of two C–C bonds and the addition of two functional groups across the double bond of an unactivated olefin. The three-component reaction (3-CR) proceeds through the addition of a radical species α- to an electron-withdrawing group, attached to **A** (ester, ketone, amide, etc.), onto the less hindered end of an olefin **B**, followed by the coupling of the resulting electron-rich radical with an unsaturated sulfonyl acceptor **C** (Figure 1).[3d,8] A scope and limitation of the method was defined that emphasizes on the importance of the electronic nature of the sulfonyl acceptor **C**.

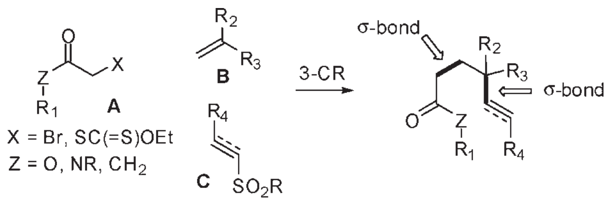
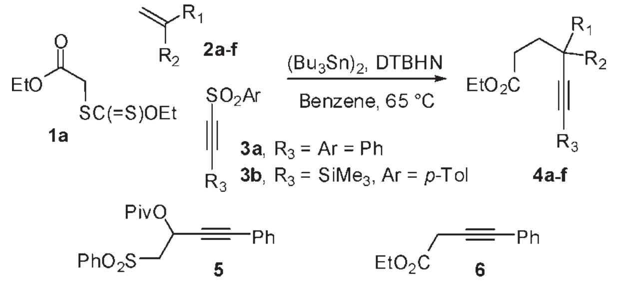


Figure 1. Three-component carboalkynylation and -alkenylation of olefins.

Preliminary experiments were carried out using xanthate **1a**, as an electrophilic radical precursor, vinyl pivalate **2**, and alkynylsulfone **3a** as a final acceptor. When 1.5 equiv of $(Bu_3Sn)_2$ and 0.15 equiv of di-*tert*-butyl hyponitrite (DTBHN) were used to initiate the process, we were pleased to find that the carboalkynylation product **4a** was obtained, albeit in poor yield (Table 1, entry 1). Increasing the amount of olefin led to a slightly better yield of **4a**, along with the unexpected formation of alkynes **5** and **6** (entry 2). Increasing the amount of sulfone to 1.5 equiv slightly improved the yield of **4a** but also increased in the meantime the amount of **5** and **6** (entry 3), illustrating the high reactivity of sulfone **3** (vide infra). Under similar conditions, a good radical acceptor such as allylsilane **2b**[9] also provided **4b**, albeit in a modest 43% yield (entry 4). The high reactivity of **3a** was then altered by introducing a $SiMe_3$ group onto the alkyne.[4e] Pleasingly, this modification led to a significant yield improvement. **2b** and enol ether **2c** thus led to **4c** and **4d** respectively in satisfying yields (entry 5–6). Generation of a quaternary center was also possible as shown by the formation of alkyne **4e**–**f** (entries 7–8). Finally, less nucleophilic oct-1-ene **2f** also reacted to provide the alkyne ester **4g** in reasonable yield (entry 9).

Table 1. Three-Component Carboalkynylation



entry	olefin (equiv)	R_1	R_2	sulfone (equiv)	product	yield[a] (%)
1	**2a** (2)	OPiv	H	**3a** (1.5)	**4a**	24
2	**2a** (4)	OPiv	H	**3a** (1.2)	**4a**	35[b]
3	**2a** (4)	OPiv	H	**3a** (1.5)	**4a**	38[c]
4	**2b** (4)	CH_2SiMe_2Ph	H	**3a** (1.2)	**4b**	43
5	**2b** (4)	CH_2SiMe_2Ph	H	**3b** (1.2)	**4c**	76
6	**2c** (4)	OEt	H	**3b** (1.2)	**4d**	60
7	**2d** (4)	$(CH_2)_2OTBDPS$	Me	**3b** (1.2)	**4e**	86
8	**2e** (4)	$-(CH_2)_5-$		**3b** (1.2)	**4f**	54
9	**2f** (4)	$(CH_2)_5CH_3$	H	**3b** (1.2)	**4g**	59

[a] Isolated yield. [b] Ratio **4**/**5**/**6** 1:0.2:0.3. [c] Ratio **4**/**5**/**6** 1:0.4:0.6.

We then extended the three-component process to the analogous carboalkenylation. Vinyl bisphenylsulfone **7**[8b] was designed as a sulfone candidate. It was first reacted with xanthate **1a** and allylsilane **2b**. Pleasingly, the desired vinylsulfone **8a** was obtained in an excellent 96% yield (Table 2, entry 1). While xanthates provide the best results, simple bromide **1b** was also shown to react efficiently with **2b** (entry 2). Monosubstituted alkene **2f** was found to be less reactive (entry 3) and led to **8b** in moderate yield. Not only increasing the amount of sulfone to 2 equiv (entry 4) but also changing the nature of the solvent, using 1,2-DCE (entry 5), significantly improved the yield. The increased amount of sulfone was only required when using poorly activated olefins (entries 5, 11–12). The three-component reaction was particularly efficient with electron-rich olefins (entries 1–2, 7–8), emphasizing again the crucial role of polar effects in these processes. Quaternary centers could also be generated using 1,1-disubstituted olefins **2d**–**2e** (entries 6, 9). Vinyl acetate **2h** led to the expected product **8g** in moderate yield (entry 10), along with a diacetate **9** (as a 1:1 mixture of two diastereomers). A similar behavior was observed with olefin **2a**. The formation of **9** may be rationalized invoking the dual reactivity of vinyl acetate **2h** toward nucleophilic and electrophilic radical species.[10] Silyl protected allylic alcohol **2j** (entry 12) led to the 3-CR product **8i** in reasonable yield, while the corresponding free alcohol provided only traces of the desired vinylsulfone, showing that free hydroxyl groups are not compatible with reaction conditions. Finally, styrenes, vinylsilanes, and enamines were

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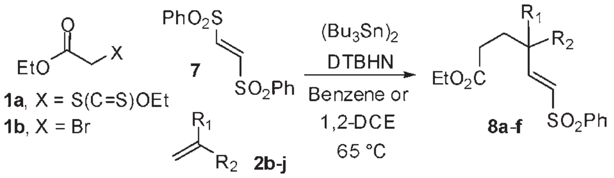
(8) For reactions using sulfone acceptors under radical conditions, see: (a) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190. (b) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809. (c) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524. (d) Kim, S.; Yoon J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982. (e) Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *C. R. Acad. Sci.* **2001**, *4*, 547. (f) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. L.; Pla-Dalmau, A.; Khanna, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 3530. (g) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847.

(9) Allylsilanes as radical traps; see: (a) Porter, N. A.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773. (b) Chabaud, L.; Landais, Y.; Renaud, P.; Robert, F.; Castet, F.; Lucarini, M.; Schenk, K. *Chem.—Eur. J.* **2008**, *14*, 2744.

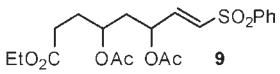
(10) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201.

Table 2. Three-Component Carboalkenylation



entry	ester	olefin (equiv)	R_1	R_2	product	yield^{a,b} (%)
1	**1a**	**2b** (4)	CH_2SiMe_2Ph	H	**8a**	96^c
2	**1b**	**2b** (4)	CH_2SiMe_2Ph	H	**8a**	82
3	**1a**	**2f** (4)	$(CH_2)_5CH_3$	H	**8b**	53^c
4	**1a**	**2f** (4)	$(CH_2)_5CH_3$	H	**8b**	68^{c,d}
5	**1a**	**2f** (4)	$(CH_2)_5CH_3$	H	**8b**	83^d
6	**1a**	**2d** (4)	$(CH_2)_2$OTBDPS	Me	**8c**	59^d
7	**1a**	**2c** (4)	OEt	H	**8d**	72^c
8	**1a**	**2g** (4)	O*t*-Bu	H	**8e**	82
9	**1a**	**2e** (4)	-$(CH_2)_5$-		**8f**	76
10	**1a**	**2h** (4)	OAc	H	**8g**	56^e
11	**1a**	**2i** (4)	$(CH_2)_3Cl$	H	**8h**	79
12	**1a**	**2j** (4)	CH_2OTBDMS	H	**8i**	53

^{a} Isolated yield. ^{b} Conditions: 1,2-dichloroethane (1,2-DCE) as solvent and sulfone **7** (1.2 equiv). ^{c} Benzene as solvent. ^{d} Sulfone **7** (2 equiv). ^{e} 12% of diacetate **9** was also formed.



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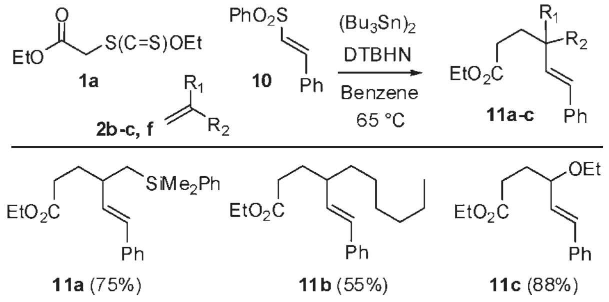
found to be poor substrates for this reaction, providing no product or complex mixtures.

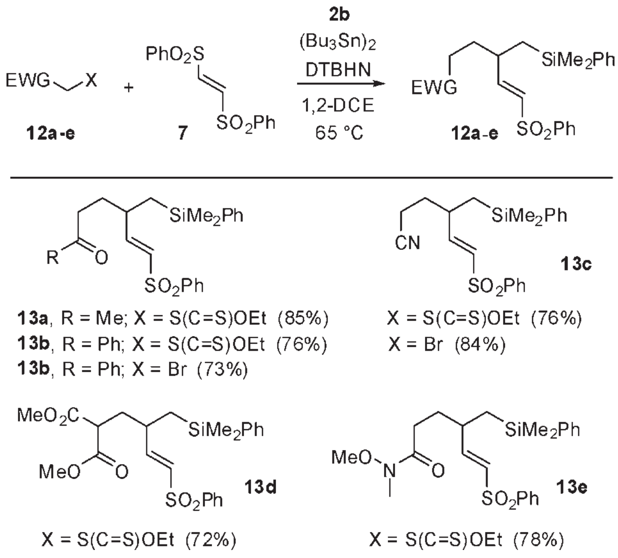
In contrast to sulfone **3a**, styrylsulfone **10** exhibited good reactivity, providing, in the presence of electronically differentiated olefins, three-component reaction products **11a–c** in moderate to excellent yields (Scheme 1).

Scheme 1. Three-Component Carboalkenylation Using Sulfone **10**

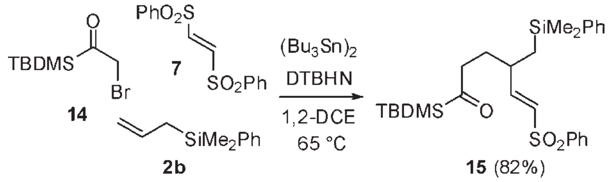


The nature of the radical precursor could also be varied as shown in Scheme 2. Using 1.2 equiv of sulfone **7** and allylsilane **2b** (4 equiv), methyl- and benzylketones **13a–b** were obtained in good yields, starting from the corresponding xanthates **12a–b** or bromide. Similarly, nitrile **13c** was prepared efficiently from the corresponding xanthate **12c** or bromide. Dimethyl malonate **13d** and Weinreb amide **13e** were finally accessible in satisfying and reproducible yields under the same conditions.

Scheme 2. Three-Component Carboalkenylation: Variation of the Nature of the Electrophilic Radical



Scheme 3. Three-Component Carboalkenylation with Acylsilanes



We finally studied these radical processes using acylsilanes as electrophilic radical precursors. While acylsilane enolates are well-known and behave similarly to ester enolates,[11] α-acylsilyl radicals have not been reported so far. These were easily generated from the corresponding α-bromoacylsilane **14**, prepared in two steps from ethylvinyl ether.[12] The three-component process with sulfone **7** and olefin **2b** provided good yields of acylsilane **15** (Scheme 3). Such difunctional building blocks are attractive, considering the dual electrophilic and nucleophilic reactivity of the acylsilane functional group.[13]

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(11) (a) Kuwajima, I.; Abe, T.; Minami, N. *Chem. Lett.* **1976**, 993. (b) Yoshida, J.; Matsunaga, S.; Ishichi, Y.; Maekawa, T.; Isoe, S. *J. Org. Chem.* **1991**, *56*, 1307. (c) Verlhac, J. B.; Kwon, H.; Pereyre, M. *J. Organomet. Chem.* **1992**, *437*, C13.

(12) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113.

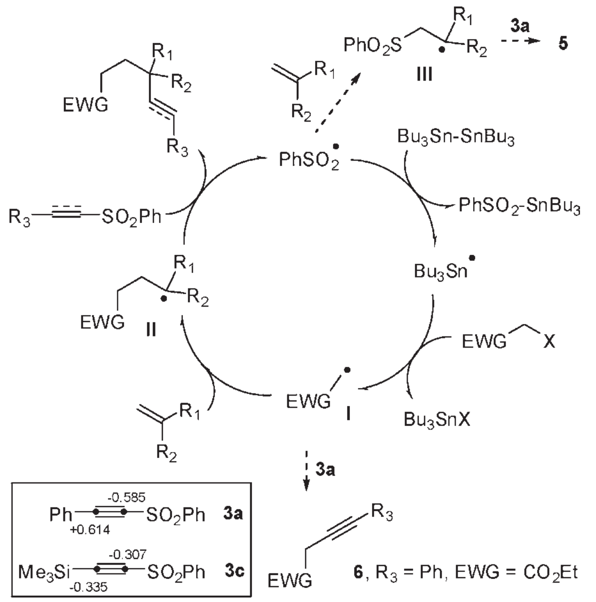

Figure 2. Three-component carboalkynylation and alkenylation radical chain.

As mentioned above, the success of such three-component reactions heavily relies on the matched polarity between the three partners.[7] A possible radical chain is depicted in Figure 2,[3] taking into account the electrophilic nature of radical precursor **I** and the nucleophilic character of **II**, generated through the addition of **I** onto the olefinic partner. An electrophilic $PhSO_2$ radical readily adds to electron-rich olefins[14] including **2a** to generate **III** (R_1 = H, R_2 = OPiv), explaining the formation of alkyne **5** as a byproduct. The relatively slow β-fragmentation of **III**, likely at the origin of the formation of **5**, is worth noticing.[15] DFT calculations at the B3LYP 6-311+G(d, p)//B3LYP 6-31G(d) level were also carried out, as to gain further insights into the reactivity of alkynylsulfones, and particularly that of **3a**–**b**. Calculations of the energy of the LUMO for **3a** and **3c** (an analogue of **3b**) revealed that they are almost identical. In contrast, a significant polarization of the alkyne triple bond was observed in **3a**, the Mulliken population analysis[16] leading to a partial negative charge on the alkyne carbon center α- to the sulfone (Figure 2), thus explaining the apparent mismatch reactivity of **3a** toward electron-poor radical species such as **I**, and the formation of **6**. In contrast, little or no polarization was observed on silylalkyne **3c**, likely as a result of the strong π–d interaction between silicon (a π-acceptor) and the carbon center.[17,18]

In summary, we reported here novel free-radical mediated carboalkynylation and alkenylation processes, starting from readily available bromides or xanthates, olefins, and sulfone acceptors. Addition across the olefin double bond gives rise to the formation of two new carbon–carbon bonds and the incorporation of two functional groups in systems that should find useful applications, for instance in the preparation of polysubstituted cyclic building blocks. Further investigations in this direction are underway and will be reported in due course.

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

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[13] (a) Page, P. C. B.; McKenzie, M. J. *Acylsilanes* in *Science of Synthesis*; Fleming, I., Ed.; Georg Thieme Verlag: 2002; Vol. 4, p 513. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (c) Tsai, Y.-M.; Tang K.-H.; Jiaang, W.-T. *Tetrahedron Lett.* **1996**, *37*, 7767.

[14] For instance, addition of a $MeSO_2$ radical to hexene is nearly diffusion controlled ($k = 1 \times 10^9$ s^{-1} M^{-1}). See: Gozdz, A.; Maslak, P. *J. Org. Chem.* **1991**, *56*, 2179.

[15] The rate constant for the β-fragmentation of a closely related β-tosyl benzoyl radical was determined to be 2.7×10^5 s^{-1} M^{-1}. See: Timokhin, V. L.; Gastaldi, S.; Bertrand, M. P.; Chatgilialoglu, C. *J. Org. Chem.* **2003**, *68*, 3532.

[16] Similar results were obtained by performing Natural Bond Orbital (NBO) analysis (see Supporting Information).

[17] Steric effects of the bulky $SiMe_3$ group should also favor the approach of the radical α- to the sulfone.

[18] (a) Rubin, M.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10243. (b) Vasilevsky, S. F.; Baranov, D. S.; Mamatyuk, V. I.; Gatilov, Y. V.; Alabugin, I. V. *J. Org. Chem.* **2009**, *74*, 6143.