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Synthesis of Fluorenone and Anthraquinone Derivatives from Aryl- and Aroyl-Substituted Propiolates

Florian Pünner, Justin Schieven, and Gerhard Hilt*

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Str.,
35043 Marburg, Germany

hilt@chemie.uni-marburg.de

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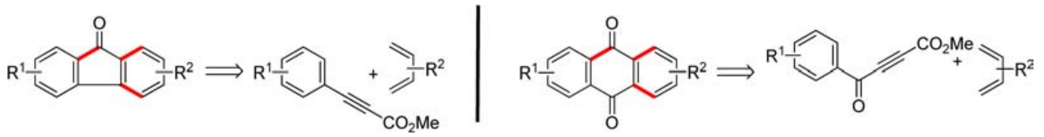
ABSTRACT



Fluorenone derivatives were generated from aryl-substituted propiolates via a cobalt-catalyzed Diels–Alder reaction/DDQ-oxidation and Friedel–Crafts-type cyclization. Several functional groups are tolerated, and good to excellent overall yields (up to 89%) could be achieved. For the synthesis of anthraquinone derivatives, aroyl-substituted propiolates were applied in a zinc iodide catalyzed Diels–Alder reaction with 1,3-dienes. The subsequent DDQ oxidation and Friedel–Crafts-type cyclization led to symmetrical as well as some unsymmetrical anthraquinones in good to excellent yields of up to 87% over the three-step reaction sequence.

Fluorenone and anthraquinone moieties can be found in nature as part of natural products,[1] and many applications of fluorenone- and anthraquinone-type materials appear in material chemistry and related sciences. The syntheses of fluorenones and anthraquinones are well documented, and several synthetic approaches exist with different scope and limitations, such as the double Friedel–Crafts-type cyclizations of phthalic anhydride[2] and thermal Diels–Alder reactions of naphthoquinones.[3] Most recently, C–H activation of diarylketones to fluorenones[4] and biomimetic synthesis via cyclization reactions of appropriate polyketides toward anthraquinones were also reported.[5]

Based on our cobalt-catalyzed Diels–Alder reactions of alkynes with 1,3-dienes,[6] we investigated the possibilities of using an aryl-substituted propiolate (**1**) as a synthon for an

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(1) (a) Thomson, R. H. *Naturally Occurring Quinones IV*; Blackie Academic & Professional: London, 1997; pp 309–483. (b) Huang, Q.; Shen, H.-M.; Chung, M. C. M.; Ong, C. N. *Med. Res. Rev.* **2007**, *27*, 609. (c) Dhananjeyan, M. R.; Milev, Y. P.; Kron, M. A.; Nair, M. G. *J. Med. Chem.* **2005**, *48*, 2822. (d) Pickhardt, M.; Gazova, Z.; von Bergen, M.; Khlistunova, I.; Wang, Y.; Hascher, A.; Mandelkow, E.-M.; Biernat, J.; Mandelkow, E. *J. Biol. Chem.* **2005**, *280*, 3628. (e) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679. (f) Tierney, M. T.; Grinstaff, M. W. *J. Org. Chem.* **2000**, *65*, 5355. (g) González-Cantalapiedra, E.; de Frutos, O.; Atienza, C.; Mateo, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2006**, 1430. (h) Shultz, D. A.; Sloop, J. C.; Washington, G. *J. Org. Chem.* **2006**, *71*, 9104. (i) Itami, K.; Tonogaki, K.; Nokami, T.; Ohashi, Y.; Yoshida, J.-I. *Angew. Chem., Int. Ed.* **2006**, *45*, 2404. (j) Usta, H.; Facchetti, A.; Marks, J. T. *Org. Lett.* **2008**, *10*, 1385. For selected recent reviews, see: (k) Ormond, A. B.; Freeman, H. S. *Materials* **2013**, *6*, 817. (l) Zhang, X.; Guo, Y.; Liu, M.; Zhang, S. *RSC Advances* **2013**, *3*, 2846.

(2) For historical examples, see: (a) Baeyer, A. *Chem. Ber.* **1871**, *4*, 663. (b) Grimm, F. *Chem. Ber.* **1873**, *6*, 506. (c) Baeyer, A.; Caro, H. *Chem. Ber.* **1875**, *8*, 152. (d) Lagodzinski, K. *Chem. Ber.* **1895**, *28*, 1427. (e) Harrop, D.; Norris, R. V.; Weizmann, C. *J. Chem. Soc.* **1909**, *95*, 1317.

(3) (a) Krohn, K.; Klimars, M.; Köhle, H.-J.; Ebeling, E. *Tetrahedron* **1984**, *40*, 3677. (b) Kelly, T. R.; Parekh, N. D. *J. Org. Chem.* **1982**, *47*, 5009. (c) Brisson, C.; Brassard, P. *J. Org. Chem.* **1981**, *46*, 1810.

(4) (a) Wertz, S.; Leifert, D.; Studer, A. *Org. Lett.* **2013**, *15*, 928. (b) Gandeepan, P.; Hung, C.-H.; Cheng, C.-H. *Chem. Commun.* **2012**, *48*, 9379. (c) Chinnagolla, R. K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 5246. (d) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462 –9465.

(5) (a) Cordes, J.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2013**, 1318. (b) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 652. (c) Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5748. (d) Miyatake-Ondozabal, H.; Barrett, A. G. M. *Tetrahedron* **2010**, *66*, 6331. (e) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.

(6) (a) Danz, M.; Hilt, G. *Adv. Synth. Catal.* **2011**, *353*, 303. (b) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893. (c) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (d) Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952. (e) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (f) Hilt, G.; Hengst, C. *J. Org. Chem.* **2007**, *72*, 7337. (g) Hilt, G.; Hengst, C. *Synlett* **2006**, 3247. (h) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204. (i) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537.

10.1021/ol4023276

aroyl moiety to generate fluorenones (**3**) and aroyl-substituted propiolates (**2**) to generate anthraquinones of type **4** (Figure 1).[7]

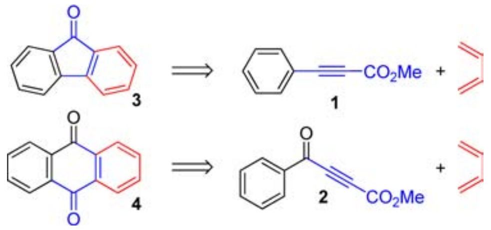
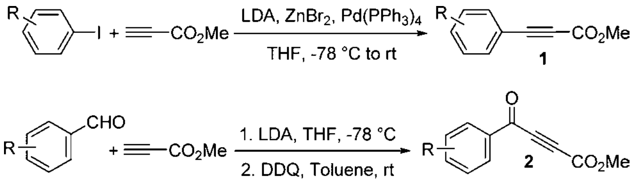


Figure 1. Retrosynthetic approach toward fluorenones (**3**) and anthraquinones (**4**).

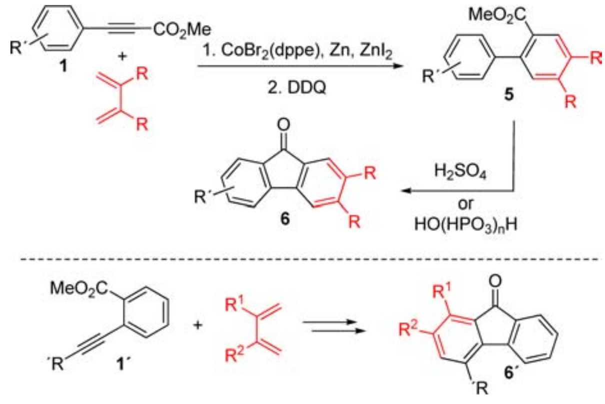
For the synthesis of starting materials of type **1** (Scheme 1), a Negishi cross-coupling of the corresponding aryl iodide with methyl propiolate gave the desired materials in excellent yields (90−96%, see Supporting Information (SI)).[8] The synthesis of the aroyl-substituted starting materials of type **2** was realized by addition of the deprotonated propiolate ester to various aldehydes[9] and subsequent oxidation of the propargylic alcohol to the corresponding ketone. This sequence could be realized in up to 84% yield over two steps (see SI).

Scheme 1. Synthesis of the Aryl- (**1**) and Aroyl-Substituted Propiolates (**2**)



For the synthesis of fluorenones, the aryl-substituted propiolates of type **1** were reacted with symmetrical 1,3-dienes such as 1,3-butadiene and 2,3-dimethyl-1,3-butadiene applying a cobalt catalyst mixture comprising $CoBr_2$(dppe), zinc powder, and zinc iodide (Scheme 2).[10] The dihydroaromatic intermediates were immediately oxidized with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) to afford the corresponding diaryl esters **5** which were then converted to the desired fluorenones **6** with H_2SO_4 (concd) or polyphosphoric acid. Alternatively, we also investigated the application of alkynyl-substituted benzoates (**1′**) as starting materials in the cobalt-catalyzed Diels−Alder reaction. Following the same reaction sequence of oxidation and Friedel−Crafts-type cyclization, fluoreneone derivatives of type **6′** were obtained. The results of this three step reaction sequence are summarized in Table 1.

Scheme 2. Synthesis of Fuorenones (**6**) via Cobalt-Catalyzed Diels−Alder/DDQ Oxidation/Friedel−Crafts Reaction Sequence



The synthesis of the fluorenone derivatives could be accomplished in good to excellent yields. The cobalt-catalyzed Diels−Alder reaction could be realized with 1,3-butadiene to afford fluorenone (**6a**) in an excellent overall yield of 89% over three steps (entry 1). Also, 2,3-dimethyl-1,3-butadiene was applied successfully, leading to the 3,4-dimethyl-substitution pattern in one of the rings of the fluorenones (entries 2−6). Moreover, the alternative route applying 2-alkynyl benzoates (**1′**) for the synthesis of other fluorenone derivatives (entries 7−10) could be realized with good success. Thereby, fluorenones were generated under the same reaction conditions to achieve other substitution patterns.

The Friedel−Crafts-type cyclization proves to be problematic for several substrates when concentrated sulfuric acid was used. In some cases (entries 3, 8, 9) polyphosphoric acid with mechanical stirring proved to be advantageous. Only in one case (entry 7) when the derivative with the hydroxy group was applied the desired product **6g** could only be obtained in trace amounts. Interestingly, the halide substituted aryl-propiolates could be applied with good success. The functionalized derivatives **6d**/**6e** were obtained in good yields without any sign of protodehalogenation. Accordingly, similar derivatives can be envisaged as a platform for the synthesis of more complex fluorenones.

Encouraged by these results we turned our attention to the synthesis of anthraquinone-type molecules. Therefore, we envisaged that alkynols, such as **7** (Scheme 3), would undergo the cobalt-catalyzed Diels−Alder reaction in a similar fashion and that subsequent oxidation and cyclization would lead to anthraquinones.

Unfortunately, all attempts to react **7** with 2,3-dimethyl-1,3-butadiene under the conditions of the previously

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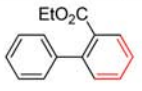
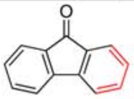
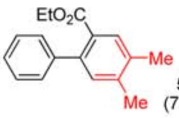
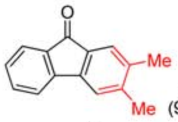
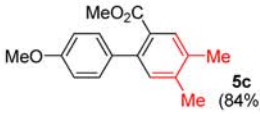
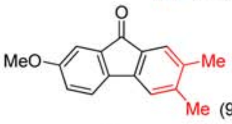
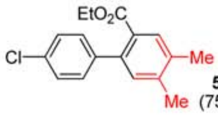
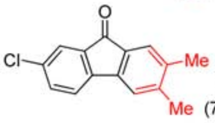
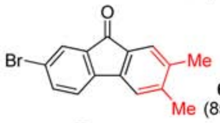
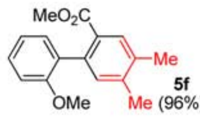
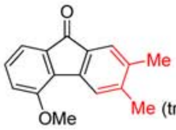
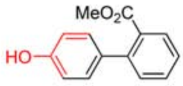
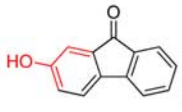
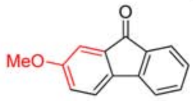
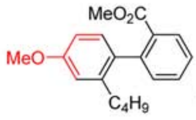
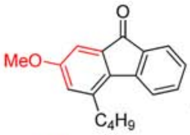
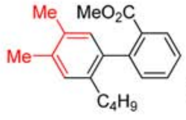
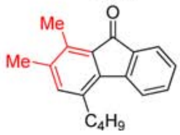
[7] For a Diels−Alder reaction of aroyl propiolate type starting materials, see: (a) Khalaf, A.; Grée, D.; Abdallah, H.; Jaber, N.; Hachem, A.; Grée, R. *Tetrahedron* **2011**, *67*, 3881. (b) Thiemann, T.; Fujii, H.; Ohira, D.; Arima, K.; Li, Y.; Mataka, S. *New J. Chem.* **2003**, *27*, 1377. (c) Obrecht, D.; Zumbrunn, C.; Müller, K. *J. Org. Chem.* **1999**, *64*, 6182. (d) Obrecht, D. *Helv. Chim. Acta* **1991**, *74*, 27. (e) Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 1772.

[8] Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.

[9] Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657.

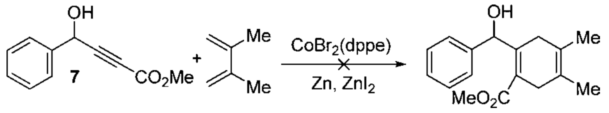
[10] No conversion was observed in the absence of the cobalt complex under otherwise identical reaction conditions.

Table 1. Results for the Cobalt-Catalyzed Diels–Alder Reaction/DDQ Oxidation to **5** and Friedel–Crafts Cyclization to **6**[a]

no.	product **5** (yield)	product **6** (yield)
1	 **5a** (93%)	 **6a** (96%)
2	 **5b** (77%)	 **6b** (96%)
3[b]	 **5c** (84%)	 **6c** (94%)
4	 **5d** (75%)	 **6d** (79%)
5	 **5e** (82%)	 **6e** (85%)
6[c]	 **5f** (96%)	 **6f** (traces)
7[d]	 **5g** (79%) (*p*/*m* = 10:1)	 **6g** (traces)
8[b]	 **5h** (51%)	 **6h** (95%)
9[b]	 **5i** (61%)	 **6i** (92%)
10	 **5j** (71%)	 **6j** (96%)

[a] $CoBr_2$(dppe) (10 mol %), zinc powder (20 mol %), zinc iodide (20 mol %), alkyne **1** (1.0 equiv), and diene (2.0 equiv), CH_2Cl_2, 16 h, rt, then DDQ (1.1 equiv), toluene, rt; unless otherwise noted: concd H_2SO_4, rt, 1–2 h. [b] Polyphosphoric acid, 2 h, 80 °C. [c] The product was obtained as a mixture of **6f** and **10** (see below). [d] Cyclization attempts using H_2SO_4 or polyphosphoric acid did not lead to the product.

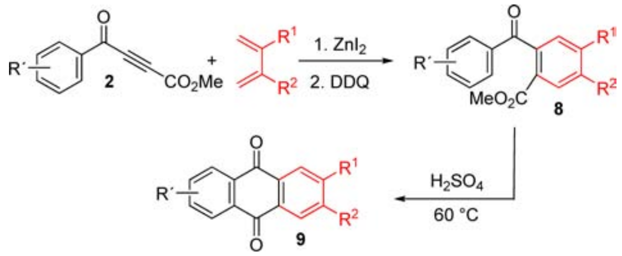
Scheme 3. Attempted Synthesis of the Anthraquinones via Cobalt-Catalyzed Diels–Alder Reaction from Alkynols of Type **7**



successful conversions with cobalt catalysts failed, leading only to a number of unidentified side products.

Therefore, we decided to oxidize the propargylic alcohol before the cycloaddition reaction and to test the aroyl-substituted propiolate **2** in the cycloaddition process (Scheme 4). To our delight, this approach was successful and led to the desired cycloaddition product **8** after DDQ oxidation.

Scheme 4. Synthesis of Anthraquinones (**9**) via ZnI_2-Catalyzed Diels–Alder Reaction/Oxidation/Friedel–Crafts Cyclization



However, in control experiments, we realized that, unlike in the case of the fluorenone synthesis (Scheme 2), the cobalt catalyst was not necessary for the cycloaddition of **2** to proceed efficiently. Actually, zinc iodide proved to be a very mild but efficient catalyst for this Lewis acid catalyzed Diels–Alder reaction to proceed. The results of the ZnI_2-catalyzed Diels–Alder reaction/DDQ oxidation/Friedel–Crafts-type cyclization sequence are summarized in Table 2.

The ZnI_2-catalyzed Diels–Alder reaction gave good to excellent yields with 2,3-dimethyl-1,3-butadiene whereas with 1,3-butadiene (entries 8/9) and 2-methoxy-1,3-butadiene (entry 11) only moderate yields could be obtained.[11] The acid-promoted cyclization could be realized for most substrates, while only for the bromo-substituted derivative **9c** (entry 3) a low yield was obtained. The cyclization of the 2- and 4-methoxy derivatives **8c**/**8e** failed completely, and only decomposition was observed. The cyclization most likely failed based on the mismatching directing effects of the carbonyl group as well as of the methoxy substituent in **8c**/**8e** for the Friedel–Crafts-type cyclization. Accordingly, when the 3-methoxy derivative **8d** was applied, the *para*-position is activated and the Friedel–Crafts acylation gave the desired product **9c** in 44% yield which was identical to the previously addressed product. In that reaction sequence the other possible regioisomere (**9d**) was also obtained in 9% yield whereas the application of **8e** did not led to product **9d**. For the other dimethoxy- and trimethoxy-substituted derivatives, the

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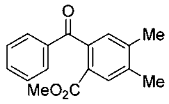
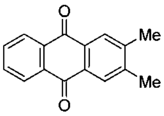
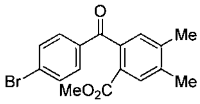
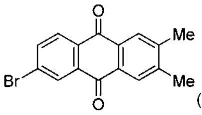
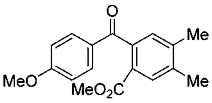
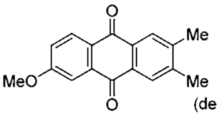
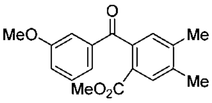
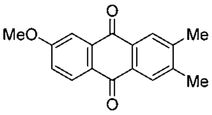
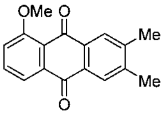
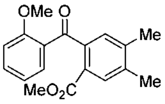
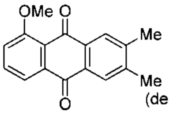
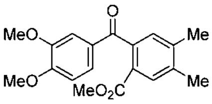
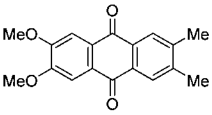
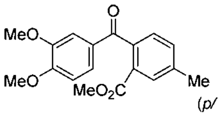
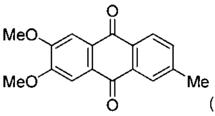
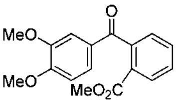
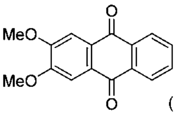
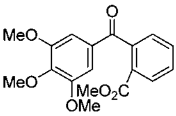
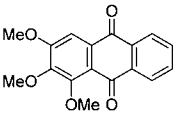
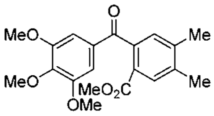
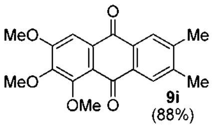
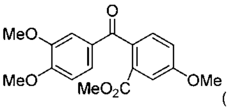
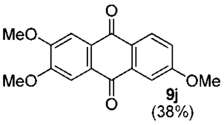
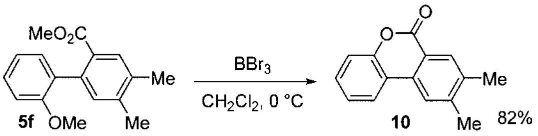
[11] Only up to 15% of the Diels–Alder adduct were detectable by GCMS in the absence of zinc iodide after 24 h at room temperature.

Table 2. Results for the Zinc Iodide Catalyzed Diels–Alder Reaction/DDQ Oxidation to **8** and Friedel–Crafts Cyclization to **9**[a]

no.	product **8** (yield)	product **9** (yield)
1	 **8a** (92%)	 **9a** (90%)
2[b]	 **8b** (88%)	 **9b** (24%)
3	 **8c** (98%)	 **9c** (decomp)
4	 **8d** (82%)	 **9c** (44%)  **9d** (9%)
5	 **8e** (82%)	 **9d** (decomp)
6	 **8f** (91%)	 **9e** (96%)
7	 **8g** (65%) (*p*/*m* = 87:13)	 **9f** (91%)
8[c]	 **8h** (51%)	 **9g** (87%)
9[c]	 **8i** (65%)	 **9h** (92%)
10	 **8j** (78%)	 **9i** (88%)
11	 **8k** (40%)	 **9j** (38%)

[a] Unless otherwise noted: zinc iodide (10 mol %), alkyne **2** (1.0 equiv) and diene (2.0 equiv), CH_2Cl_2, 16 h, rt, then DDQ (1.1 equiv), toluene, rt; concd H_2SO_4, 60 °C. [b] Cyclization was performed at 120 °C. [c] Diels–Alder reaction and DDQ oxidation were performed at 40 °C.

Scheme 5. Synthesis of 6*H*-Benzo[*c*]chromen-6-one **10**



Friedel–Crafts-type cyclization could be performed without problems and the desired anthraquinones could be obtained in good yields.

The presented protocol led to the product **9f** which was isolated from *Hedyotis diffusa*.[12] Also, product **9h** can be found in nature,[13] and both products were generated in short reaction sequences in good overall yields of 59% and 60% respectively.

Finally, we also identified a side product from the Friedel–Crafts-type cyclization for the synthesis of fluorenone derivative **6f** (Table 1, entry 6). The product was obtained as an inseperable mixture with the corresponding lactone in low yield. In order to facilitate this reaction the Lewis acid BBr_3 was applied.[14] In this case the benzo-[*c*]chromen-6-one derivative **10** could be obtained as a single product in 82% yield (Scheme 5).

In conclusion, we were able to demonstrate that cobalt, as well as ZnI_2-catalyzed Diels–Alder reactions of aryl- and aroyl-substituted propiolates, can be used for the synthesis of multifunctionalized fluorenone and anthraquinone derivatives in short reaction sequences in good to excellent overall yields. Therefore, interesting functionalized fluorenone and polysubstituted anthraquinone derivatives were addressable which can be used for follow-up transformations. The scopes and some limitations of the cyclization for both types of products could be evaluated and, as expected, the more electron-donating alkyl- or methoxy-groups that are present in the ring, the more efficient the Friedel–Crafts-type cyclization proceeds. The flexibilty of the synthetic approach also allows the possibility of circumventing some limitations imposed by the requirements for the Friedel–Crafts-type cyclization.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft for financial support.

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

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