

Accepted Manuscript

Facile synthesis of α , β -unsaturated esters through a one-pot copper-catalyzed aerobic oxidation-Wittig reaction

Cheng Ren, Zhenyu Shi, Weijie Ding, Zhiqing Liu, Huile Jin, Xiaochun Yu, Shun Wang

PII: S0040-4039(17)31137-1

DOI: <http://dx.doi.org/10.1016/j.tetlet.2017.09.020>

Reference: TETL 49290

To appear in: *Tetrahedron Letters*

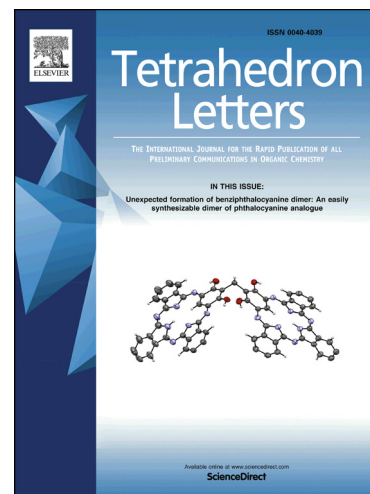
Received Date: 25 July 2017

Revised Date: 10 September 2017

Accepted Date: 12 September 2017

Please cite this article as: Ren, C., Shi, Z., Ding, W., Liu, Z., Jin, H., Yu, X., Wang, S., Facile synthesis of α , β -unsaturated esters through a one-pot copper-catalyzed aerobic oxidation-Wittig reaction, *Tetrahedron Letters* (2017), doi: <http://dx.doi.org/10.1016/j.tetlet.2017.09.020>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



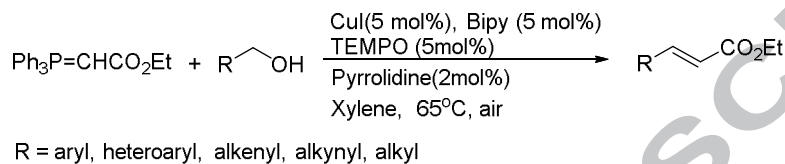
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Facile synthesis of α, β -unsaturated esters through a one-pot copper-catalyzed aerobic oxidation-Wittig reaction

Leave this area blank for abstract info.

Cheng Ren, Zhenyu Shi, Weijie Ding, Zhiqing Liu, Huile Jin, Xiaochun Yu* and Shun Wang*





Facile synthesis of α , β -unsaturated esters through a one-pot copper-catalyzed aerobic oxidation-Wittig reaction

Cheng Ren^a, Zhenyu Shi^a, Weijie Ding^a, Zhiqing Liu^a, Huile Jin^a, Xiaochun Yu^{a,*} and Shun Wang^{a,*}

^a College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, People's Republic of China

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Aerobic oxidation reaction

Alcohol

Phosphonium ylide

Copper catalyst

Carbon-carbon double bond

ABSTRACT

An efficient one-pot synthesis of α , β -unsaturated esters through the aerobic oxidation - Wittig tandem reaction of alcohols and phosphorous ylide is developed. This new method operates under mild reaction conditions, and uses CuI/TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidine -N-oxyl) as co-catalyst and air (O_2) as the oxidant. It tolerates a wide range of functionalized benzylic alcohol and aliphatic alcohols.

2009 Elsevier Ltd. All rights reserved.

Introduction

The formation of carbon-carbon double bond through Wittig reaction¹ is one of the most important processes for the production of functional organic compounds, such as drugs, dye and spice etc.² It is well known that classical Wittig reaction usually utilizes aldehydes as the starting materials (Scheme 1-a), in which aldehydes are generally prepared from the oxidation of alcohols. In comparison to aldehydes, alcohols are cheaper, less toxic and easier to handle. Therefore, the direct one-pot tandem oxidation-Wittig reaction of alcohols with ylides is an appealing approach to construct carbon-carbon double bonds. There are increasing research activities in developing various oxidants (Swern³, Dess-Martin⁴, IBX⁵, BaMnO₄⁶, MnO₂⁷, PhI(OAc)₂ with TEMPO (cat.)⁸, NMO with catalytic amount of TPAP⁹, PCC¹⁰, SO₃Py¹¹, and so on) for the tandem oxidation-Wittig reaction of alcohol with ylides (Scheme 1-b). These methods require large excess or at least full equivalent amounts of oxidants. The subsequent removal of oxidant does not only complicate the synthetic procedure, but also increases the final cost, which seriously limits their large-scale application. Moreover, some used oxidants themselves are hazardous and difficult to handle.

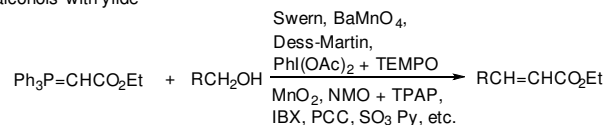
To avoid the use of excessive amounts of oxidants, there is significant interest in the design of new catalysts and use of green oxidants. Chang¹² and J. Park¹³ both reported the aerobic oxidation-Wittig reaction of alcohol with ylide by using ruthenium as catalyst and O_2 as oxidant (Scheme 1-c). These two catalytic systems exhibit impressive safety. However, the Chang's method required stoichiometric Cs₂CO₃ and had poor yields when aliphatic alcohols were used, and the J. Park's method typically used pure O_2 . Certainly the high cost of the catalyst also hampers its massive commercial application. Recently, several catalytic oxidation-olefination methods were

developed. For example, TMEDAO₂ (*N,N,N',N'*-tetramethylethylenediamine dioxide) could be used as co-oxidant in a tandem TPAP catalyzed oxidation Wittig protocols, but the sequential addition protocol was needed, and 2 equivalent of ylides was used for some cases.¹⁴ Gold/palladium bimetallic nanoparticles were also utilized as a catalyst in oxidation Horner-Wadsworth-Emmons reaction, where 1.5 equivalent of triethyl phosphonoacetate and 3.0 equivalent of base were needed.¹⁵ Diruthenium complex catalyzed aerobic oxidation Wittig reaction was reported, where the catalyst is not commercially available and complicated procedures were required to prepare it.¹⁶ Therefore, more attention should be devoted to development of novel catalysts which have excellent catalytic activity, green oxidant, low cost and mild conditions.

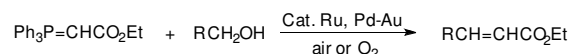
a. Classical Wittig reaction



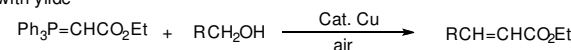
b. Large excess amounts of oxidant were employed for the tandem reaction of alcohols with ylide



c. Transition metal catalyzed tandem reaction of alcohols with ylide



d. **This work:** copper catalyzed aerobic oxidation-Wittig reaction of alcohols with ylide



Scheme 1

Copper has been known as an effective catalyst for aerobic alcohol oxidations.¹⁷ Yet, an efficient and practical Cu-catalyzed aerobic oxidation-Wittig tandem method has not been reported. In this article, a high yield one-pot synthesis of α , β -unsaturated esters through the aerobic oxidation-Wittig tandem reaction are developed which uses CuI as the catalyst and O₂ in air as the green oxidant (Scheme 1-d).

Results and Discussion

The optimization of copper catalytic system was accomplished through investing the reaction of *p*-nitrobenzyl alcohol **2a** with phosphonium ylide **1**, and the results are summarized in Table 1. We found that the reaction could not be effectively carried out without the addition of TEMPO (Entry 1), base (Entry 2),

Table 1. Condition screening by exploring the bases, ligands and solvent.

$\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et} + \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_2\text{OH} \xrightarrow[\text{Ligand (5 mol\%), Base, Solvent, Air}]{\text{CuI (5 mol\%), TEMPO (5 mol\%)}} \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}=\text{CHCO}_2\text{Et}$					
1	2a			3a	
Entry ^a	Ligand	Base (mol%)	T/°C	Solvent	3a(%) ^b
1 ^c	Bipy	<i>t</i> -BuOK(20)	65	CH ₃ CN	9
2	Bipy	none	65	CH ₃ CN	31
3	Bipy	<i>t</i> -BuOK(20)	65	CH ₃ CN	78
4	-	BuOK (20)	65	CH ₃ CN	40
5	Bipy	KOH(20)	65	CH ₃ CN/H ₂ O	22
6	Bipy	Pyrrolidine (20)	65	CH ₃ CN	84
7	Bipy	TEA (20)	65	CH ₃ CN	30
8	Bipy	DABCO (20)	65	CH ₃ CN	35
9	Bipy	Pyridine	65	CH ₃ CN	51
10	Bipy	Pyrrolidine (2)	65	CH ₃ CN	86
11	TMEDA	Pyrrolidine (2)	65	CH ₃ CN	70
12	DMAP	Pyrrolidine (2)	65	CH ₃ CN	74
13	Phen	Pyrrolidine (2)	65	CH ₃ CN	72
14	TMDP	Pyrrolidine (2)	65	CH ₃ CN	68
15	Bipy	Pyrrolidine (2)	65	DMSO	70
16	Bipy	Pyrrolidine (2)	65	Xylene	93
17	Bipy	Pyrrolidine (2)	65	Toluene	67
18	Bipy	Pyrrolidine (2)	65	CH ₂ Cl ₂	46
19	Bipy	Pyrrolidine (2)	65	THF	40
20	Bipy	Pyrrolidine (2)	65	Dioxane	74
21	Bipy	Pyrrolidine (2)	65	DMF	78
22	Bipy	Pyrrolidine (2)	r.t.	Xylene	35
23	Bipy	Pyrrolidine (2)	40	Xylene	70

^a The mixture of **1** (1.2 mmol, 1.2 equiv.), **2** (1.0 mmol), CuI (5 mol%), TEMPO (5 mol%), ligand (5 mol%), and Base in Solvent (1.5 mL) was stirred in a sealed 100 mL Schlenk tube with a air balloon for 24 h, monitored by TLC, and then isolated by column chromatography.

^b Isolated yields.

^c without the addition of TEMPO

or ligand (Entry 4). To improve this transformation 2,2'-bipyridine (Bipy) was used as ligand in the presence of CuI (5 mol%) and cocatalyst TEMPO (5 mol%). Selected bases such as *t*-BuOK, KOH, pyrrolidine, Et₃N, DABCO (1,4-diazabicyclo [2.2.2] octane), and pyridine were screened. Pyrrolidine was found to be the best one, giving the highest isolated yield (86%) of the product (Entry 10), even though only 2 mol% of the pyrrolidine was used. Next, *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA), 4-dimethylaminopyridine (DMAP), 1,10-phenanthroline (Phen), and 4,4'-trimethylenedipyridine (TMDP) were also tested as the ligands for this catalytic system. While all of these ligands appear to be effective showing good yield of **2a** (Entries 11-14), Bipy was proved to be the best (Entry 10). Then, various types of Cu compounds (CuCl, Cu(OAc)₂, CuBr, CuSO₄, CuO) were tested as the catalyst. CuI was found to be the best one (See *Supporting information* Table 1).

The effect of solvent was also investigated. All commercial solvents (DMSO, xylene, Toluene, CH₂Cl₂, THF, dioxane, and DMF) were used directly without any pretreatment (Entries 15-21). In comparison, xylene is the best one, in which 93% isolated yield of **3a** was obtained. It should be noted that all the reactions were conducted under air condition. Moreover, no over oxidized product (*p*-nitrobenzoic acid or *p*-nitrobenzoate) was detected by GC-MS analysis of the crude reaction mixtures during the optimized process. And we found the reaction

temperature had great influence on the Wittig reaction, but had little effect on the aerobic oxidation of alcohols. Because a lot of aldehyde were observed by TLC and GC-MS analysis with the decrease of the temperature, while the yield of **3a** was reduced greatly (Entries 22, 23).

Using the above optimized conditions various alcohols were subsequently employed in the one-pot aerobic oxidation-Wittig reaction with ylide **1** in order to examine the application scope of this method. Results summarized in Table 2 illustrate that the expected α , β -unsaturated esters are formed with a moderate to excellent *E/Z* selectivity and yield. Substituent electronic effect was not significant in the tandem reactions, in which various electron-donating (4-CH₃- (**3k**), and 4-CH₃O- (**3g**)) or electron-withdrawing groups (4-NO₂- (**3a**), 4-Cl- (**3b**), 4-F- (**3e**), and 4-Br- (**3f**)) substituted benzylic alcohols all reacted efficiently with phosphorous ylide **1** to form α , β -unsaturated esters with an excellent isolated yield. Substituent steric effect was not significant either, and more hindered *ortho*-substituted alcohols such as (2-chlorophenyl)methanol (**3d**) and (2-methoxyphenyl)methanol (**3j**) all reacted smoothly and produced products with a high yield. Those with reactive functional groups such as fluoro, chloro, bromo and nitro were also compatible with the reaction conditions, and no other byproduct was detected by GC-MS. Naphthalen-2-yl, naphthalen-1-ylsubstituted methanol reacted

efficiently with ylide **1** to form alkenes with an excellent yield and a very high stereoselectivity (**3n**, **3o**).

Our catalytic system was also applicable for the alcohols containing heteroatom (N, S, O) (**3p-3t**) aromatic ring. It is particularly notable that the reaction of pyridine-3-ylmethanol with ylide **1** in our copper-catalyzed system was much more efficient than those using RuAlO(OH)¹³ as the catalyst, which generated α , β -unsaturated ester with a 44% yield, and 90% yield of the product was achieved using our catalytic system.

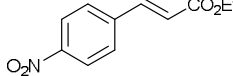
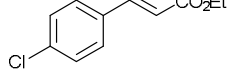
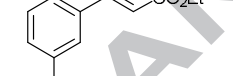
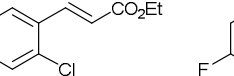
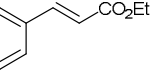
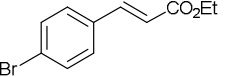
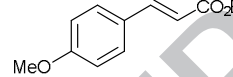
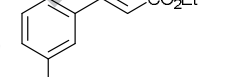
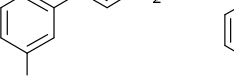
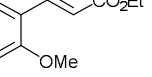
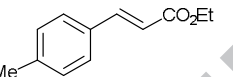
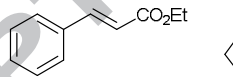
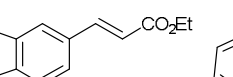
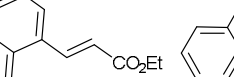
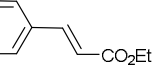
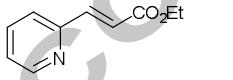
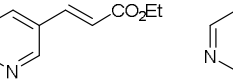
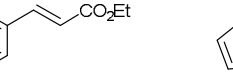
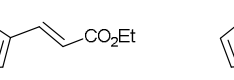
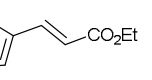
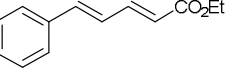
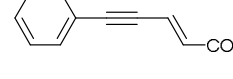
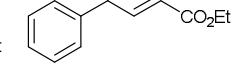
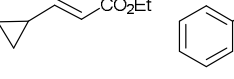
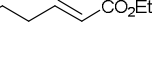



For 3-phenylprop-2-en-1-ol (**3u**), the reaction was as efficient as benzylic alcohol, forming the product with a 86% yield. The reaction of 3-phenylprop-2-yn-1-ol (**3v**) was inferior, no target product was obtained under air condition. However, the reactions were improved greatly when the tandem reactions were conducted under O₂ atmosphere, in which the products were obtained with 85% isolated yield. The two isomeric products of ethyl 5-phenylpent-2-en-4-ynoate (**3v**) could be separated by column chromatography, and its *E/Z* ratio was calculated by weight of the isomers.

Other aliphatic alcohols (**3w-3ab**) were also examined under the optimized reaction conditions. Similarly, reactions of these aliphatic alcohols were inferior under air condition, and considerable amounts of unidentified byproducts were generated. These products could not be separated successfully. However, if the reactions were carried out under O₂ atmosphere, the yield of the target products could be increased greatly.

Meanwhile, larger scale reactions were also possible. For example, under the optimized condition **3a** was synthesised on gram scale (10 mmol) with 88% isolated yield.

It should be mentioned that secondary alcohol such as 1-phenylethan-1-ol was also examined at the optimized reaction conditions. We found that 1-phenylethan-1-ol could be oxidized into acetophenone efficiently, but the Wittig reaction of the ketone with ylide **1** failed, where no corresponding α , β -unsaturated ester was formed. This outcome may be attributed to the fact that acetophenone was not so reactive to react with stabilized ylide in the Wittig reaction.

Table 2. Reactions of ethyl (triphenylphosphoranylidene) acetate and benzylic or aliphatic alcohols.^a

$\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$		$+ \text{RCH}_2\text{OH}$	$\xrightarrow[\text{Pyrrolidine (2 mol\%)}]{\text{CuI (5 mol\%), Bipy (5 mol\%)}, \text{TEMPO (5 mol\%)}}$	$\text{RCH}=\text{CHCO}_2\text{Et}$
1	2		Xylene, 65°C, Air	3
				
3a , 93% [98:2] ^c gram scale, 88% (1.94g)	3b , 97% [89:11] ^c	3c , 97% [93:7] ^c	3d , 91% [82:18] ^c	3e , 86% [91:9] ^c
				
3f , 94% [>99:1] ^c	3g , 92% [92:8] ^c	3h , 86% [89:11] ^c	3i , 83% [99:1] ^c	3j , 99% [79:21] ^c
				
3k , 88% [93:7] ^c	3l , 98% [93:7] ^c	3m , 93% [>99:1] ^c	3n , 97% [93:7] ^c	3o , 98% [96:4] ^c
				
3p , 92% [>99:1] ^c	3q , 90% [89:11] ^c	3r , 90% [91:9] ^c	3s , 79% [95:5] ^c	3t , 78% [98:2] ^c
				
3u , 86% [83:17] ^c	3v , 0% (85%) ^b [63:37]	3w , 0% (48%) ^b [67:33] ^c	3x , 38% (72%) ^b [99:1] ^c	3y , 0% (63%) ^b [80:20] ^c
				
3z , 0% (78%) ^b [85:15] ^c	3aa , 0% (80%) ^b [86:14] ^c	3ab , 0% (75%) ^b [70:30] ^c		

^a All reactions were carried out with 1.2 mmol of ylide **1**, 1.0 mmol of alcohol **2**, CuI (5 mol%), 2,2'-bipyridine (5 mol%), TEMPO (5 mol%), and pyrrolidine (2 mol%) in xylene (1.5 mL) was stirred in 100 mL Schlenk tube with an air or O₂ balloon at 65°C for 24 h.

^b isolated yield in parenthesis under O₂ atmosphere.

^c The *E/Z* ratio was determined by ¹H NMR.

Conclusions

In conclusion, this study presents a new, green, and efficient Cu-catalyzed system for the aerobic oxidation-Wittig tandem reaction. The reaction can be readily carried out with an air or O₂ balloon under mild conditions. Using mild reaction conditions enables the Wittig tandem aerobic oxidation reaction to tolerate a wide range of functionalized alcohol partners as well as the aliphatic alcohols. Relying on environmentally benign oxidant and abundant transition metal catalysts makes this simple and practical method more appealing.

Acknowledgments

Financial supports from the National Natural Science Foundation of China (Nos. 21302143 and 51572198), Natural Science Foundation of Zhejiang Province (Nos. LY13B020006, and LZ17E020002) are greatly appreciated.

References and notes

1. Wittig; Geissler, G. *Liebigs Ann. Chem.* **1953**, 580, 44-57.
2. a) Takeda, T. *Modern Carbonyl Olefination*, Wiley-VCH, Weinheim, 2004; b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863-927; (c) Shen, Y. *Acc. Chem. Res.*, **1998**, 31, 584-592.
3. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, 50, 2198-2200.
4. Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.*, **1997**, 62, 9376-9378.
5. Maiti, A.; Yadav, J. S. *Synth. Commun.* **2001**, 31, 1499-1506.
6. a) Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, 63, 4489-4493; b) Gholinejad, M.; Firouzabadi, H.; Bahrani, M.; Nájera, C. *Tetrahedron Lett.* **2016**, 57, 3773-3775.
7. a) Nakamura, M.; Mori, Y.; Okuyama, K.; Tanikawa, K.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Org. Biomol. Chem.* **2003**, 1, 3362-3376; b) Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem.*

- Commun.* **1999**, 1337-1338; c) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, 38, 851-869.
8. Vatele, J. M. *Tetrahedron Lett.* **2006**, 47, 715-718.
 9. MacCoss, R. N.; Blaskus, E. P.; Ley, S. V. *Tetrahedron Lett.* **2003**, 44, 7779-7781.
 10. Bressette, A. R.; Glover, L. C. *Synlett.* **2004**, 738-740.
 11. Crisóstomo, F. R. P.; Carrillo, R.; Martín, T.; García-Tellado, F.; Martín, V. S. *J. Org. Chem.* **2005**, 70, 10099-10101.
 12. Kim, G.; Lee, D. G.; Chang, S. *Bull. Korean Chem. Soc.*, **2001**, 22, 943-944.
 13. Lee, E. Y.; Kim, Y.; Lee, J. S.; Park, J. *Eur. J. Org. Chem.* **2009**, 2943-2946.
 14. Read, C. D. G.; Moore, P. W.; Williams, C. M. *Green Chem.* **2015**, 17, 4537-4540.
 15. Miyamura, H.; Suzuki, A.; Yasukawa, T.; Kobayashi, S. *Adv. Synth. Catal.* **2015**, 357, 3815.
 16. Dutta, I. D.; Sarbajna, A.; Pandey, P.; Rahaman, S. M. W.; Singh, K.; Bera, J. K. *Organometallics*. **2016**, 35, 1505-1513.
 17. For reviews on copper catalyzed oxidation of alcohol, please see: a) Ryland, B. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2014**, 53, 8824-8838; b) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. L. *Chem. Commun.* **2014**, 50, 4524-4543; c) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Gautier, A.; Dumeunier, R.; Philippart, F.; Doda, K.; Mutookole, J. L.; Brown, S. M.; Urch, C. J. *Adv. Inorg. Chem.* **2004**, 56, 211-240; d) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, 346, 1051-1071.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Click here to remove instruction text...

Highlights

Facile synthesis of α ,
 β -unsaturated esters through a
one-pot copper-catalyzed aerobic
oxidation-Wittig reaction

Cheng Ren, Zhenyu Shi, Weijie Ding, Zhiqing Liu,
Huile Jin, Xiaochun Yu* and Shun Wang*

*College of Chemistry and Materials Engineering, Wenzhou University,
Chashan University Town, Wenzhou, Zhejiang Province 325035, People's
Republic of China.*

The highlights were elucidated as below:

1. Developed a green and efficient one-pot aerobic oxidation-Wittig tandem.
2. The reaction is catalyzed by CuI.
3. Air or O₂ is used as the economic and green oxidant.
4. A diverse range of α , β -unsaturated esters were synthesized in high yield.