Oxidative Coupling of Alkenes with Aldehydes and Hydroperoxides: One-Pot Synthesis of 2,3-Epoxy Ketones

Wen-Ting Wei,^a Xu-Heng Yang,^a Hai-Bing Li,^a and Jin-Heng Li^{a,*}

^a State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, People's Republic of China Fax: (+86)-731-8871-3642; phone: (+86)-731-8871-3642; e-mail: jhli@hnu.edu.cn

Received: June 27, 2014; Published online:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400629.

Abstract: A new transition metal-free oxidative coupling of unactivated terminal alkenes with aldehydes and hydroperoxides in the presence of 10 mol% potassium *tert*-butanolate (*t*-BuOK) is described thereby realizing trifunctionalization of alkenes toward 2,3-epoxy ketones. This method is applicable to a wide range of aldehydes, including aryl and alkyl aldehydes, with excellent functional group tolerance, and provides for the one-step assembly of 2,3-epoxy ketones.

Keywords: aldehydes; alkenes; 2,3-epoxy ketones; oxidative coupling

Alkenes are abundant organic molecules and useful chemical feedstock, and methods for their direct, selective functionalization are attractive as an important means to assemble more complex molecular entities. The transition metal-catalyzed Heck couplings of alkenes with organic electrophiles have become one of the most efficient and common methods for alkene functionalization due to operational simplicity, commercially available starting materials and the versatility of the resulting alkenes in synthesis.^[1] Despite their widespread applications, the Heck coupling routes are typically protracted by the need to pre-functionalize the C-H bond toward the C-X bond (X = halides and pseudohalides). Therefore, an attractive alternative would involve a C-H functionalization that directly couples unactivated alkenes to a broad diversification of functional groups with excellent selectivity control.

The oxidative coupling methodology involving C– H functionalization has attracted much attention for replacing the conventional cross-coupling procedures, in part due to its step-economy by the avoidance of the pre-functionalization process.^[2–5] Despite remarkable advances in the oxidative coupling field, approaches for the coupling of alkenes, particularly unactivated alkenes, with the carbonyl $C(sp^2)$ -H bonds are rare and limited.^[3-5] These oxidative transformations focused on the coupling with the aldehyde $C(sp^2)$ -H bonds (Scheme 1a), including (i) the cou-

a) Previous work:



Scheme 1. Oxidative coupling of alkenes with aldehydes.

pling of electron-deficient alkenes with aldehydes (often alkyl aldehydes) initiated by air or *N*-hydroxyphthalimide (NHPI) combined with dibenzoyl peroxide (BPO) leading to saturated ketones,^[3] (ii) the Heck-type coupling of unactivated alkenes with aryl aldehydes using the [(Cp*RhCl₂)₂]/C₅H₂Ph₄/Cu(OAc)₂ or the CuCl₂/*tert*-butyl hydroperoxide (TBHP) system for synthesizing α , β -unsaturated ketones,^[4] and (iii) the difunctionalization of arylalkenes with aldehydes and TBHP catalyzed by FeCl₂ so accessing β -peroxy ketones.^[5] Herein, we report a new transition metalfree oxidative coupling of terminal alkenes with aldehydes and hydroperoxides using base catalysis (Scheme 1b). In the presence of a catalytic amount of *t*-BuOK, a variety of terminal alkenes successfully un-

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Wiley Online Library

These are not the final page numbers! **77**





Entry	[O] (equiv.)	Base (mol%)	Solvent	Yield [%]
1	TBHP (2)	_	MeCN	0
2	TBHP (2)	t-BuOK (5)	MeCN	48
3	TBHP (2)	<i>t</i> -BuOK (10)	MeCN	84
4	TBHP (2)	<i>t</i> -BuOK (20)	MeCN	83
5	TBHP (2)	$K_2CO_3(10)$	MeCN	78
6	TBHP (2)	DBU (10)	MeCN	64
7	TBHP (2)	DABCO (10)	MeCN	37
8 ^[b]	TBHP (2)	<i>t</i> -BuOK (10)	MeCN	79
9	TAHP (2)	<i>t</i> -BuOK (10)	MeCN	52
10	CHP(2)	<i>t</i> -BuOK (10)	MeCN	31
11	DTBP(2)	<i>t</i> -BuOK (10)	MeCN	trace
12	BPO (2)	<i>t</i> -BuOK (10)	MeCN	trace
13	_	<i>t</i> -BuOK (10)	MeCN	0
14	TBHP (2)	<i>t</i> -BuOK (10)	1,4-dioxane	5
15	TBHP (2)	<i>t</i> -BuOK (10)	tolune	10
16	TBHP (2)	<i>t</i> -BuOK (10)	DMSO	trace
17 ^[c]	TBHP (2)	t-BuOK (10)	MeCN	26
18 ^[d]	TBHP (2)	<i>t</i> -BuOK (10)	MeCN	82
19 ^[e]	TBHP (2)	t-BuOK (10)	MeCN	83

[a] Reaction conditions: 1a (0.4 mmol), 2a (0.8 mmol), [O] (2 equiv.), base and solvent (2 mL) at 100 °C for 12 h. TBHP (5M in decane).

^[b] TBHP (70% in water).

^[c] At 80 °C. ^[d] At 120 °C.

^[e] **1a** (1 g, 7.22 mmol) for 48 h.

derwent the trifunctionalization reaction with a wide range of aldehydes and hydroperoxides, giving in onestep 2,3-epoxy ketones in high yields.^[6] Notably, the oxygen atoms in the new formed 2,3-epoxy moiety are from hydroperoxides.

We began our investigations by exploiting the oxidative coupling of 1-chloro-4-vinylbenzene (1a) with 4-methylbenzaldehyde (2a) for optimization of the reaction conditions (Table 1). Initially, alkene 1a was treated with aldehyde 2a and TBHP in MeCN at 100°C for 24 h, but no coupled products were observed (entry 1). Gratifyingly, we found that a catalytic amount of *t*-BuOK could trigger the reaction, and 10 mol% *t*-BuOK was preferred leading to the desired 2,3-epoxy ketone 3aa in 84% yield (entries 2–4). Subsequently, a series of other bases, including K₂CO₃, DBU and DABCO, was examined: they could promote the reaction, but they were less efficient than *t*-BuOK (entry 3 *vs.* entries 5–7). Screening of peroxides revealed that only hydroperoxides, TBHP, TAHP (tert-amyl hydroperoxide) and CHP (cumene hydroperoxide), could initiate the coupling (entries 2 and 8–10), and other peroxides without a hydroxy group, DTBP and BPO, had no activity at all (entries 11 and 12). However, product **3aa** was not observed without oxidants (entry 13). The effect of solvents was also evaluated, and the results showed that the other solvents, including 1,4-dioxane, toluene and DMSO, are less effective than MeCN (entry 2 vs. entries 14–16). After varying the temperature, the reaction at 100°C provided the best results (entry 2 vs. entries 17 and 18). Notably, the reaction of alkene **1a** was successfully performed on a 1-gram scale, delivering 2,3-epoxy ketone 3aa in high vield (entry 19). The structure of 2,3-epoxy ketone **3aa** was assigned as the *trans*-isomer according to the chemical shift of the hydrogen atom on the epoxide ring by comparison with the known ¹H NMR spectral data of 2,3-epoxy ketones.^[5,6]

With the optimal conditions in hand, we next turned our attention to investigate the scope of this oxidative coupling procedure by testing various terminal alkenes 1 and aldehydes 2 (Table 2). In the presence of 4-methylbenzaldehyde (2a), TBHP and t-BuOK, the successful process was consistent with a wide range of alkenes 1 involving arylalkenes, a heteroarylalkene, an alkylalkene and 1,1-disubstituted alkenes, and also readily accommodated several substituents such as Me, MeO and Br on the aromatic ring (2,3-epoxy ketones **3ba-la**). Also styrene (**1b**) or 1-methyl-4-vinylbenzene (1c) reacted with aldehyde 2a, giving 2,3-epoxy ketones 3ba and 3ca in 77% and 91% yields, respectively. The MeO-substituted alkenes 1-methoxy-4-vinylbenzene (1d), 1-methoxy-3-vinylbenzene (1f) or 1-methoxy-2-vinylbenzene (1g) were also examined, and the order of their reactivity is as follows: *para* > *meta* > *ortho* (2,3-epoxy ketones 3da, 3fa and 3ga). Importantly, the optimal conditions were consistent with 1-bromo-4-vinylbenzene (1e), thereby enabling subsequent modifications at the halogenated positions (86% yield; 2,3-epoxy ketone **3ea**). We were pleased to find that 2-vinylnaphthalene (1i) and 4-vinylpyridine (1j) were viable substrates for the reaction with aldehyde 2a, TBHP and t-BuOK, providing 2,3-epoxy ketones 3ia and 3ja in moderate yields. Remarkably, alkylakene **1h** reacted with aldehyde 2a, TBHP and t-BuOK to afford 1-para-tolylnonan-1-one (**3ha**), not the 2,3-epoxy ketone. It was noted that 1,1-disubstituted alkenes, 1,1-diphenylethylene (1k) and 1-methyl-1-phenylethylene (1l), reacted successfully to access 2,3-epoxy ketones 3ka and 3la in 81 and 71% yield, respectively.

The optimal conditions were found to be applicable to a wide range of other aldehydes, including aryl aldehydes **2b–h** and alkyl aldehydes **2i** and **2j**, furnishing 2,3-epoxy ketones **3ab–3aj**, **3cb** and **3cc** in good to excellent yield. Moreover, this coupling allows several

2

KK These are not the final page numbers!







[a] Reaction conditions: 1 (0.4 mmol), 2 (0.8 mmol), t-BuOK (10 mol%), TBHP (2 equiv.; 5M in decane) and MeCN (2 mL) at 100°C for 12 h.

substituents including MeO, Cl, Me and Br on the aryl ring to be readily accommodated (2,3-epoxy ketones **3ab–3ah**). For example, treatment of benzalde-hyde (**2b**) with alkene **1a**, TBHP and *t*-BuOK afforded the desired 2,3-epoxy ketone **3ab** in 80% yield. Gratifyingly, *p*-MeO- or *p*-Cl-substituted aryl alde-hydes **2c** and **2d** were converted into the corresponding 2,3-epoxy ketones **3ac** and **3ad** in high yields. Although the reactivity of *ortho*-substituted aldehydes **2e–2g** was lower, 2,3-epoxy ketones **3ae–3ag** were also constructed in good yields. Naphthalen-1-yl-sub-

stituted aldehyde **2h** was viable for the reaction, delivering 2,3-epoxy ketone **3ah** in 46% yield. Reaction of alkyl aldehydes **2i** or **2j** with alkene **1a**, TBHP and *t*-BuOK successfully generated 2,3-epoxy ketones **3ai** and **3aj** in moderate yields. The reactions of 1-methyl-4-vinylbenzene (**1c**) with two aldehydes, benzaldehyde (**2b**) and 4-methoxybenzaldehyde (**2c**), are successfully performed, giving 2,3-epoxy ketones **3cb** and **3cc** in 72% and 71% yields, respectively.

As illustrated in Scheme 2, the absence of bases resulted in the selectivity toward 3-(*tert*-butylperoxy)-3-



Scheme 2. Control experiments.

Adv. Synth. Catal. 0000, 000, 0-0

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

asc.wiley-vch.de

These are not the final page numbers! **77**



Scheme 3. Possible mechanism.

(4-chlorophenyl)-1-*para*-tolylpropan-1-one (4aa), not 2,3-epoxy ketone 3aa, in 45% yield [Eq. (1)]. Interestingly, product 4aa could be readily converted into 2,3epoxy ketone 3aa in 95% yield using 10 mol% *t*-BuOK [Eq. (1)].^[5,6] However, 3 equiv. of 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) completely suppressed the coupling of alkene 1a with aldehyde 2c and TBHP by forming product 5 from aldehyde 2c and TEMPO [Eq. (2)]. Moreover, other radical inhibitors, hydroquinone and BHT, also resulted in no detectable product 3ac. These findings imply that the reaction involves a radical process.

The results of entries 3 and 8–12 in Table 1 demonstrated that only hydroperoxides could trigger the reaction, suggesting that the oxygen atoms in the new formed 2,3-epoxy group of products **3** might be from hydroperoxides. To verify this, a control experiment between alkene **1a** and aldehyde **2a** using 4 equiv. $H_2^{18}O$ was performed: product **3aa** did not include the ¹⁸O atom, ruling out the oxygen atom from H_2O . Notably, the results of Table 1 and Table 2 indicated that the peroxy esters were not observed from the reactions of aldehydes and hydroperoxide, and only some acids were detected by GC-MS analysis.

A possible mechanism as outlined in Scheme 3 was proposed for this current oxidative coupling.^[2-6] Initially, TBHP is split into t-BuO radical and OH radical under heating, and the 'OH radical can react with TBHP to afford a *t*-BuOO' radical and H₂O.^[2] Alkyl radical A is readily formed from aldehyde 1 with t-BuOO', followed by addition with alkene 1 which affords the other alkyl radical **B**. Intermediate **C**, generated from alkyl radical **B** and *t*-BuOO', is not stable and is converted into product 3 and t-BuOH by a catalytic amount of *t*-BuOK.^[5,6] This is because the hydrogen atom (H⁺ cation) from the deprotonation process is consumed to form t-BuOH, thus making the reaction system alkaline to initiate the conversion of intermediate C. For alkylalkenes, alkyl radical B is not stable enough versus the alkyl group (\mathbf{R}^{1}) , leading to protonolysis with water prior to reaction with t-BuOO' radical.

In summary, we have developed a new oxidative coupling of unactivated terminal alkenes with aldehydes and hydroperoxides using base catalysis for the selective synthesis of 2,3-epoxy ketones. This method proceeds *via* a new tandem C–H/alkene functionalization step that occurs through an oxidative radical pathway with a broad substrate scope and excellent selectivity control.

Experimental Section

Typical Experimental Procedure for the the Coupling of Alkenes 1 with Aldehydes 2, TBHP and *t*-BuOK

To a Schlenk tube were added alkenes 1 (0.4 mmol), aldehydes 2 (0.8 mmol), TBHP (0.8 mmol, 5M in decane), *t*-BuOK (10 mol%), and CH₃CN (2 mL). Then the tube was stirred at 100 °C for the indicated time until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired product **3**.

[3-(4-Chlorophenyl)oxiran-2-yl](para-tolyl)methanone

(3aa):^{[7] 1}H NMR (400 MHz, CDCl₃): δ =7.90 (d, J=7.2 Hz, 2H), 7.36 (d, J=7.2 Hz, 2H), 7.29 (d, J=6.8 Hz, 4H), 4.23 (s, 1H), 4.05 (s, 1H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =192.2, 145.2, 134.8, 134.1, 132.9, 129.5, 128.9, 128.4, 127.1, 60.7, 58.5, 21.7.

Acknowledgements

We thank the Natural Science Foundation of China (No. 21172060), the Specialized Research Fund for the Doctoral Program of Higher Education (No. 20120161110041), and the Hunan Provincial Natural Science Foundation of China (No. 13JJ2018) for financial support.

References

a) R. F. Heck, J. P. Nolley, J. Org. Chem. 1972, 37, 2320;
b) T. Mizoroki, K. Mori, A. Ozaki, Bull. Chem. Soc. Jpn. 1971, 44, 581; for selected reviews: c) A. de Meijere, F. E. Meyer Jr, Angew. Chem. 1994, 106, 2473; Angew. Chem. Int. Ed. Engl. 1994, 33, 2379; d) M. Oestreich, The Mizoroki-Heck Reaction, Wiley, Hoboken, NJ, 2008; e) I. P. Beletskaya, A. V. Cheprakov, Chem. Rev.

asc.wiley-vch.de

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

KK These are not the final page numbers!

2000, *100*, 3009; f) D. McCartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122.

- [2] a) C.-J. Li, Acc. Chem. Res. 2009, 42, 335; b) G. P. Mcglacken, L. M. Bateman, L. Bateman, Chem. Soc. Rev. 2009, 38, 2447; c) D. Shabashov, Acc. Chem. Res. 2009, 42, 1074; d) J. A. Ashenhurst, Chem. Soc. Rev. 2010, 39, 540; e) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, Chem. Soc. Rev. 2011, 40, 5068; f) J. Le Bras, J. Muzart, Chem. Rev. 2011, 111, 1170; g) C. Liu, H. Zhang, W. Shi, A. Lei, Chem. Rev. 2011, 111, 1780; h) Y.-X. Xie, R.-J. Song, J.-N. Xiang, J.-H. Li, Chin. J. Org. Chem. 2012, 32, 1555; i) C. Zhang, C. Tang, N. Jiao, Chem. Soc. Rev. 2012, 41, 3464; j) F. Guo, M. D. Clift, R. J. Thomson, Eur. J. Org. Chem. 2012, 4881; k) M. Grzybowski, K. Skonieczny, H. Butenschön, D. T. Gryko, Angew. Chem. 2013, 125, 10084; Angew. Chem. Int. Ed. 2013, 52, 9900; 1) S. A. Girard, T. Knauber, C.-J. Li, Angew. Chem. 2014, 126, 76; Angew. Chem. Int. Ed. 2014, 53, 74.
- [3] a) V. Chudasama, R. J. Fitzmaurice, S. Caddick, Nat. Chem. 2010, 2, 592; b) S. Tsujimoto, T. Iwahama, S. Sakaguchi, Y. Ishii, Chem. Commun. 2001, 2352; c) S. Tsujimoto, S. Sakaguchi, Y. Ishii, Tetrahedron Lett. 2003, 44, 5601.
- [4] a) Z. Shi, N. Schröder, F. Glorius, Angew. Chem. 2012, 124, 8216; Angew. Chem. Int. Ed. 2012, 51, 8092; b) J. Wang, C. Liu, J. Yuan, A. Lei, Angew. Chem. 2013, 125, 2312; Angew. Chem. Int. Ed. 2013, 52, 2256.
- [5] a) W. Liu, Y. Li, K. Liu, Z. Li, J. Am. Chem. Soc. 2011, 133, 10756; b) L. Lv, B. Shen, Z. Li, Angew. Chem. 2014, 126, 4248; Angew. Chem. Int. Ed. 2014, 53, 4164.
- [6] K. Liu, Y. Li, W. Liu, X. Zheng, Z. Zong, Z. Li, Chem. Asian J. 2013, 8, 359.
- [7] B. Wang, C. Miao, S. Wang, C. Xia, W. Sun, Chem. Eur. J. 2012, 18, 6750.

COMMUNICATIONS

6 Oxidative Coupling of Alkenes with Aldehydes and Hydroperoxides: One-Pot Synthesis of 2,3-Epoxy Ketones

Adv. Synth. Catal. 2014, 356, 1-6

Wen-Ting Wei, Xu-Heng Yang, Hai-Bing Li, Jin-Heng Li*

TBHP R¹ R^1 *t*-BuOK (10 mol%) MeCN, 100 °C, 12h R^2 R^1 = aryl, heteroaryl, alkyl R^2 = H, Me, Ph R = aryl, alkyl transition metal-free one-pot trifunctionalization of alkenes general: 23 examples, up to 91% yield, 1 gram scale

6