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A Convergent Radical-Based Route to Biaryls

Béatrice Quiclet-Sire, Guillaume Revol,* and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652, Département de Chimie, Ecole Polytechnique, 91128 Palaiseau, France

revol@dcso.polytechnique.fr; zard@poly.polytechnique.fr

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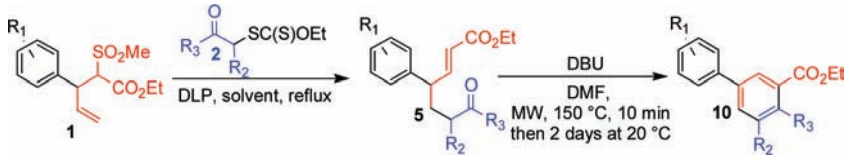
ABSTRACT

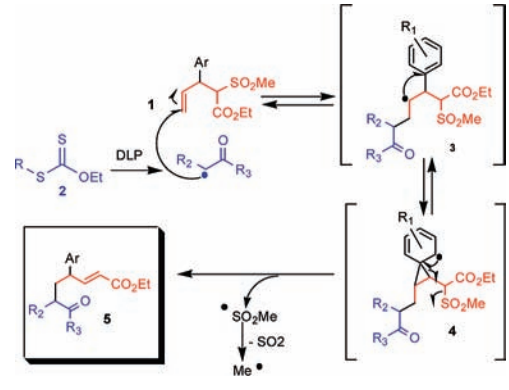


A route to biaryl-3-carboxylate esters involving a radical 1,2-aryl migration has been developed. This strategy hinges on the radical addition of xanthate 2 to olefin 1 causing a 1,2-aryl shift leading to α,β-unsaturated ester 5, which is then converted into biaryl 10 by treatment with DBU under microwave heating.

Biaryls and, more generally, polyaryls are important building blocks in organic chemistry. They are present in various natural products,[1] as pharmacophores in potential drugs,[2] and as ligands for many catalysts.[3] The most common approaches to these compounds involve a transition-metal-mediated coupling of two monoaryl units such as the Suzuki,[4] Stille,[5] Negishi,[6] and Kharasch[7] coupling. Although these methods are broadly used and very efficient, alternative strategies[8] are still of interest for the synthesis of highly functionalized biaryls. While radical chemistry is often used to create new C−C bonds, there are only a few syntheses of biaryls involving direct arylation of arenes under photochemical or reductive radical conditions.[9]

We now describe a two-step sequence to biaryls by a two-step sequence: the radical addition of a xanthate onto a δ,γ-unsaturated sulfone and the one-pot isomerization of the resulting α,β-unsaturated ester, cyclization, elimination, and aerial oxidation (Schemes 1 and 2).

Scheme 1. 1,2-Aryl Migration



As part of our studies of the chemistry of xanthates,[10] we found that the radical addition of xanthate **2** to an alkene such as **1** led to an α,β-unsaturated ester **5**. The addition gives first adduct radical **3**, which undergoes a reversible *ipso* cyclization to form intermediate radical **4** (Scheme 1).

(1) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248.
(2) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Gossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473. (c) Boisnard, S.; Carbonnelle, A. C.; Zhu, J. *Org. Lett.* **2001**, *3*, 2061.
(3) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.
(4) Miyaura, N.; Suzuki, A. *Chem. Rev.* **2002**, *102*, 1359.
(5) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(6) King, O.; Okukado, N.; Negishi, E. J. *J. Chem. Soc., Chem. Commun.* **1977**, 683.
(7) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.
(8) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 262.

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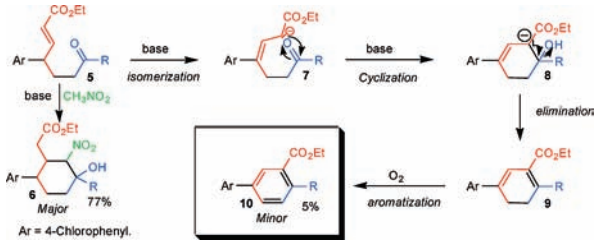
Scheme 2. Annulation−Aromatization Process



The α,β-unsaturated ester **5** is then produced through a 1,2-aryl shift[11] and, for all practical purposes, irreversible loss of a methanesulfonyl radical by β-elimination.[12] The latter gives off sulfur dioxide to form a methyl radical that can propagate the chain.

We previously applied the aryl migration sequence to efficiently form 3-arylpiperidines,[13] yet the α,β-unsaturated esters **3** could also be interesting precursors to biaryls. We initially considered the approach in Scheme 2 involving a Michael addition and Henry reaction of nitromethane followed by elimination of the elements of water and nitrous acid and ultimate oxidation.[14]

Olefin **1a** was easily prepared in two steps by the Knoevenagel condensation of ethyl methanesulfonylacetate on *p*-chlorobenzaldehyde, followed by conjugate addition of vinylmagnesium cuprate onto the resulting α-unsaturated ester. Our first attempt at an annulation−aromatization sequence under classical conditions ($MeNO_2$, K_2CO_3, EtOH) afforded the expected nitro intermediate **6a** but also surprinsingly a little biaryl **10a**.

We suspected that this biaryl arose from a one-pot, four-step reaction (Scheme 2). The sequence began with the isomerization of the double bond under basic conditions.

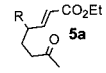
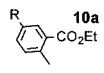
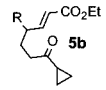
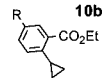
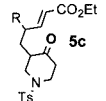
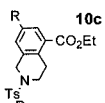
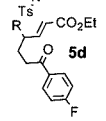
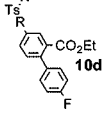
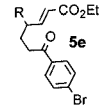
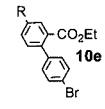
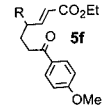
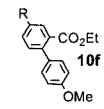
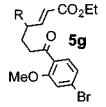
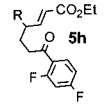
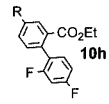
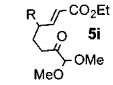
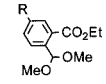
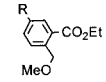
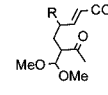
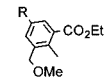
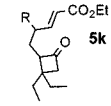
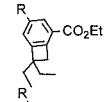
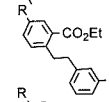
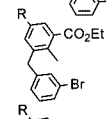
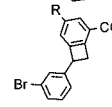
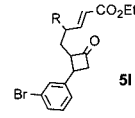
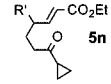
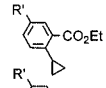
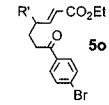
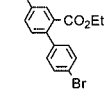
Deprotonation in the α-position of the ester group to give **7**, followed by intramolecular cyclization on the ketone to form alcohol **8**, elimination of water to give **9**, and aromatization by aerial oxidation. We confirmed this sequence by reacting **5a** in ethanol with K_2CO_3 at 50 °C under air and isolated the same product **10a** in a useful yield of 55%. The corresponding elimination intermediate **9a** was observed by NMR, suggesting that the limiting step is the oxidation to the desired biaryl. It is important, at this stage, to emphasize the crucial, even if indirect, role played by the aromatic ring present in substrates **3** in controlling the regiochemistry of the process. By facilitating and favoring the migration of the olefin to give isomer **7** (this isomerization occurs readily and practically quantitatively, even with a weak base such as triethylamine), *the possibility of initial unsaturated ester acting as a Michael acceptor for the enolate of the ketone*

Table 1. Synthesis of α,β-Unsaturated Ester **5a**−**o** (R = 4-Chlorophenyl, R′ = 3-Fluorophenyl)

entry	olefin 1	xanthate 2	product 5	yield[a] (%)	method
1	**1a**	**2a**	**5a**	63	A
2	**1a**	**2b**	**5b**	62	A
3	**1a**	**2c**	**5c**	41[b]	B
4	**1a**	**2d** R_1 = F	**5d** R_1 = F	70	B
	1a	**2e** R_1 = Br	**5e** R_1 = Br	59	B
	1a	**2f** R_1 = OMe	**5f** R_1 = OMe	54	B
5	**1a**	**2g**	**5g**	44	B
6	**1a**	**2h**	**5h**	54	B
7	**1a**	**2i**	**5i**	52	A
8	**1a**	**2j**	**5j**	44	A
9	**1a**	**2k**	**5k**	64	A[c]
10	**1a**	**2l**	**5l**	66	A[c]
11	**1a**	**2m**	**5m**	81	A[c]
12	**1b**	**2b**	**5n**	59	A
13	**1b**	**2e**	**5o**	57	B

[a] Yields refer to isolated pure product. [b] NMR calculated yield. All products were identified spectroscopically except **5c**. Method A: Olefin **1** (1 equiv) and xanthate **2** (1.5 equiv) were heated in refluxing 1,2-dichloroethane (2 mL/mmol), and 5 mol % of DLP was added every hour during 7 h. [c] The reaction time was extended to 15 h. Method B: Olefin **2** (1 equiv) and xanthate **2** (1.5 equiv) were heated in refluxing chlorobenzene (2 mL/mmol), and 5 mol % of DLP was added every 15 min for 2 h 15.

Table 2. Biaryls Obtained **4a**−**o** (R = 4-Chlorophenyl, R′ = 3-Fluorophenyl)

entry	substrate 5	product 10	method	yield[a] (%)
1		 **10a**	A B C	55 56 41
2		 **10b**	C	69
3		 **10c**	C B	66 0
4		 **10d**	C	89
5		 **10e**	A	59
6		 **10f**	B	65
7		 **10g**	C	64
8		 **10h**	C	66
9	 **5i**	 **10i**  **10i′**	C B C	47 6 11
10	 **5j**	 **10j**	C	92
11	 **5k**	 **10k**  **10l″**  **10l′**  **10l**	C B 11 C 8[b]	49 0 7[b]
12	 **5l**			
13	 **5n**	 **10n**	B	47
14	 **5o**	 **10o**	B	47

[a] Yields refer to isolated pure product. [b] Yields refer to isolated slightly impure product. All products were identified spectroscopically. Method A: Substrate **5** (1 equiv), K_2CO_3 (2 equiv), in ethanol (2 mL/mmol), 50 °C for 2 days. Method B: Substrate **5** (1 equiv), DBU (5 equiv), 20 °C, 5 days. Method C: Substrate **5** (1 equiv), DBU (1 equiv), DMF (10 mL/mmol), 150 °C for 10 min under microwave irradiation then 20 °C for 2 days under air.

is completely eliminated. Such an alternate mode of cyclization leading to a simple cyclohexanone would have been expected to dominate in the absence of the aromatic ring, in view of the greater acidity of ketones as compared to ordinary esters. Another indirect role of the aromatic ring is to *sterically force the alkene to adopt the E-geometry* (as shown for **7** in Scheme 2), which is absolutely necessary for the ring closure.

Having inadvertently found a convenient route to biaryls, we next prepared further precursors by radical addition of various xanthates **2** to olefins **1a** and **1b**. (Table 1). This method is effective in producing the required complex α,β-unsaturated esters **5a**−**o** in yields ranging from 52 to 81%. Cyclobutanone xanthates **2k**−**m** were obtained through a new route we recently developed.[15] Two sets of conditions were used to carry out the radical addition: mild conditions (refluxing 1,2-dichloroethane) for sligthly sensitive alkyl xanthates such as cyclobutanone-, cyclopropyl ketone-, or acetal-containing derivatives and harsher conditions (reflux-

(9) (a) Martinez-Barrasa, V.; Garca de Viedma, A.; Burgos, C.; Alvarez-Builla, J. J. *Org. Lett.* **2000**, *2*, 3933. (b) Sharma, R. K.; Kharasch, N. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 36. (c) Taylor, E. C.; Kienzie, F.; McKillop, A. *J. Am. Chem. Soc.* **1970**, *92*, 6088. (d) Bonfand, E.; Forslund, L.; Motherwell, W. B.; Vasquez, S. *Synlett* **2000**, *4*, 475. (e) Terashima, M.; Seki, K.; Yoshida, C.; Ohkura, K.; Kanaoka, Y. *Chem. Pharm. Bull.* **1985**, *33*, 1009, and references cited therein.

(10) For reviews of the xanthate transfer, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Zard, S. Z. In *Radicals in Organic Synthesys*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

(11) (a) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072. (b) Parker, T. L.; Spero, D. M.; Irman, K. *Tetrahedron Lett.* **1986**, *27*, 2833. (c) McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 543. (d) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022. (e) Ishibashi, H.; Ohata, K.; Niihara, M.; Sato, T.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 547. (f) Ouvry, G.; Zard, S. Z. *Synlett* **2003**, 1627.

(12) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209.

(13) Georghe, A. Quiclet-Sire, B. Villa, X. Zard, S. Z. *Tetrahedron* **2007**, *63*, 7187. See also ref 11f.

(14) For conceptually similar approaches, see: (a) Zhang, Q.; Sun, S.; Hu, J.; Liu, Q.; Tan, J. *J. Org. Chem.* **2007**, *72*, 139. (b) Ballini, R.; Palmieri, A.; Rizhi, P. *Tetrahedron* **2007**, *63*, 12099.

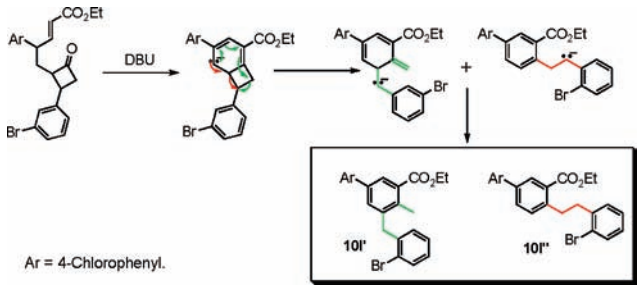
(15) Heng, R.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2009**, *50*, 3613.

ing chlorobenzene) leading to shorter reaction times and suitable for more robust xanthates such as **2c**−**h**.

Unfortunately, when we subjected the various substrates to the above conditions, many biaryls were obtained in poor yield (Table 2, entries 3, 5, 9, and 11). As mentioned previously, we believed that the slow step was the aromatization, but a more careful monitoring of the reaction allowed us to also observe the intermediate alcohol resulting from the cyclization **8**. Clearly, the slow steps of the reaction were both the elimination and the aromatization at 20 °C in DBU. We chose therefore to use microwave heating to enhance the elimination of the alcohol and improve the aerial oxidation. Thus, alkene **5a** was dissolved in DMF with 1 equiv of DBU and then heated to 150 °C for 10 min and left at room temperature for 2 days under air. These proved to be very useful conditions as triaryls **10d**,**g**,**h** (Table 2, entries 2−4 and 7−10) and biaryls from hindered ketones **10c**,**l**,**k**, which did not form under the previous conditions, could be readily obtained.

In the case of **5i**, the normal oxidative aromatization to give **10i** was in competition with aromatization through elimination of one of the methoxy groups leading to **10i′** (Table 2, entry 9). Loss of the methoxy groups was the dominant pathway for **5j** (Table 2, entry 10), and compound **10j** was practically the only product. The α,β-unsaturated ester **5l** featuring a cyclobutanone ring (Table 2, entry 12) also did not react as expected. Indeed, two other biaryls **10l′** and **10l″** were detected by NMR, and **10l″** was isolated in a small yield. These products result from the opening of the aryl−cyclobutanone ring under the basic conditions. As outlined in Scheme 3, it appears that the ring-opening is

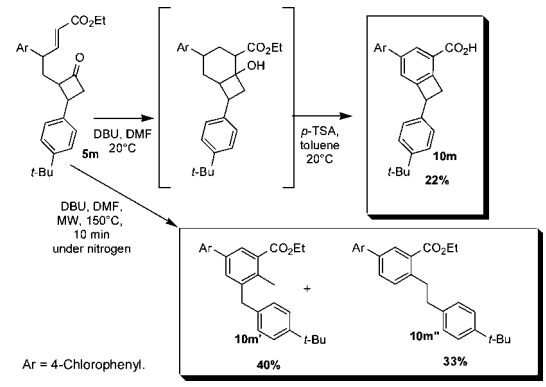
Scheme 3. Ring-Opening Mechanism



favored by the bromophenyl group which stabilizes the anion and encourages the ring-opening. Indeed, no ring-opening product was detected for cyclobutanone precurssor **5k** (Table 2, entry 11) containing only an ethyl substituent.

These observations are supported by the two experiments summarized in Scheme 4. Heating substrate **5m** in the

Scheme 4



microwawe oven in degassed DMF and under an inert atmosphere gave rise to two ring-opened products **10m′** and **10m″** in a good combined yield of 73%. In contrast, exposure to DBU at room temperature furnished the intermediate cyclized alcohol, which without purification, was treated with *p*-toluenesulfonic acid in toluene at room temperature for 1 day to provide compound **10m** in modest yield. Under these conditions, hydrolysis and saponification occurred but the cyclobutane ring remained intact.

Numerous approaches to biaryls already exist, as diverse strategies as metal-catalyzed couplings,[16] as Diels−Alder cycloadditions,[17] or through direct arylation, in addition to radical couplings.[9] The present route to complex bi- or triaryls complements previous methods. It employs cheap and readily available starting materials, enables the formation of relativly sensitive biarylcylobutanones such as **4k**−**m**, and allows the introduction of a number of functional groups in a pattern otherwise not easily accessible.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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