MnO_2-Catalyzed Oxidative Alkylation of Enamides with Ethers via $C(sp^3)$–H/$C(sp^2)$–H Cross-Dehydrogenative Coupling and Hydrolysis Sequence

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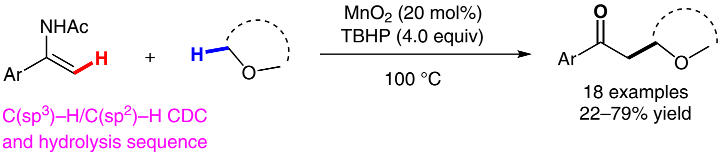

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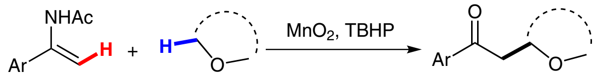
Abstract A new MnO_2-catalyzed oxidative alkylation of enamides with a $C(sp^3)$–H bond adjacent to an oxygen atom is described. This method achieves a $C(sp^3)$-H/$C(sp^2)$-H cross-dehydrogenative coupling and hydrolysis, thus providing efficient and general access to a variety of β-oxo ketones.

Key words $C(sp^3)$–H/$C(sp^2)$–H cross-dehydrogenative coupling, ethers, enamides, β-oxo ketones, radicals

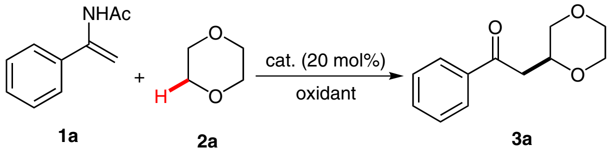
The direct functionalization of C–H bonds has proved to be one of the most powerful tools for the construction of C–C and C–X bonds.[1] In particular, great progress has been achieved with respect to the functionalization of $C(sp^3)$–H bonds of ethers via radical process.[2] However, the functionalization of $C(sp^3)$–H bond of ethers via cross-dehydrogenative coupling (CDC) with a $C(sp^2)$–H bond gained less attention.[2g]

Enamides, which can be readily prepared by the reductive acylation of ketoximes, are powerful building blocks in organic synthesis.[3] Great progress has been achieved with respect to the palladium(II)-catalyzed functionalization of vinylic C_β–H bond of enamides, such as arylation with organoboron,[4a] organosilane reagents,[4b] or arenes,[4c] and nucleophilic addition to isocyanates.[5] Recently, palladium-free functionalization of vinylic C_β–H bond of enamides via radical process have attracted much attention. Loh and co-workers reported a iron(II)-catalyzed alkoxycarbonylation reaction between *N*-vinylacetamides and carbazates, which provided an efficient strategy for the preparation of useful highly substituted (β-acylamino)acrylates.[6] A valuable approach to arylvinyl sulfides via silver-mediated oxidative vinylic C–H sulfenylation of enamides with diaryl disulfides has been developed by Deng and co-workers.[7] Very recent-



Scheme 1 Oxidative cross-coupling of ethers with enamides

Table 1 Optimization of Reaction Conditions[a]

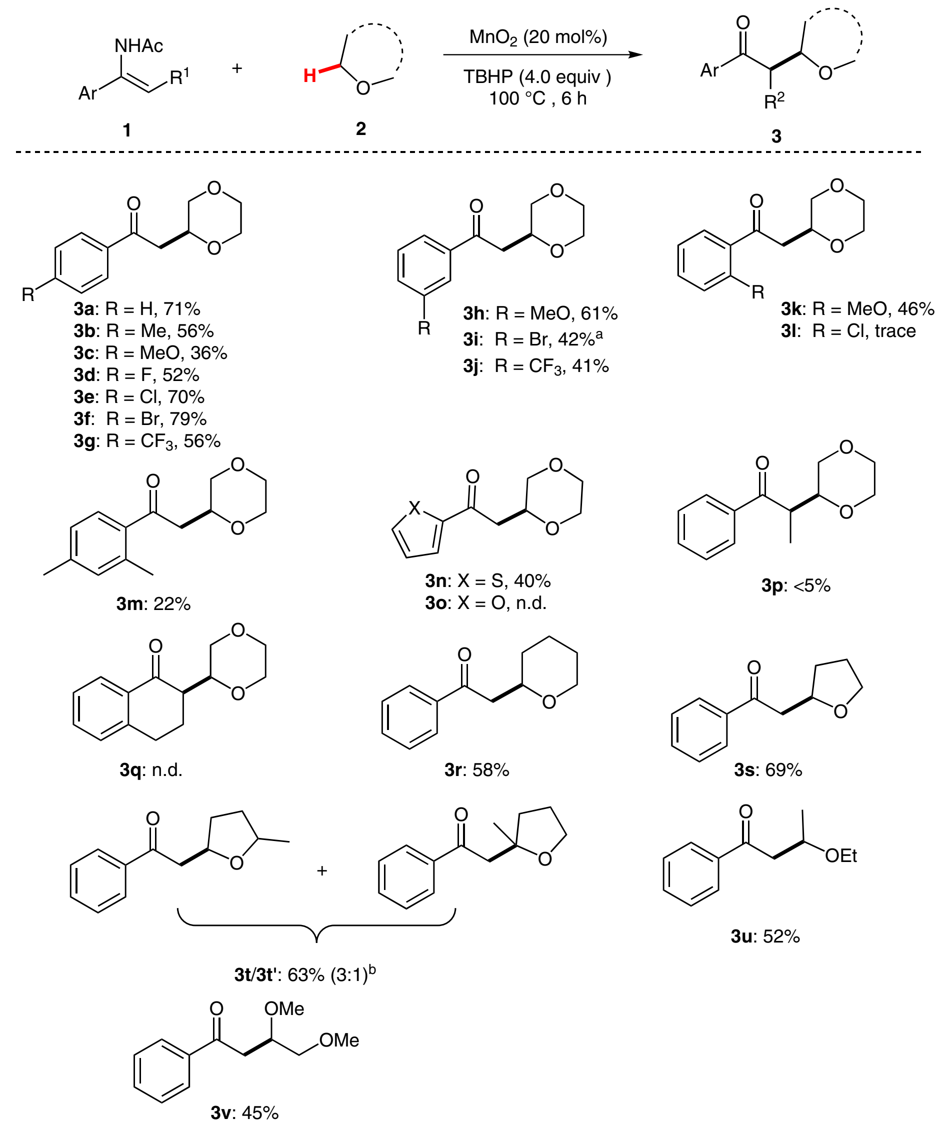


Entry	Catalyst	Oxidant	Yield (%)[b]
1	–	TBHP	50
2	$FeCl_3·6H_2O$	TBHP	n.d.
3	$FeCl_2·4H_2O$	TBHP	26
4	$Cu(OAc)_2$	TBHP	57
5	CuI	TBHP	38
6	TBAI	TBHP	trace
7	$NiCl_2·6H_2O$	TBHP	20
8	$Co(OAc)_2·4H_2O$	TBHP	56
9	$Co(acac)_2$	TBHP	48
10	MnO_2	TBHP	71
11	MnO_2	TBPB	25
12	MnO_2	DTBP	10
13	MnO_2	BPO	31
14[c]	MnO_2	TBHP	17

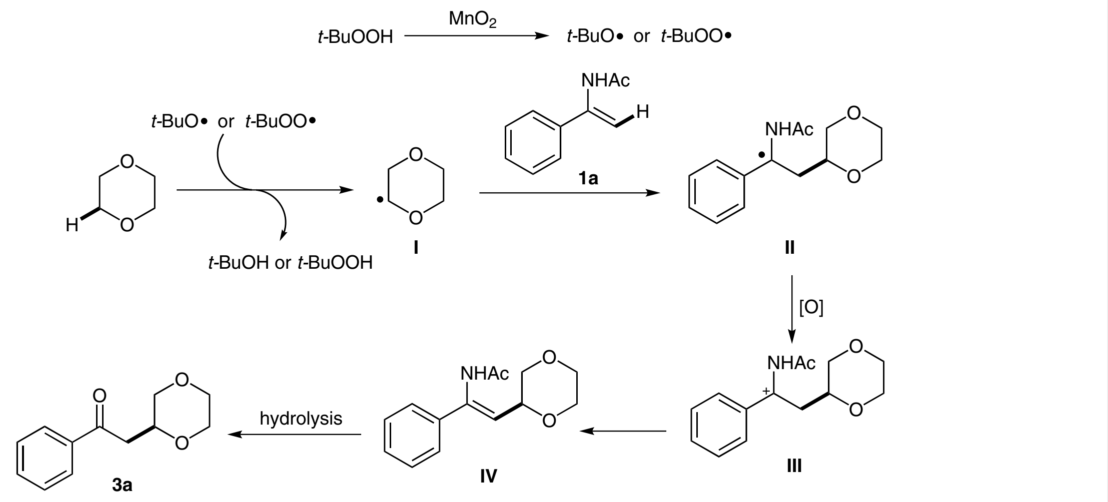
[a] Reaction conditions: **1a** (0.25 mmol), **2** (1.5 mL), catalyst (20 mol%), oxidant (4.0 equiv), 100 °C, 6 h.
[b] Isolated yield.
[c] 80 °C.

ly, we also developed a facile synthetic route towards pharmaceutically interesting β-keto sulfones by tetrabutylammonium iodide (TBAI)/*tert*-butyl hydroperoxide (TBHP) mediated sulfonylation of vinylic C_β–H bond of enamides with sulfonylhydrazides.[8] However, to the best of our knowledge, examples of functionalization of vinylic C_β–H bond of enamides via $C(sp^3)$–H/$C(sp^2)$–H CDC have been rarely studied. Herein, we report the first radical $C(sp^3)$–H/$C(sp^2)$–H CDC of enamides with ethers (Scheme 1). The reaction proceeds with TBHP oxidation using MnO_2 as catalyst, thereby providing a general and straightforward means of accessing various β-oxo ketones.

Our investigation started with *N*-vinylacetamide **1a** and 1,4-dioxane (**2a**) at 100 °C using TBHP (70% aq) as oxidant under catalyst-free conditions. To our delight, the desired product **3a** was obtained in 50% yield (Table 1, entry 1). Inspired by the initial result, we first tested different catalysts. We found that the oxidative coupling occurs with a higher yield of **3a** when using MnO_2 (71% yield) as catalyst (Table 1, entry 10), while the use of other catalysts, including $FeCl_3·6H_2O$, $FeCl_2·4H_2O$, $Cu(OAc)_2$, CuI, TBAI, $Co(OAc)_2·4H_2O$, and $Co(acac)_2$ was less efficient (Table 1, entries 2–9). A number of other oxidants, including *tert*-butyl peroxybenzoate (TBPB), di-*tert*-butyl peroxide (DTBP), benzoyl peroxide (BPO), were subsequently investigated (Table 1, entries 11–13), and they were found to be less effective than TBHP. When the reaction was carried out at 80 °C, the yield of **3a** decreased to 17%.



Scheme 2 Reaction of enamides with ethers. *Reagents and conditions*: **1** (0.25 mmol), **2** (1.5 mL), MnO_2 (20 mol%), TBHP (4.0 equiv) at 100 °C for 6 h. Isolated yields are given. [a] 10 h. [b] Determined by the ^1H NMR spectra of the isolated products.



Scheme 3 Proposed preliminary mechanism

After the optimal reaction conditions were established, the scope of this oxidative alkylation with regard to enamides as well as the C(sp^3)–H bonds adjacent to an oxygen atom was exploited (Scheme 2).[9] First, substitution effects of enamides were examined. The reaction proceeded smoothly not only for the enamides bearing an electron-donating group (products **3b**,**c**,**h**,**k**) but also for those substrates having halides (products **3d**–**f**,**i**) or strong electron-withdrawing CF_3 substituent (**3g**,**j**). Surprisingly, attempt to carry out the corresponding oxidative alkylation of 2-Cl-substituted enamide was unsuccessful. The application of polysubstituted enamide provided the desired product **3m** as well. The oxidative alkylation with enamide containing the thiophene delivered the desired product **3n** in 40% yield, while the enamide containing furan and benzofurans was unreactive and resulted in no formation of **3o**. The enamides derived from propiophenone and dihydronaphthalene failed in the reaction to give the desired products **3p** and **3q** due to the steric effect. We next set out to investigate the scope of the C(sp^3)–H bonds adjacent to an oxygen atom. When using tetrahydro-2*H*-pyran and tetrahydrofuran, the reaction afforded 58% and 69% yields of the corresponding **3r** and **3s**. To investigate the regioselectivity of the transformation, 2-methyltetrahydrofuran was also treated with *N*-vinylacetamide under the optimized conditions, and a mixture of two regioisomers (products **3t**/**3t′**) was generated in the ratio of 3:1. Importantly, this procedure is not limited to the cyclic ethers. For example, ethoxyethane and dimethoxyethane afforded the desired products **3u** and **3v** in 52% and 45% yields, respectively.

According to the above experimental results and previous reports, a plausible mechanism is proposed (Scheme 3). Initially, MnO_2-assisted decomposition of TBHP generated *tert*-butoxyl and *tert*-butylperoxy radicals,[10] which abstracted the α-H of ether and generated radical intermediate (**I**).[2] The addition of the resultant radical intermediate (**I**) to a C–C double bond in the enamide furnished carbon-centered radical intermediate (**II**), followed by oxidation with TBHP to afford carbocation intermediate (**III**). The intermediate (**III**) then eliminated a proton to form enamide intermediate (**IV**). Finally, hydrolysis reaction of enamide intermediate (**IV**) afforded the product **3a**.

In conclusion, we have developed a novel MnO_2-catalyzed oxidative alkylation of enamides with a C(sp^3)–H bonds adjacent to a oxygen atom. The process involves a C(sp^3)–H/C(sp^2)–H CDC and hydrolysis sequence. This reaction provided a simple and practical protocol for the synthesis of β-oxo ketones.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560180.

References and Notes

(1) For reviews on C–H functionalization, see: (a) Mkhalid, I.; Barnard, J.; Marder, T.; Murphy, J.; Hartwig, J. *Chem. Rev.* **2010**, *110*, 890. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

(e) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (f) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (g) Chen, X.; Engle, K. M.; Wang, D.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (h) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (i) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (j) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (k) Davies, H. M.; Bois, J. D.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855.

(2) For some representative examples, see: (a) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (b) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085. (c) Zhang, S.; Guo, L.-N.; Duan, X.-H. *Org. Biomol. Chem.* **2013**, *11*, 4308. (d) Kumar, G. S.; Pieber, B.; Reddy, K. R.; Kappe, C. O. *Chem. Eur. J.* **2012**, *18*, 6124. (e) Guo, S.-R.; Yuan, Y.-Q.; Xiang, J.-N. *Org. Lett.* **2013**, *15*, 4654. (f) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 4453. (g) Cao, J.-J.; Zhu, T.-H.; Wang, S.-Y.; Gu, Z-Y.; Wang, X.; Ji, S.-J. *Chem. Commun.* **2014**, *50*, 6439.

(3) For reviews, see: (a) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (b) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292.

(4) (a) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, *48*, 3472. (b) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2009**, *48*, 5355. (c) Pankajakshan, S.; Xu, Y.-H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5701.

(5) Hesp, K. H.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430.

(6) Ding, R.; Zhang, Q.-H.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 11661.

(7) Yang, L.; Wen, Q.; Xiao, F.-H.; Deng, G.-J. *Org. Biomol. Chem.* **2014**, *12*, 9519.

(8) Tang, Y.; Zhang, Y.; Wang, K.; Li, X.; Xu, X.; Du, X. *Org. Biomol. Chem.* **2015**, *13*, 7084.

(9) **General Procedure of the MnO$_2$-Promoted C(sp^3)–H/C(sp^2)–H Oxidative Cross-Coupling of Ethers with Enamides**
To a suspension of *N*-vinylacetamides **1** (0.25 mmol), MnO$_2$ (0.05 mmol), and 1,4-dioxane (**2**) (1.5 mL) was added TBHP (70% aq solution, 1.0 mmol), and the mixture was stirred at 100 °C for 6 h. After the solvent was removed under reduced pressure, the residual was treated with silica gel chromatography (EtOAc–PE) to give products **3**.

(10) Vanjari, R.; Guntreddi, T.; Singh, K.-N. *Org. Lett.* **2013**, *15*, 4908.