

ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

COMMUNICATION

A Transition-Metal-Free, One-Pot Procedure for the Synthesis of α,β -Epoxy Ketones by Oxidative Coupling of Alkenes and Aldehydes by Base Catalysis

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Qingping Ke,^{ab} Bingyan Zhang,^b Bolun Hu,^b Yangxin Jin^b and Guanzhong Lu^a

A new strategy for the synthesis of epoxides is presented. This process allows the direct synthesis of epoxides from alkenes and aldehydes through C-H functionalization and C-C/O bond formation.

In the mid-20th century, the chemical industry was transformed by the development of effective methods of functionalizing alkenes. The aerobic oxidative coupling of ethylene and water to give acetaldehyde, as developed by Wacker Chemie in 1959,^[1] represented the first of numerous Pd-catalyzed functionalization reactions.^[2] Recently, the transition metal-catalyzed or metal-free-catalyzed oxidative cross-coupling of alkenes with simple reagents for the purpose of forming C-C bonds has received significant attention.^[3] As an example, Li *et al.* reported the iron-catalyzed synthesis of β -peroxy ketones from alkenes.^[3d] Lei *et al.* also reported the catalytic synthesis of α,β -unsaturated ketones from alkenes and aldehydes over a copper catalyst.^[4] This renewed interest in the functionalization of alkenes has led to the discovery of new transition-metal-free-catalyzed C-C bond-forming reactions, many of which show remarkable synthetic potential.^[3c]

To date, however, there have been only relatively few studies of the synthesis of many important alkene-derived products, such as ketones and epoxides, which are widely employed in organic synthesis as very useful intermediates.^[5] Thus, there remains a requirement to synthesize these compounds by simple, transition metal-free catalytic methods, because of their importance in synthetic chemistry and commercial applications. Herein, we report the transition metal-free, one-pot synthesis of α,β -epoxy ketones through an unprecedented intermolecular oxidative coupling reaction between alkenes and aldehydes over a K_2CO_3 catalyst, as presented in Scheme 1.



Scheme 1. One-pot synthesis of α,β -epoxy ketones.

We initially studied the reaction of 4-methylbenzaldehyde with 4-bromostyrene in the presence of an oxidant and a basic catalyst, with the results shown in Table 1. In the presence of TBHP and Na_2CO_3 , the oxidative coupling reaction of 4-bromostyrene and 4-methylbenzaldehyde occurs to give the corresponding product (3-(4-bromophenyl)oxiran-2-yl)(p-tolyl)methanone with 7% yield. K_2CO_3 exhibited the best catalytic activity for this oxidative coupling reaction among all the catalysts tested, generating a 95% yield of the product (Table 1, entry 7) at 100 °C. The results in Table 1 show that the optimal reaction temperature is 100 °C and that the most appropriate solvent is MeCN. It was also found that using H_2O_2 or BQ as oxidants in combination with the K_2CO_3 catalyst in MeCN produced only a trace of the desired product, as determined by GC analysis (Table 1, entries 15–16), while a 33% yield was obtained in the absence of TBHP (Table 1, entry 14). These results indicate that the desired ketone product, (3-(4-bromophenyl)oxiran-2-yl)(p-tolyl)methanone, can be obtained by a one-pot synthetic procedure over our transition-metal-free catalyst, K_2CO_3 .

Table 1. Oxidative coupling reaction between 4-methylbenzaldehyde and 4-bromostyrene.

Entry	Catalyst	Solvent	Oxidant	Yield (%)
1	Na_2CO_3	MeCN	TBHP	7
2	Cs_2CO_3	MeCN	TBHP	trace
3	NaOH	MeCN	TBHP	61
4	KOH	MeCN	TBHP	trace
5	K_2CO_3	MeCN	TBHP	n.d. ^[a]
6	K_2CO_3	MeCN	TBHP	8 ^[b]
7	K_2CO_3	MeCN	TBHP	95 (88) ^[c]
8	K_2CO_3	PhMe	TBHP	trace
9	K_2CO_3	PhCl	TBHP	10
10	K_2CO_3	1,4-dioxane	TBHP	Trace
11	K_2CO_3	DMF	TBHP	Trace
12	K_2CO_3	DCE	TBHP	36
13	K_2CO_3	DMSO	TBHP	n.d.

14	K ₂ CO ₃	MeCN	—	33
15	K ₂ CO ₃	MeCN	H ₂ O ₂	trace
16	K ₂ CO ₃	MeCN	BQ	trace

Reaction conditions: 4-methylbenzaldehyde (1 mmol), 4-bromostyrene (0.5 mmol), oxidant (1 mmol), and solvent (2 mL) under air at the temperature of 100 °C for 12 h. TBHP= tert-butyl hydrogen peroxide (70% in water), BQ = 1,4-benzoquinone, DMSO = dimethyl sulfoxides, DCE=1,2-dichloroethane. GC yield. [a] not detected, reaction temperature of 40 °C; [b] reaction temperature of 80 °C; [c] isolated yield within parentheses.

The scope of both styrenes and aldehydes was investigated at 100 °C using K₂CO₃ as the catalyst and TBHP as the oxidant (Tables 2 and 3). The results in Table 2 show that the oxidative coupling reaction of 4-methylbenzaldehyde successfully proceeded with either electron-withdrawing or electron-donating substituents on the styrene ring. With the exception of certain substituents (Table 2, entry 4), the addition of an electron-withdrawing group at any position on the styrene ring allows its coupling reaction with 4-methylbenzaldehyde to form the desired product in 70–93% yield (Table 2, entries 2–7). The above results also show that the appropriate product is obtained with higher yield when an electron-withdrawing substituent was used as the reactant. It is interesting to note that the use of a substrate having an electron-donating methyl group located at the para position on the styrene ring resulted in a moderate yield (43%, Table 2, entry 8), whereas a substrate with a methyl group at the α -position generates a relatively high yield (78%, Table 2, entry 9). The use of 4-methylstyrene as the reactant allowed only a 43% yield due to the occurrence of various side reactions. Finally, none of the desired product could be obtained when using cyclohexene as the substrate (Table 2, entry 10).

Table 2. Scope of styrene compounds.

Entry	Substrate	Product	Yield (%)	dr ^[a]
1			72	80:1
2			85	80:1
3			88	70:1
4			67	92:7
5			81	50:1
6			83	50:1
7			93	40:1
8			43	50:1

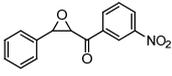
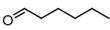
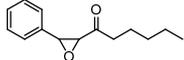
9			78	2:1
10		—	0	—

Reaction conditions: 4-methylbenzaldehyde (1 mmol), styrene substrate (0.5 mmol), TBHP (1 mmol), and MeCN (2 mL) under air at 100 °C for 12 h. Isolated yield. ^[a]determined by GC-MS of the crude product.

From the results in Table 3, it is evident that benzaldehyde with various substituents (such as Cl, Br, CH₃, OCH₃, CH₂CH₃ and CF₃) at the para position can react with styrene to form the desired products in high yields (64–93%, Table 3, entries 1–6). Using 2- or 3-methoxy benzaldehyde as the reactant, the product yields following the oxidative coupling reaction with styrene were 41% and 61% (Table 3, entries 8, 9), respectively. Additionally, 3-nitro benzaldehyde was found to react with styrene to form the oxidative coupling product in 63% yield. Compared with the high reactivities of these aryl aldehydes, the alkyl aldehyde (caproaldehyde) was less reactive, generating a product yield of only 23% (Table 3, entry 11). These results demonstrate that changing the para position substituent of the aldehyde has no obvious influence on this oxidative coupling reaction, and that the resulting product yields are similar to that obtained with benzaldehyde (88% yield, Table 3, entry 7). This transition-metal-free synthetic procedure can therefore be successfully extended to a variety of styrene- and aldehyde-based substrates.

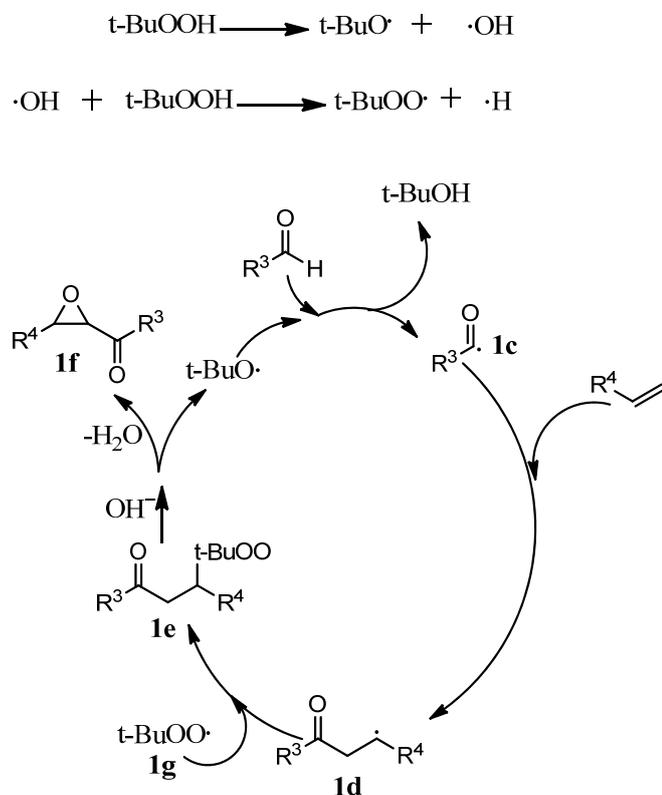
Table 3. Scope of aldehyde compounds.

Entry	Substrate	Product	Yield (%)	dr ^[a]
1			90	92:7
2			88	84:15
3			93	85:14
4			64	37:1
5			93	33:1
6			77	14:1
7			88	39:1
8			41	93:6
9			61	97:2

10			63	5:1
11			23	4:1

Reaction conditions: Aldehyde substrates (1 mmol), styrene (0.5 mmol), TBHP (1 mmol), and MeCN (2 mL) under air at 100 °C for 12 h. Isolated yield. ^[a] determined by GC-MS of the crude product.

In initial attempts to elucidate a possible reaction mechanism, the radical inhibitor 2,2,6,6-tetramethyl piperidine-N-oxyl (TEMPO) was added to the reaction mixture. It was found that the reaction was blocked under these conditions and that the TEMPO derivative **1b** was formed, as shown in Scheme S1. This result provides direct evidence of the formation of an acyl radical during the reaction, indicating that this oxidative reaction involves a radical intermediate. The results in Table S1 show that the desired α,β -epoxy ketone product was only obtained in the presence of K_2CO_3 (Table 4, entries 1 and 2), which is evidence of base catalysis. In the absence of K_2CO_3 (entry 3), the product **1a** cannot be formed.



Scheme 2. Proposed reaction mechanism for the oxidative coupling reaction.

Previously, Li *et al.* found that generation of β -ketone **1c** was an important step during the synthesis of α,β -epoxy ketones over an iron catalyst.^[6a] With regard to the syntheses of α,β -unsaturated ketones, Lei *et al.* suggested that **1c** might be involved in the reaction but should not be considered as an intermediate in the main pathway of the oxidative coupling reaction^[4]. Interestingly, only 4-(3-(tert-butylperoxy)-3-phenylpropanoyl)-benzoic acid was obtained in this study in the absence of the K_2CO_3 catalyst,^[7] and this is obtained from

the oxidation of **1c** by TBHP. On the basis of the above analysis, it is believed that the reaction proceeds through the oxidative coupling of an alkene and an aldehyde by the tentative radical reaction mechanism presented as Scheme 2. Firstly, TBHP is readily split into alkyloxy and hydrogen radicals under the heating condition. Hydrogen from the aldehyde is abstracted by alkyloxy radicals to yield aldehydic radical **1c** (which could also be occurred for the hydrogen radicals)^[3c], then a radical **1d** was formed by addition reaction of **1c** with styrene. The compound **1e** was proved to be existed since its oxidation product of 4-(3-(tert-butylperoxy)-3-phenylpropanoyl)-benzoic acid was obtained in the absence of K_2CO_3 catalyst. The compound **1e** could be obtained by free-radical addition of **1d** with **1g**. Considered the high catalytic performance was obtained over the both K_2CO_3 and NaOH catalyst, it is believed that the "K" is not the catalytic active ingredient and the oxidative coupling reaction is catalyzed by base catalyst.

Conclusions

In summary we have developed a new base-catalyzed, one-pot synthetic procedure for the oxidative coupling of styrene derivatives with aldehydes in the absence of transition-metal species. We also determined that various functional groups could be substituted on both the aldehyde and styrene. This work demonstrates a facile method for the synthesis of α,β -epoxy ketones and further investigation of this reaction is underway in our laboratory.

Notes and references

^a Key Laboratory for Advanced Materials and Research Institute of Industrial Catalysis, East China University of Science and Technology, Shanghai 200237, P. R. China, Fax: +86 21 6425 3703, E-mail: gzhlu@ecust.edu.cn

^b College of Chemistry and Materials Engineering, Wenzhou University, Zhejiang 325000, P. R. China .

[†] This work was supported by the National Basic Research Program of China (2013CB933201), the National Natural Science Foundation of China (21306142)

Electronic Supplementary Information (ESI) available: [Experimental Section, Table S1, Scheme S1 and NMR data]. See DOI: 10.1039/c000000x/

- J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, H. Kojer, *Angew. Chem.* 1959, **71**, 176.
- a) Z. K. Wickens, B. Morandi, R. H. Grubbs, *Angew. Chem. Int. Ed.* 2013, **52**, 11257; b) R. Jira, *Angew. Chem. Int. Ed.* 2009, **48**, 9034; c) M. M. Konnick, B. A. Gandhi, I. A. Guzei, S. S. Stahl, *Angew. Chem.* 2006, **118**, 2970; d) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* 2004, **43**, 3368; e) G. Liu, G. Yin, L. Wu, *Angew. Chem.* 2008, **120**, 4811; f) M.-K. Zhu, J.-F. Zhao, T.-P. Loh, *J. Am. Chem. Soc.* 2010, **132**, 6284; g) Y. Su, N. Jiao, *Org. Lett.* 2009, **11**, 2980; h) J. Tsuji, H. Nagashima, H. Nemoto, *Organic Syntheses* 1990, **7**, 137; i) X. F. Wu, H. Neumann, M. Beller, *Chemistry—An Asian Journal* 2012, **7**, 1199; j) R. F. Heck, J. P. Nolley, *J. Org. Chem.* 1972, **37**, 2320; k) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* 1979, **20**, 3437; l) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* 2010, **132**, 14596; m) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* 1977, **42**, 1821; n)

- A. O. King, E. Negishi, F. J. Villani Jr, A. Silveira Jr, *J. Org. Chem.* 1978, **43**, 358; o) M. Alami, G. Linstrumelle, *Tetrahedron Lett.* 1991, **32**, 6109; p K. Iritani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* 1988, **29**, 1799; q) J. K. Stille, *Angew. Chem. Int. Ed. in Eng.* 1986, **25**, 508.
- 3 a) X. F. Wu, H. Neumann, M. Beller, *ChemSusChem* 2013, **6**, 229; b) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* 2011, **50**, 10788; c) J.-H. Li, M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng, *Chem. Sci.* 2013, **4**, 2690; d) R. Zhang, J. Liu, S. Wang, J. Niu, C. Xia, W. Sun, *ChemCatChem* 2011, **3**, 146; e) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* 2009, **1**, 28; f) X. F. Wu, H. Neumann, M. Beller, *Angew. Chem.* 2010, **122**, 5412; g) I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed.* 2011, **50**, 1869.
- 4 J. Wang, C. Liu, J. Yuan, A. Lei, *Angew. Chem.* 2013, **125**, 2312.
- 5 a) Y.-H. Xu, J. Lu, T.-P. Loh, *J. Am. Chem. Soc.* 2009, **131**, 1372; b) Y. Shang, X. Jie, J. Zhou, P. Hu, S. Huang, W. Su, *Angew. Chem. Int. Ed.* 2013, **52**, 1299.
- 6 a) W. Liu, Y. Li, K. Liu, Z. Li, *J. Am. Chem. Soc.* 2011, **133**, 10756; b) W. Wei, C. Zhang, Y. Xu, X. Wan, *Chem. Comm.* 2011, **47**, 10827-10829; c) K. Liu, Y. Li, X. Zheng, W. Liu, Z. Li, *Tetrahedron* 2012, **68**, 10333; d) H. Kawai, S. Okusu, Z. Yuan, E. Tokunaga, A. Yamano, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* 2013, **52**, 2221.
- 7 The 4-(3-(tert-butylperoxy)-3-phenylpropanoyl)benzoic acid was detected by the GC-MS, m/z: 341, 333, 281, 267, 221, 207, 178, 128, 103, 77, 58, 51.