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A Highly Efficient, Metal-Free and Convenient Diarylallyl Ether/Thioether Formation *via* Oxidative C-H Activation

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Abstract: A metal free highly efficient and concise oxidative-coupling ether formation between 1,3-diarylallylic sp^3 C-H and aliphatic alcohols promoted by 2,3-dichloro-5,6-dicyanoquinone (DDQ) is reported. This system is also applied to form C−S bonds from 1,3-diarylpropylene and thiols/thiophenols. The corresponding diarylallyl ethers/thioethers are obtained in good yields.

Keywords: alcohols; C−H activation; C−O, C−S bond formation; cross-coupling; 1,3-diarylpropylenes; 2,3-dichloro-5,6-dicyanoquinone (DDQ)

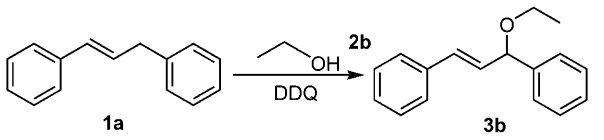
The formation of carbon-heteroatom bonds from a common intermediate is of great significance to the drug discovery process.[1] In particular, the construction of an ether linkage adjacent to a sterically hindered carbon centre is important for the synthesis of many biologically active compounds.[2] The conventional method for ether synthesis is the direct S_N2-type *O*-alkylation (Williamson ether synthesis). However, this protocol is sometimes synthetically impractical owing to the strong basicity of the alkoxide anion, which may be incompatible with other functional groups presented in the system.[3] Therefore some modified methods were developed,[4,5,6] for example, transition metal-catalyzed cross-coupling of aryl halides with phenols or alcohols.[4b,c,e,f,l] However, transition metal-based protocols, although successful, usually have some inherent limitations such as moisture sensitivity, costly metal catalysts and environmental toxicity.[4c] With the prevalence of "atom economy"[7] and "green chemistry",[8] the cross-coupling reaction for constructing C−O bonds *via* transition metal-catalyzed direct C−H functionalization has attracted great interest for its atom economy. Recently, a method to form C−O bonds using relatively cheap CuCl and $PhI(OAc)_2$ was developed.[6a] Although great progress has been made in generating C−O bonds through C−H activation, examples of the reactions without any metal have rarely been reported.

Allylic acetate or its derivatives were employed for the construction of C−X (X = C/N/O, etc.) bonds.[9,10] Alkylation directly from the allylic sp^3 C−H bond was also reported.[11] Recently, we have developed a new oxidative coupling reaction between diarylallylic sp^3 C−H and active methylenic sp^3 C−H bonds mediated by DDQ.[12] It is worthy of note that alkoxylation directly from allylic sp^3 C−H bonds without a metal catalyst has been only studied sporadically.

Herein, we report a highly efficient and concise metal-free oxidative coupling reaction promoted by 2,3-dichloro-5,6-dicyanoquinone (DDQ) between 1,3-diarylallylic sp^3 C−H bonds and alcohols/thiols to form C−O/C−S bonds.

DDQ is a well-known oxidation reagent for organic synthesis.[13] In our study, we first examined the oxidative coupling between **1a** and **2b** with DDQ in CH_2Cl_2 at room temperature. After a few minutes, the desired product **3b** was obtained in 75% yield (Table 1, entry 5). We then set the temperature to 0 °C in order to slow down the reaction. However, the yield did not alter obviously. Then several solvents were screened. The reaction can proceed in all the solvents tested (Table 1). The product yield declined to 67% without any solvent (Table 1, entry 6). Some undesired products were observed when the reaction was carried out in THF, CH_3CN or dioxane. When CH_3NO_2 was used as solvent, the reaction was slower and the yield was decreased. The yield was improved when the reaction was performed in $CHCl_3$. As for the effect of the DDQ dosage, it was found that decreasing the amount of DDQ resulted in reduced yields while with 1.5 equiv. DDQ added, the yield was not improved obviously. Therefore, the optimized condition was **1a** (0.6 mmol)/**2b** (0.5 mmol)/DDQ (0.6 mmol)/$CHCl_3$ (2 mL) at room temperature. Then, a scale-up experi-

Table 1. Screening of reaction conditions.[a]



Entry	Solvent	T [°C]	Yield [%][b]
1	CH_3CN	r.t.	50
2	THF	r.t.	63
3	CH_3NO_2	r.t.	37
4	dioxane	r.t.	55
5	CH_2Cl_2	r.t.	75
6	neat	r.t.	67[c]
7	$CHCl_3$	r.t.	87
8	CH_2Cl_2	0	74
9	$CHCl_3$	r.t.	81[d]
10	$CHCl_3$	r.t.	88[e]
11	$CHCl_3$	r.t.	86[f]

[a] 0.6 mmol of **1a**, 0.5 mmol of **2b**, 2 mL of solvent, 0.6 mmol of DDQ, 15 min.

[b] Isolated yield.

[c] 0.5 mmol of **1a**, 2 mL of **2b**, 0.6 mmol of DDQ.

[d] 0.5 mmol of DDQ.

[e] 0.75 mmol of DDQ.

[f] 8 mmol of **1a**, 6.67 mmol of **2b**, 30 mL of $CHCl_3$, 8 mmol of DDQ. Yield was determined by GC.

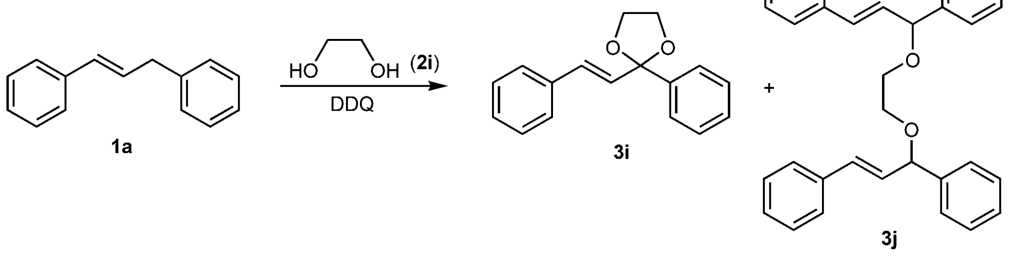
ment was carried out: 8 mmol of **1a**, 6.67 mmol of **2b**, 30 mL of $CHCl_3$, 8 mmol of DDQ, and the yield was 86% (Table 1, entry 11).

Based on the above study, various substrates were subjected to the reaction under the optimized conditions (Table 2). An effect of steric hindrance of the alcohols in the reaction was observed. Primary alcohol can proceed smoothly. The bulkier the R^3 group, the lower the products yields. The use of secondary or tertiary alcohols as the substrate resulted in a decrease in the yields of the desired ether and formation of the self-coupling product of 1,3-diarylpropylene. In order to avoid the generation of the by-product, the ratio of alcohol to the 1,3-diarylpropylene was changed to 5:1 or more. For *tert*-butyl alcohol, the solvent $CHCl_3$ was not needed (Table 2, entry 4). The electronic effect of the substituents on the aromatic ring of **1** was examined. Substrates bearing an electron-withdrawing group on the aromatic ring resulted in good yields and a rapid reaction rate (Table 2, entries 11, 12, and 13). When an electron-donating group was introduced, the result was the opposite (Table 2, entry 10).

Encouraged by the above results, we further investigated the similar reactions between 1,3-diarylpropylenes and thiols. To our delight, the corresponding thioethers could be successfully formed at low temperature (−10 °C). And further oxidation did not occur. Various substituted thiophenols were also found to be reactive. All the thioethers were produced in good yields. However, as for the phenol, although the aryl ether can be formed, the product decomposed easily owing to the leaving group ability of the phenolate anion.

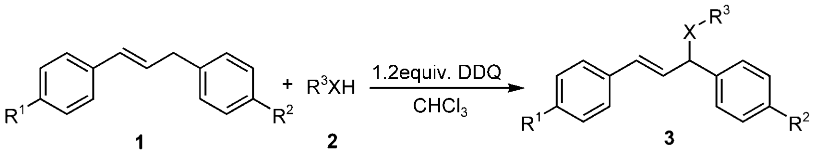
As indicated in Table 2, when ethane-1,2-diol (**2i**) was used as the substrate, both dioxolane (**3i**) and diether (**3j**) were obtained **(**Scheme 1**).** On changing the ratios of **1a** and **2i**, **3i** or **3j** was obtained separately as the main product. When **1a**:**2i** was 2.2:1, **3j** was the main product (**3j** 85%, **3i**:**3j** = 1:8.1), whereas, when**1a**:**2i** was 1:1.5, **3i** was the main product (**3i** 89%, **3i**: **3j** = 10:1).

According to the literature and the observations in our reactions, a possible mechanism was proposed (Scheme 2). The formation of product may follow two pathways, hydride transferred directly from allylic position and/or proton abstraction after an electron was transferred from the allylic double bond to DDQ.[13a,14] In our experiment, we observed the self-coupling product of 1,3-diarylpropylene. This coupling reaction may indicate a single-electron transfer in the process. However, compounds **1b**, **1c** and **1d** reacted with ethanol to give the corresponding α- and γ-ether products **3k, 3l** and **3m**. The allylic cation is more likely to be rearranged between the α- and γ-positions. The incoming nucleophile attacked at the original allylic or γ-position to form the isomerized products. When **1b** and **1d** were used as the substrates, the α-ethers were more stable than the γ-ethers. As for **1c**, the γ-ether was the main product. These results may support our proposed mechanism.



Scheme 1.

Table 2. Formation of ethers and thioethers.[a]



Entry	R^1,R^2	R^3	X	Time [min]	T [°C]	Product	Yield [%][b]
1	H, H **1a**	CH_3 **2a**	O	12	r.t.	**3a**	90
2	**1a**	CH_3CH_2 **2b**	O	10	r.t.	**3b**	87
3	**1a**	$(CH_3)_2CH$ **2c**	O	30	r.t.	**3c**	85[c]
4	**1a**	$(CH_3)_3C$ **2d**	O	40	r.t.	**3d**	50[d]
5	**1a**	cyclohexyl **2e**	O	30	r.t.	**3e**	88[c]
6	**1a**	$CH_2{=}CHCH_2$ **2f**	O	11	r.t.	**3f**	95
7	**1a**	4-$CH_3OC_6H_4CH_2$ **2g**	O	12	r.t.	**3g**	85
8	**1a**	4-$ClC_6H_4CH_2$ **2h**	O	15	r.t.	**3h**	90
9	**1a**	$HOCH_2CH_2$ **2i**	O	10	r.t.	**3i, 3j**	40, 37
10	H, CH_3 **1b**	**2b**	O	20	r.t.	**3k**[e]	55
11	H, Cl **1c**	**2b**	O	12	r.t.	**3l**[e]	89
12	Cl, H **1d**	**2b**	O	15	r.t.	**3m**[e]	85
13	Cl, Cl **1e**	**2b**	O	12	r.t.	**3n**	90
14	**1a**	CH_3CH_2 **2j**	S	10	−10	**3o**	89
15	**1a**	C_6H_5 **2k**	S	15	−10	**3p**	80
16	**1a**	4-$CH_3C_6H_4$ **2l**	S	10	−10	**3q**	92
17	**1a**	2-$CH_3C_6H_4$ **2m**	S	10	−10	**3r**	90
18	**1a**	$C_6H_5CH_2$ **2n**	S	10	−10	**3s**	90
19	**1a**	3,5-dimethylpyrimidinyl **2o**	S	25	−10	**3t**	70

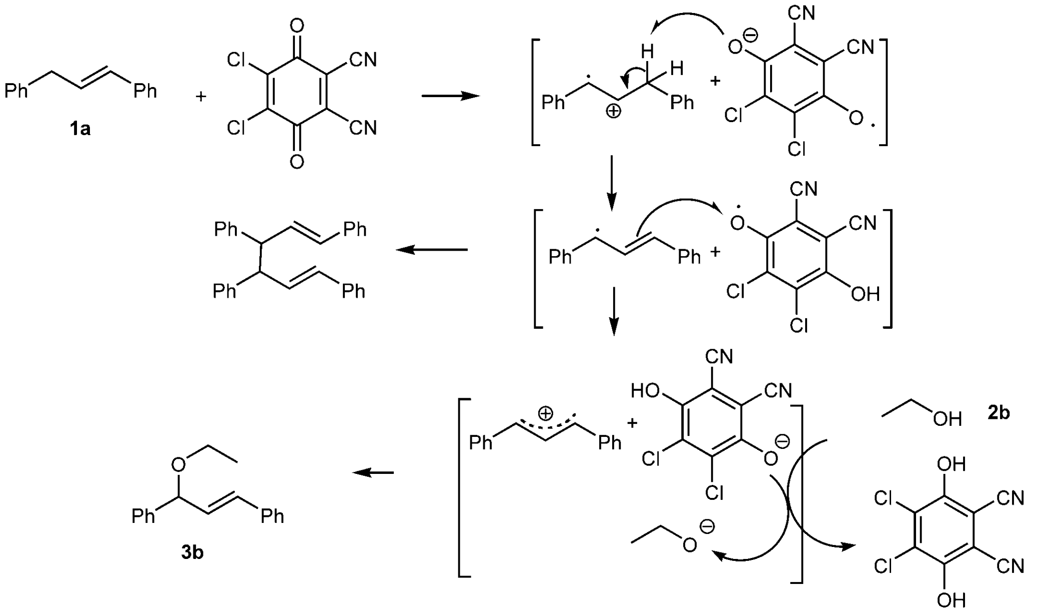
[a] 0.6 mmol of **1**, 0.5 mmol of **2**, 2 mL of $CHCl_3$, 0.6 mmol of DDQ unless noted.

[b] Isolated yield.

[c] 0.5 mmol of **1**, 2.5 mmol of **2**, 2 mL of $CHCl_3$, 0.6 mmol of DDQ.

[d] 0.5 mmol of **1**, 2 mL of **2**, 0.6 mmol of DDQ.

[e] For all of these substrates both α- and γ-ethers were formed. For **3k**, **3l** and **3m**, the ratios of the α- and γ-ethers were separately 2:1, 1:2, 1.6:1, determined by the synthesis of pure α-ether of **3m** and γ-ether of **3k**.



Scheme 2. A possible mechanism.

In conclusion, we have developed a highly efficient oxidative coupling reaction between 1,3-diarylallylic compounds and aliphatic alcohols, thiols or thiophenols promoted by DDQ. It provides a highly efficient, fast and convenient approach to synthesize diarylallyl ethers/thioethers.

Experimental Section

General Procedures

Formation of ethers: A 25-mL round-bottom flask was charged with ethanol (0.5 mmol) and 1,3-diarylpropene (0.6 mmol) in 2 mL $CHCl_3$ and DDQ (0.6 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate (30:1) as the eluent to give the pure product.

Formation of thioethers: A 25-mL round-bottom flask was charged with ethanethiol (0.5 mmol) and 1,3-diarylpropene (0.6 mmol) in 2 mL $CHCl_3$ and DDQ (0.6 mmol) was added. The mixture was stirred at $-10\,°C$ and monitored by TLC. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate (30:1) as the eluent to give the pure product.

Acknowledgements

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References

[1] For examples of medicinally important diaryl ethers, see: a) P. Cristau, J.-P. Vors, J. Zhu, *Tetrahedron* **2003**, *59*, 7859–7870; b) S. B. Singh, G. R. Pettit, *J. Org. Chem.* **1990**, *55*, 2797–2800; c) M. E. Jung, J. C. Rohloff, *J. Org. Chem.* **1985**, *50*, 4909–4913; d) D. Sames, R. Polt, *J. Org. Chem.* **1994**, *59*, 4596–4601.

[2] J. Buckingham, *Dictionary of Natural Products*, University Press, Cambridge, MA, **1994**.

[3] F. K. Lam, T. T.-L. Au-Yeung, F. Y. Kwong, Z. Zhou, K. Y. Wong, A. S. C. Chan, *Angew. Chem.* **2008**, *120*, 1300–1303; *Angew. Chem. Int. Ed.* **2008**, *47*, 1280–1283.

[4] For transition metal-catalyzed ether formation, see: a) Y. Kayaki, T. Koda, T. Ikariya, *J. Org. Chem.* **2004**, *69*, 2595–2597; b) G.-Y. Gao, J. V. Ruppel, K. B. Fields, X. Xu, Y. Chen, X. P. Zhang, *J. Org. Chem.* **2008**, *73*, 4855–4858; c) J. J. Niu, H. Zhou, Zh. G. Li, J. W. Xu, Sh. J. Hu, *J. Org. Chem.* **2008**, *73*, 7814–7817; d) G. Sh. Chen, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2007**, *48*, 473–476; e) S. Kuwabe, K. E. Torraca, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206; f) A. V. Vorogushin, X. H. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149; g) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; h) C. Lim, J.-E. Kang, J.-E. Lee, S. Shin, *Org. Lett.* **2007**, *9*, 3539–3542; i) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077; j) Y. Liu, R. M. Hua, H.-B. Sun, X. Q. Qiu, *Organometallics* **2005**, *24*, 2819–2821; k) J. S. Sawyer, *Tetrahedron* **2000**, *56*, 5045–5065; l) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.

[5] For metal-free ether formation, see: a) A. Patra, A. K. Roy, B. S. Joshi, R. Roy, S. Batra, A. P. Bhaduri, *Tetrahedron* **2003**, *59*, 663–670; b) S. Protti, M. Fagnoni, A. Albini, *J. Am. Chem. Soc.* **2006**, *128*, 10670–10671.

[6] For transition metal-catalyzed direct C–H functionalization to form C–O bonds, see: a) J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824–7825; b) A. J. Canty, M. C. Denney, G. Koten, B. W. Skelton, A. H. White, *Organometallics* **2004**, *23*, 5432–5439; c) J. M. Lee, S. Chang, *Tetrahedron Lett.* **2006**, *47*, 1375–1379.

[7] a) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[8] N. Winterton, *Green Chem.* **2001**, *3*, G73.

[9] a) B. M. Trost, C. Lee, in: *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima,), Wiley-VCH, Weinheim, **2000**, chap. 8; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944; c) J. Tsuji, *Palladium Reagents and Catalysis*, Wiley, New York, **2004**; d) A. Pfaltz, M. Lautens, in: *Comprehensive Asymmetric Catalysis*, Vol. 2, (Eds.: E. N. Jacobsen, A, Pfaltz, H. Yamamoto), Springer, New York, **1999**, p 833.

[10] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387–4388.

[11] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56–57.

[12] D. P. Cheng, W. L. Bao, *Adv. Synth. Catal.* **2008**, *350*, 1263–1266.

[13] a) P. P. Fu, R. G. Harvey, *Chem. Rev.* **1978**, *78*, 317–361; b) D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153–195.

[14] a) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243; b) B.-P. Ying, B. G. Trogden, D. T. Kohlman, S. X. Liang, Y. C. Xu, *Org. Lett.* **2004**, *6*, 1523–1526; c) P. C. Montevecchi, M. L. Navacchia, *J. Org. Chem.* **1998**, *63*, 8035–8037; d) B. A. Snider, *Chem. Rev.* **1996**, *96*, 339–363.