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Synthesis and Characterization of Polycarbonyl Compounds via their BF_2-Adducts

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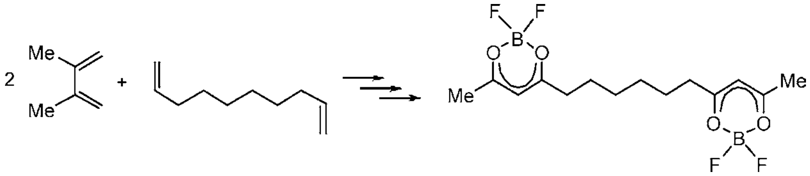
ABSTRACT

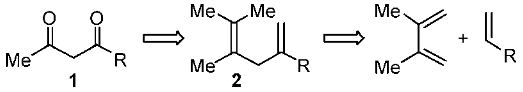


A cobalt-catalyzed 1,4-hydrovinylation reaction is the key step in the synthesis of 1,3-dicarbonyl and higher tri- and tetracarbonyl compounds after ozonolysis of the 1,4-diene intermediates. For the isolation and characterization of the products, the 1,3-dicarbonyl subunits were complexed with a BF_2- or a BR_2-fragment eliminating the keto−enol tautomerisation. Other 2,3-disubstituted 1,3-butadienes can be generated by a Grubbs enyne metathesis of a symmetrical internal alkyne with ethene. After hydrovinylation and ozonolysis, other 1,3-diketones are accessible.

Compounds with a 1,3-dicarbonyl group have found a large number of various applications in modern synthetic organic chemistry whereas tricarbonyl, tetracarbonyl and polycarbonyl derivatives are far less often described in the literature.[1,3e] Nature, on the other hand, regularly utilizes polycarbonyl compounds as starting materials for the synthesis of phenoles and other polycyclic aromatic natural products such as tetracyclines.[2]

Our approach toward the synthesis of 1,3-dicarbonyl derivatives starts with the synthesis of linear precursors generated by a cobalt-catalyzed 1,4-hydrovinylation reaction (Scheme 1).[3] The 1,4-dienes (**2**) derived therefrom can be easily purified and thereafter converted into the corresponding 1,3-dicarbonyl derivatives **1** by ozonolysis. In this context we recently reported the synthesis of some small natural products.[4]

Scheme 1. Synthesis of 1,3-Dicarbonyl Derivatives from a 1,3-Diene and a Terminal Alkene



To investigate the synthetic approach toward unsymmetrical 1,3-dicarbonyl compounds and then polycarbonyl derivatives, the cobalt-catalyzed 1,4-hydrovinylation of terminal alkenes was extended toward the synthesis of more complex 1,4-dienes and polyenes (Scheme 2). The results of these investigations are summarized in Table 1.

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(1) (a) Bringmann, G. *Angew. Chem., Int. Ed.* **1982**, *21*, 200. (b) Bringmann, G. *Liebigs Ann. Chem.* **1985**, 2105. (c) Krohn, K. *Eur. J. Org. Chem.* **2002**, 1351. (d) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (e) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677. (f) Reim, S.; Michalik, D.; Weisz, K.; Xiao, Z.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 3079.

(2) Leading references: *Chem. Rev.* **1997**, *97*, issue 7 gives a comprehensive introduction into biochemical and biological aspects of polyketides; see also: Sattely, E. S.; Fischbach, M. A.; Walsh, C. T. *Natural Prod. Rep.* **2008**, *25*, 757.

(3) (a) Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 387. (b) Hilt, G.; Lüers, S. *Synthesis* **2002**, 609. (c) Hilt, G.; Lüers, S.; Schmidt, F. *Synthesis* **2003**, 634. (d) Hilt, G.; Danz, M.; Treutwein, J. *Org. Lett.* **2009**, *11*, 3322. (e) Hilt, G.; Weske, D. F. *Chem. Soc. Rev.* **2009**, *38*, 3082. (f) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395.

(4) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321.

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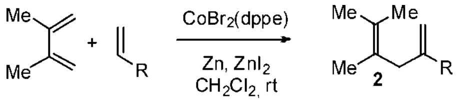
Scheme 2. Cobalt-Catalyzed 1,4-Hydrovinylation of Terminal Akenes with 2,3-Dimethyl-1,3-butadiene



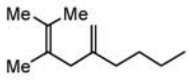
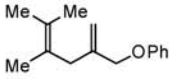
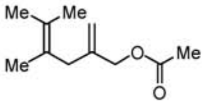
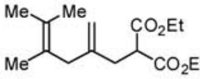
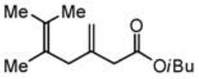
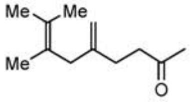
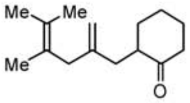
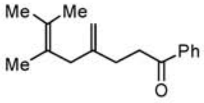
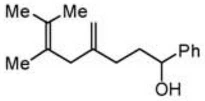
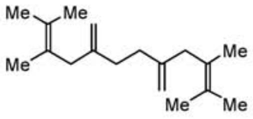
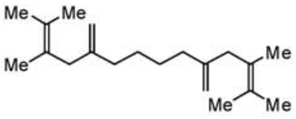
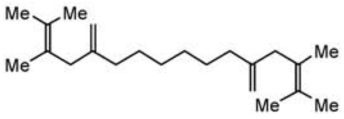
With only very few exceptions (Table 1, entries 10 and 13), the cobalt-catalyzed 1,4-hydrovinylation of terminal alkenes is a high-yielding process and results very often in clean products of type **2** after simple filtration through a small plug of silica gel to remove the inorganic components and the catalyst system from the reaction mixture. Within this investigation, we focus upon additional oxygen based functionalities present in the starting materials. Accordingly, unprotected alcohol (entry 9), ketone and ester functionalities are accepted. Even if the functional groups are considered to be good leaving groups (entries 2 and 3) the yields remain high, indicating a reduced tendency to generate π-allyl complexes from such intermediates in comparison to transformations induced by palladium.[5]

The ozonolysis of these materials of type **2** obtained by the cobalt-catalyzed 1,4-hydrovinylation reaction leads to simple 1,3-dicarbonyl derivatives such as octane-2,4-dione from **2a** as well as a more complex hexacarbonyl derivative generated from **2m**.

However, the keto−enol tautomerisation of ketones complicates the assignment of the NMR signals, even more so when multiple carbonyl groups, such as 1,3,5-tricarbonyl compounds, are present. In addition, such tri- or tetracarbonyl derivatives are very hard, if not impossible, to purify by simple column chromatography on silica gel. This is based on their strong affinity to silica gel and other usually applied stationary phases.[6] Unfortunately, the higher carbonyl derivatives are also sensitive toward acidic and basic conditions leading to unwanted degradation or condensation reactions. It is therefore advantageous to identify a protecting group to allow a simple purification and characterization of the materials generated after ozonolysis by surpressing the keto−enol tautomerisation. Under these circumstances, several approaches including complexation with main group elements and transition metals[7] can be found in the literature. Inspired by conversations with Prof. Reinhard Hoffmann, we investigated different boron-based protecting groups for 1,3-dicarbonyl compounds.

For this purpose, the commercially available compound 1-phenylbuta-1,3-dione **3** was used as the prototype substrate and converted into different boron derivatives **4** in order to identify a suitable protecting group to minimize the mentioned disadvantages when dealing with polycarbonyl derivatives (Scheme 3).

Table 1. Results of the Cobalt-Catalyzed 1,4-Hydrovinylation Reactions of Terminal Alkenes with 2,3-Dimethyl-1,3-butadiene[a]

entry	product **2**	yield
1	**2a** 	97%
2	**2b** 	98%
3	**2c** 	94%
4	**2d** 	92%
5	**2e** 	98%
6	**2f** 	97%
7	**2g** 	94%
8	**2h** 	99%
9	**2i** 	94%
10	**2j** 	57%
11	**2k** 	92%
12	**2l** 	96%
13	**2m** 	47%[a]

[a] E = CO_2Me.

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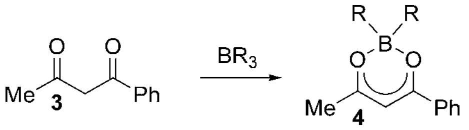
(5) Materials similar to **2c** have been used in palladium-catalyzed Tsuji−Trost reactions: Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.

(6) Personal communication with Prof. K. Krohn, Paderborn University, Germany as well as with Prof. M. Albrecht RWTH Aachen, Germany.

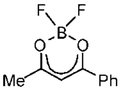
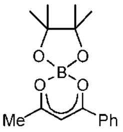
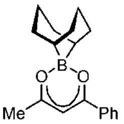
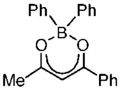
(7) Leading references: (a) Mehrotra, R. C.; Bohra, R.; Gaur, D. P. In *Metal β-Diketonates and Allied Derivatives*; Academic Press, New York, 1978. See also: . (b) Macedo, F. P.; Gwengo, C.; Lindeman, S. V.; Smith, M. D.; Gardinier, J. R. *Eur. J. Inorg. Chem.* **2008**, 3200. (c) Ono, K.; Yoshikawa, K.; Tsuji, Y.; Yamaguchi, H.; Uozumi, R.; Tomura, M.; Taga, K.; Saito, K. *Tetrahedron* **2007**, *63*, 9354.

Scheme 3. Protection of a 1,3-Dicarbonyl Compound as Dioxaborinine Derivative **4**



The results of these investigations are summarized in Table 2. The best results were obtained for the BF_2-subunit generated from simple $BF_3·OEt_2$ and the BPh_2-subunit obtained from conversion with BPh_3, whereas the latter is much more expensive. Unfortunately, the much less expensive $BPh_3·NaOH$ complex did not result in the desired compound in high yield. However, yield is not the only factor that must be considered: stability toward decomposition is also of crucial importance. Unfortunately, we identified several boron-based protecting groups R = alkyl (entry 5 and **7c**, **7d**) which showed considerable degrees of decomposition in solution ($CDCl_3$) after 12−24 h (see Supporting Information).

Table 2. Results of the Complexation of a 1,3-Dicarbonyl Functionality by Boron Derivatives

entry	BR_2 source	product 4	yield
1	$LiBF_4$	**4a** 	0%
2	[BMIM]BF_4	**4a**	0%
3	$BF_3·OEt_2$	**4a**	84%
4	(Pin)BO*i*Pr	**4b** 	0%
5	MeO-9-BBN	**4c** 	77%
6	BPh_3	**4d** 	94%
7	$BPh_3·NaOH$	**4d**	10%
8	$BPh_3·SMe_2$	**4d**	48%

On the basis of these results, we focused our attention upon the development of a process to generate, protect, isolate and characterize the desired BF_2-complexed products without isolation of the intermediates. Accordingly, the materials of type **2** generated in the cobalt-catalyzed 1,4-hydrovinylation reaction were subjected to ozonolysis followed by reductive workup with dimethyl sulfide and *in situ* complexation of the 1,3-dicarbonyl compounds with $BF_3•OEt_2$ (Scheme 4).

Scheme 4. Protection of a 1,3-Dicarbonyl Compound as Difluorodioxaborinine Derivative

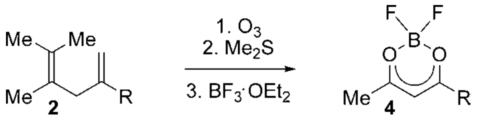
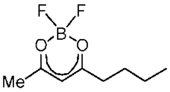
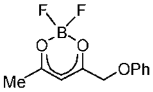
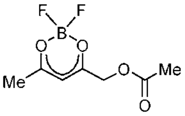
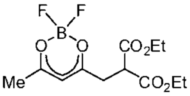
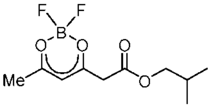
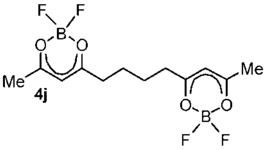
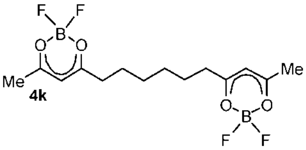
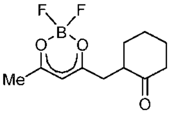
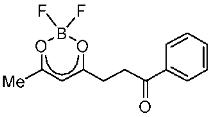


Table 3. Results of the One-Pot Procedure for the Generation of Difluorodioxaborinine Derivatives

entry	product 4	yield (over three steps)
1	**4e** 	32%
2	**4f** 	46%
3	**4g** 	56%
4	**4h** 	76%
5	**4i** 	76%
6	**4j** 	24%
7	**4k** 	30%
8	**4l** 	38%
9	**4m** 	45%

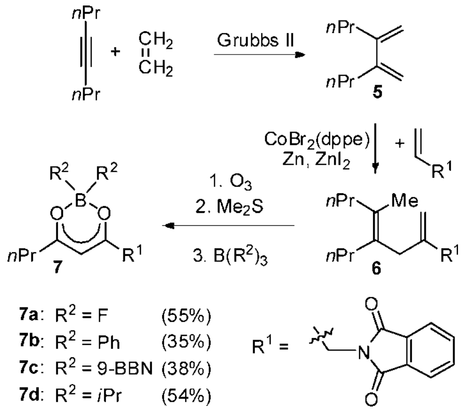
The results of this three step, one-pot procedure for the synthesis of protected 1,3-dicarbonyl derivatives of type **4** are summarized in Table 3.

Although the isolated yields of materials such as **4j** are relatively low, this is the first time that polycarbonyl derivatives have been isolated by column chromatography and characterized as a single compound by NMR as shown in the Supporting Information. In earlier reports, similar compounds are far less well characterized.[8] For those products of type **4** bearing additional ester functionalities, acceptable to good yields (entries 4 and 5) can be reported. Accordingly, we believe that the protection as a difluorodioxaborinine derivative of type **4** represents a significant improvement. Although high yields are not universally achieved at the present time, the protocol is a considerable improvement because the intermediately formed 1,3-dicarbonyl derivatives can be easily isolated and well characterized as a BF_2 adduct proving the nature of the intermediate indirectly.

The hydrovinylation utilizing the symmetrical 2,3-dimethyl-1,3-butadiene implies the limitation that one side of the 1,3-dicarbonyl product is always methyl substituted. To overcome this limitation other symmetrical 2,3-disubstituted 1,3-dienes must be used in a 1,4-hydrovinylation reaction (Scheme 5).[9]

Accordingly, we utilized a ruthenium-catalyzed enyne metathesis reaction of 4-octyne to generate the desired symmetrical 2,3-disubstituted 1,3-diene **5**. Then a cobalt-catalyzed 1,4-hydrovinylation with allyl-phthalimide as the alkene component was used to obtain the desired 1,4-dienes of type **6**. At this stage the ozonolysis/reductive workup/protection sequence was utilized to generate different BR_2-protected 1,3-diene derivatives (**7**). Although the best results for products of type **7** (R^1 = CH_2-phthalimide) in terms of isolated yields[10] were obtained for the bis-isopropyl derivative **7d** and the BF_2-adduct **7a**, the latter proved to be superior based on its higher stability.

Scheme 5. Reaction Sequence for the Flexible Generation of Various 1,3-Dicarbonyl Compounds and Protection as Difluorodioxaborinine Derivatives



Acknowledgment. This work was partly supported by the German Science Foundation.

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

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(8) Very often melting points, IR, UV or mass spectra were reported for the characterisation of polycarbonyl derivatives; see: Kirkemo, C. L.; White, J. D. *J. Org. Chem.* **1985**, *50*, 1316.

(9) The cobalt complexes investigated thus far in the 1,4-hydrovinylation reaction of unsymmetrical 1,3-dienes gave the regioisomer as major product so that the ozonolysis produces a 3-keto-aldehyde.

(10) The reported yields correspond to the yield obtained starting from **6** (R^1 = CH_2-phthalimide).