ORGANIC
LETTERS

2004
Vol. 6, No. 10
1523−1526

Oxidative C–C Bond-Forming Reaction of Electron-Rich Alkylbenzyl Ether with Trimethylvinyloxysilane

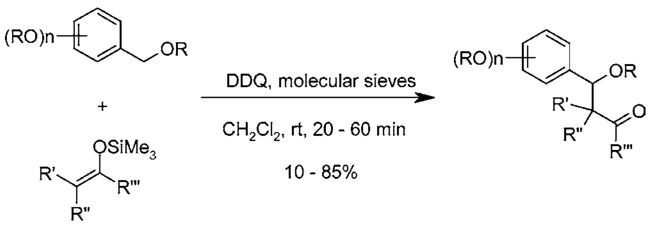
Bai-Ping Ying, Bridget G. Trogden, Daniel T. Kohlman, Sidney X. Liang, and Yao-Chang Xu*

Discovery Chemistry Research, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, Indiana 46285

xu_yao-chang@lilly.com

Received November 27, 2003

ABSTRACT

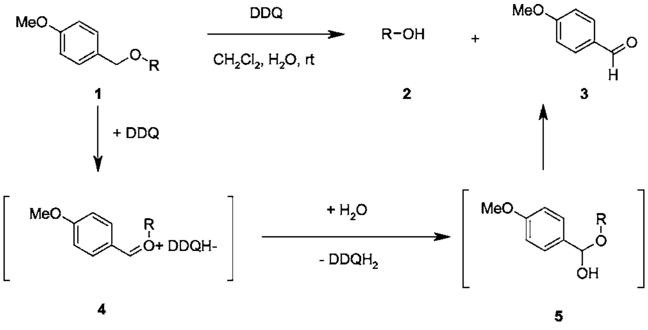


Treatment of an electron-rich benzyl ether with DDQ at ambient temperature followed by addition of a silyl enol ether undergoes a C–C bond-forming reaction to afford 3-alkoxy-3-phenyl-propionyl compound. This is a general reaction and works well with a variety of silyl enol ethers to give carbonyl products in yields ranging from 10 to 85%.

Since the initial report of using *p*-methoxybenzyl (MPM) to protect the hydroxy functional group by Oikawa in 1982,[1] this protection and deprotection methodology has been extensively utilized in organic chemistry, particularly in complicated natural product syntheses.[2] The widespread use of this technology in the organic chemistry community can be attributed to the relative stability of the MPM ether in both acidic and basic conditions and, more importantly, the ease of removing the MPM group under oxidative conditions. Many other electron-rich benzyl ethers, including 3,4-dimethoxybenzyl (DMPM), 3-methoxybenzyl (3-MPM), and 3,5-dimethoxybenzyl (3,5-DMPM) have since been developed for use in alcohol protections.[3]

The reagent of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been successfully used for the cleavage of MPM and other electron-rich benzyl protecting groups.[1−3] Operationally, treatment of MPM ether in dichloromethane and a small amount of water with slightly more than 1 equiv of DDQ at room temperature can liberate the alcohol in very high yield (Scheme 1). Besides the formation of the

Scheme 1



---

[1] Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

[2] (a) Dinh, T. Q.; Du, X.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606−6616. (b) Hirschmann, R.; Ducry, L.; Smith, A. B., III. *J. Org. Chem.* **2000**, *65*, 8307−8316. (c) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521−10532. (d) Gurjar, M. K.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552−7554.

[3] (a) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393−5396. (b) Nakajima, N.; Abe, R.; Yonemitsu, O. *Chem. Pharm. Bull.* **1988**, *36*, 4244−4247.

10.1021/ol036314j CCC: $27.50

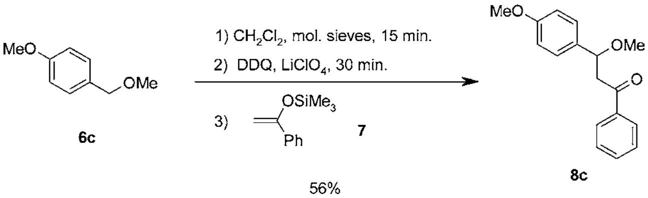
byproduct dihydroquinone ($DDQH_2$), which results from the reduction of DDQ, the reaction always produces the *p*-methoxybenzaldehyde **3** (Scheme 1). The formation of aldehyde **3** is not the focus for this operation, and **3** is usually removed by column flash chromatography.

The mechanism for this process is presented in Scheme 1. It is known that electron-rich benzyl ethers such as **1** can react with DDQ to form a charge-transfer complex.[3a] A rapid color change, usually from colorless to deep blue, is observed when a solution of **1** is combined with DDQ, an indication of the formation of the charge-transfer complex **4**. The positive charge of complex **4** is localized onto the oxygen atom as shown, which can serve as an activated electrophile, and is ready to be coupled with any potential nucleophiles. In this particular case, water serves as a nucleophile that couples with **4** to form hemiacetal **5** along with the formation of $DDQH_2$ byproduct. Hemiacetal is usually not stable, and decomposition of **5** provides the desired alcohol **2** and benzaldehyde **3**.

Understanding the mechanism, we asked which other nucleophiles could be potentially used to couple with the charge-transfer complex **4**. Herein we report our initial finding that centers on the C−C bond construction through carbon nucleophiles. It is expected that the coupling reaction of **4** or similar structures with a carbon nucleophile will lead to a product, which, unlike hemiacetal **5**, will be stable for isolation and a potentially useful substrate for organic synthesis.

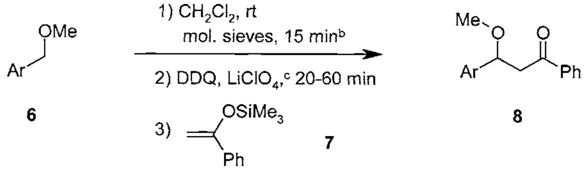
On the basis of recent findings from our laboratory that isochroman treated with DDQ can couple with silyl enol ethers[4] and many literature reports that in situ-generated cations can react with silyl enol ethers to form carbonyl products,[5] we first selected the trimethylvinyloxysilanes to test the proposed reaction. To our pleasant surprise, the C−C bond-forming reaction worked very well, as hoped. As shown in Scheme 2, *p*-methoxybenzyl methyl ether **6c**, dissolved in dichloromethane, was treated with DDQ for 30 min in the presence of a small amount of $LiClO_4$, followed by addition of trimethyl-(1-phenyl-vinyloxy)-silane **7**. The whole process was carried out under dry nitrogen at room temperature, and workup after 1 h afforded 3-methoxy-3-(4-methoxy-phenyl)-1-phenyl-propan-1-one **8c** in 56% isolated yield.

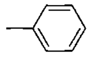
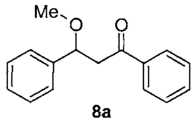
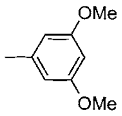
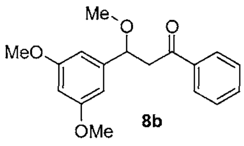
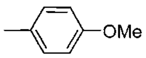
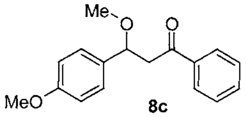
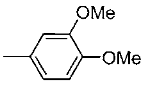
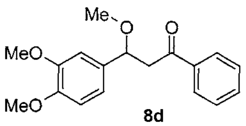
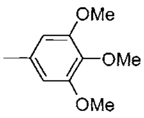
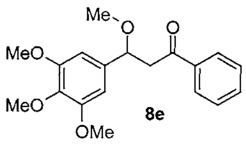
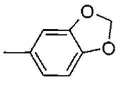
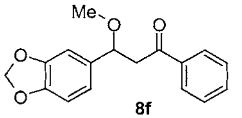
Scheme 2



The purpose of using molecular sieves is to remove water that might be present in the reaction mixture. To obtain higher yields, it is essential to use a dry agent for this reaction because the presence of water can compete with the desired C−C bond-forming process. Due to the practical difficulty of running a reaction in truly anhydrous conditions, a byproduct such as *p*-methoxybenzaldehyde, resulting from the coupling reaction with water present, has always been observed, albeit the yield for this byproduct is in the low single digits depending upon conditions.

Table 1. Study of DDQ-Assisted C−C Bond-Forming Reaction with a Variety of Electron-Rich Benzyl Ethers[a]



starting material	-Ar	product **8**[d]	yield[e]
6a		 **8a**	0%
6b		 **8b**	10%
6c		 **8c**	56%
6d		 **8d**	32%
6e		 **8e**	55%
6f		 **8f**	84%

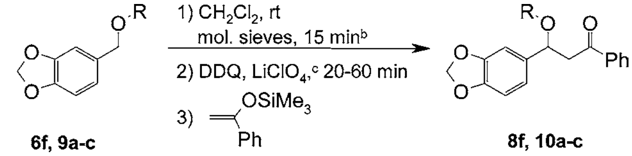
[a] All reactions were carried out in anhydrous conditions at room temperature under nitrogen pressure with 0.1 M solution of compound **6** in CH_2Cl_2. [b] Anhydrous dichloromethane purchased from Aldrich in a Sure/Seal bottle was used. [c] Performed with about 0.2−0.5 equiv of $LiClO_4$. [d] All products were characterized by ^{1}H NMR, MS, and elemental analysis. [e] Isolated yield after flash chromatography separation.

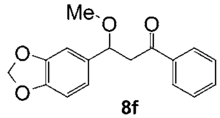
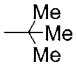
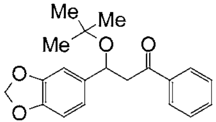
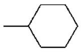
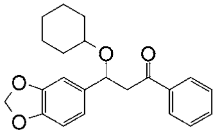
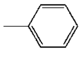
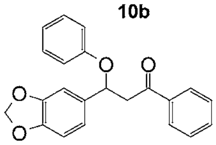
---

(4) (a) Xu, Y.-C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *34*, 8189−8192. (b) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599−1602. (c) Xu, Y.-C. *Recent Research Developments in Organic Chemistry*; Transworld Research Network: India, 2000; Vol. 4, pp 423−441.

(5) (a) Hashimoto, Y.; Mukaiyama, T. *Chem. Lett.* **1986**, 755−758. (b) Mukaiyama, T.; Hayashi, Y.; Hashimoto, Y. *Chem. Lett.* **1986**, 1627−1630. (c) Hashimoto, Y.; Mukaiyama, T. *Chem. Lett.* **1986**, 1623−1626. (d) Hayashi, Y.; Wariishi, K.; Mukaiyama, T. *Chem. Lett.* **1987**, 1243−1246.

Table 2. Study of DDQ-Assisted C−C Bond-Forming Reaction with 5-Alkoxymethyl and 5-Phenoxymethyl-benzo[1,3]dioxole[a]



starting material	-R	product[d]	yield[e]
6f	−Me	 **8f**	84%
9a		 **10a**	0%
9b		 **10b**	85%
9c		 **10c**	0%

[a] All reactions were carried out in anhydrous conditions at room temperature under nitrogen pressure with 0.1 M solution of compound **6** or **9** in CH_2Cl_2. [b] Anhydrous dichloromethane purchased from Aldrich in aSure/Seal bottle was used. [c] Performed with about 0.2−0.5 equiv of $LiClO_4$. [d] All products were characterized by ^{1}H NMR, MS, and elemental analysis. [e] Isolated yield after flash chromatography separation.

The addition of $LiClO_4$ is important for improving the efficiency for the coupling reaction. It is postulated that the ClO_4^- can undergo exchange of counterion with the charge-transfer complex **4** to form a new ion pair. Such a new ion pair usually serves as a better electrophile than the charge-transfer complex **4**.[6] Without $LiClO_4$ additive, the same reaction as indicated in Scheme 2 afforded product **8** in lower chemical yield (45%).

To understand the scope of this interesting reaction, we first tried to probe the electronic effect of the benzyl ring. Treatment of unsubstituted benzyl methyl ether **6a** with DDQ and followed by addition of silyl enol ether **7** did not yield any product **8a** (Table 1). In this case, the starting material **6a** was fully recovered. It is believed that the initial hydrogen abstraction from the benzylic position to form the charge-transfer complex is the rate-limiting step. Electron-donating substituents such as a methoxy group can stabilize the benzylic cationic species[7,8] and hence will promote the desired C−C bond-forming process. In the simple benzylic case, the absence of such a stabilizing substitution group prevents the occurrence of the initial hydrogen abstraction step. This is consistent with the fact that no color change (indicating no charge-transfer complex was formed) was observed when DDQ was added to the substrate.

From the resonance structure, the electron-donating group at the para position will provide a stronger stabilizing effect.[3a,8] The data in Table 1 support this principle. The reactions of compounds **6c**, **6d**, and **6e**, all possessing a *para*-methoxy group, with trimethyl-(1-phenyl-vinyloxy)-silane worked well to give products **8c**, **8d**, and **8e**, respectively, in moderate yields. The lower yield obtained for compound **8b** can be attributed to the less reactive starting material **6b** possessing two methoxy groups at the meta position of the benzene ring. It is interesting to observe that in the case of 5-methoxymethyl-benzo[1,3]dioxole (**6f**), the reaction with DDQ followed by trimethyl-(1-phenyl-vinyloxy)-silane provided product **8f** in the highest yield.[9]

The next area that was explored for this C−C bond-forming reaction concerned the “R” group attached to the benzylic “O” atom. As shown in Table 2, 5-alkoxymethyl-benzo[1,3]dioxole was used to study the effect of the “R” group in this coupling reaction because of the high yield achieved with this particular substrate. Following the typical protocol described earlier, the reaction of 5-*tert*-butoxymethyl-benzo[1,3]dioxole (**9a**) with trimethyl-(1-phenyl-vinyloxy)-silane did not produce any product **10a**. Both starting materials, however, were consumed, indicating that the reaction might proceed via a different pathway. Replacing the *tert*-butyl group by a cyclohexyl group, as in 5-cyclohexyloxymethyl-benzo[1,3]dioxole **9b**, worked very well in this DDQ-assisted C−C bond-forming reaction and afforded the coupling product **10b** in 85% isolated yield. In a sharp contrast to these data, the reaction of similar phenyl analogue **9c** with the same silyl enol ether **7** did not produce the desired product **10c**.

A plausible mechanism was proposed in trying to explain the results in Table 2. The DDQ-assisted hydrogen abstraction from benzyl ether leads to the formation of a cationic intermediate **11**. The relative stability of **11** is critical in

---

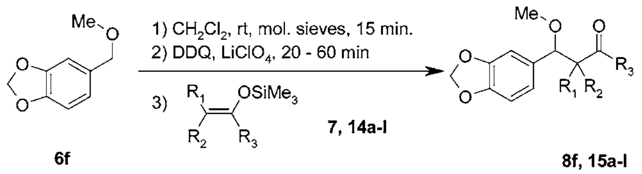
(6) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759−1762. (b) Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811−1814.

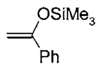
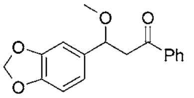
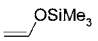
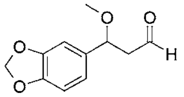
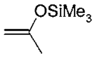
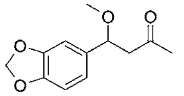
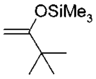
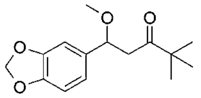
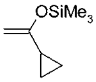
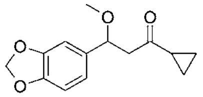
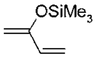
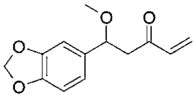
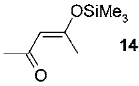
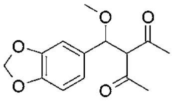
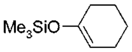
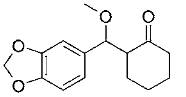
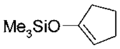
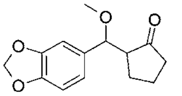
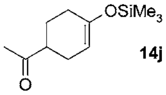
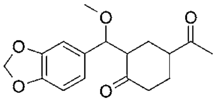
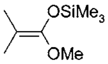
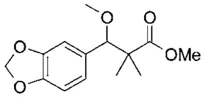
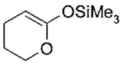
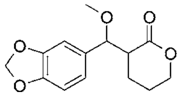
(7) (a) Becker, H. In *The Chemistry of Quinoid Compounds*; Patai, S., Ed.; Wiley: New York, 1974; p 335. (b) Becker, H.; Turner, A. B. In *The Chemistry of Quinoid Compounds*; Patai, S., Rappoport, Z., Ed.; Wiley: New York, 1988; Vol. II, p 1351.

(8) Oikawa, Y.; Horita, K.; Yoshioka, T.; Tanaka, T.; Yonemitsu, O. *Tetrahedron* **1986**, *41*, 3021−3028.

(9) A detailed typical reaction procedure for benzyl ether **6f** and silyl enol ether **7** is as follows: To a stirred solution of compound **6f** (404 mg, 2.43 mmol) in 10 mL of anhydrous dichloromethane was added activated 4 Å molecular sieves (200 mg). After 15 min of stirring, DDQ (662 mg, 2.91 mmol) and $LiClO_4$ (55 mg, 0.52 mmol) were added. The stirring was continued for 60 min, then trimethyl-(1-phenyl-vinyloxy)-silane (561 mg, 2.91 mmol) was added. After 1 h, 5% $NaHCO_3$ solution (25 mL) and dichloromethane (15 mL) were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layer was dried, filtered, and evaporated. The residue was purified by flash chromatography to give compound **8f** (580 mg, 2.04 mmol) in 84% yield. Compound **8f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, m), 7.53 (1H, m), 7.44 (2H, m), 6.93 (2H, m), 6.84 (1H, d, $J = 8.8$ Hz), 4.81 (1H, dd, $J = 8.4, 4.4$ Hz), 3.91 (3H, s), 3.88 (3H, s), 3.58 (1H, dd, $J = 16.3, 8.4$ Hz), 3.24 (3H, s), 3.10 (1H, dd, $J = 16.3, 4.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 197.37 (C), 148.93 (C), 148.34 (C), 136.65 (C), 133.67 (CH), 132.82 (C), 133.01 (CH), 128.29 (2 x CH), 127.96 (2 x CH), 118.90 (CH), 110.84 (CH), 109.14 (CH), 79.32 (CH), 56.66 (CH_3), 55.85 (CH_3), 55.81 (CH_3), 47.14 (CH); HRMS for $C_{18}H_{20}O_4$ calcd 284.1049, found 284.1055.

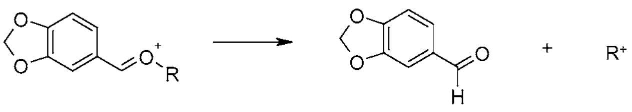
Table 3. Study of DDQ-Assisted C−C Bond-Forming Reaction of 5-Methoxymethyl-benzo[1,3]dioxole with a Variety of Trimethylvinyloxysilanes[a]



trimethylvinyloxysilane[b]		product[c]		yield[d]
	**7**		**8f**	84%
	**14a**		**15a**	65%
	**14b**		**15b**	53%
	**14c**		**15c**	69%
	**14d**		**15d**	77%
	**14f**		**15f**	68%
	**14g**		**15g**	67%
	**14h**		**15h**	75%
	**14i**		**15i**	53%
	**14j**		**15j**	30%
	**14k**		**15k**	71%
	**14l**		**15l**	44%

[a] All reactions were carried out in anhydrous conditions at room temperature under nitrogen pressure with 0.1 M solution of compound **6f** in CH_2Cl_2 with about 0.2−0.5 equivalent of $LiClO_4$ added to the reaction mixture. [b] All trimethylvinyloxysilanes were purchased from commercial resources and used without further purification. [c] All products were characterized by ^1H NMR, MS, and elemental analysis. [d] Isolated yield after flash chromatography separation.

Scheme 3


11 **12** **13**

forming the desired C−C bond with a nucleophile. A possible breakdown of **11** can lead to aldehyde **12** and another cation species **13** as indicated in Scheme 3. In the cases where R was the methyl or cyclohexyl, intermediate **11** is relatively stable, and therefore the desired C−C coupling reaction indeed took place to form the products (**8f**, **10b**) in good yield (Table 2). In the cases where the “R” group was *tert*-butyl, the cascade mechanism shown in Scheme 3 might occur because of the formation of the relatively more stable *tert*-butyl cation **13**. The fact that we did not see the coupling product **10a** and the isolation of aldehyde **12** seem to be consistent with this explanation (Table 2). However, the hydrolysis mechanism shown in Scheme 1 with possible presence of water can lead to the same aldehyde. This alternative mechanistic pathway can also explain why the same reaction of compound **9c** with **7** does not offer the coupling product **10c** (Table 2).

A variety of silyl enol ethers have been tested in order to expand the scope and utility of this DDQ-assisted C−C bond-forming reaction. As shown in Table 3, all the silyl enol ethers (**7**, **14a**−**l**) tested so far worked rather well with 5-methoxymethylbenzo[1,3]dioxole to afford 3-methoxy-3-phenyl-propionyl analogues **8a** and **15a**−**l** in isolated yield ranging from 30 to 84%. Many functional groups such as carbonyl (**14g**,**j**) and olefin (**14f**) can be tolerated under the reaction conditions. When the R_1 and R_2 substituents of the silyl enol ether are not the same, a mixture of two diastereoisomers is formed (**15h**−**j**,**l**). Starting with readily available electron-rich benzyl ether, this novel C−C bond-forming reaction provides easy access to a variety of β-alkoxycarbonyl derivatives, including 3-alkoxyl-3-phenyl-propionaldehyde (**15a**), ketones (**15b**−**j**, **8f**), propionic acid methyl ester (**15k**), and lactone (**15l**).

In conclusion, we have demonstrated a relatively simple and novel method for preparing protected aldols from benzyl ether and silyl enol ether, by means of the readily available reagent DDQ. The benzyl ether must have resonance electron-donating groups in the para-position, and the benzyl ether must be neither aromatic nor too bulky. When these conditions are met, fair to excellent yields ranging from 30 to 85% can be obtained; otherwise, poor yields are to be expected. The coupling reaction works well with a variety of silyl enol ethers possessing different functionalities. Our continuing efforts are aimed at expanding the scope of this C−C bond-forming reaction and applications of this new method to the organic synthesis of naturally occurring and biologically active compounds. We shall report on such work in due course.

OL036314J