ORGANIC LETTERS

2009
Vol. 11, No. 1
41−44

Copper-Catalyzed Tandem Oxidation−Olefination Process

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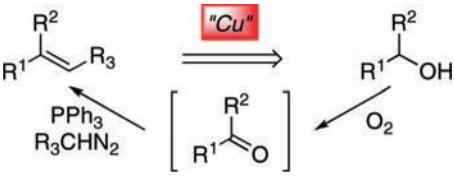
Received October 3, 2008

ABSTRACT



A novel catalytic sequence aerobic oxidation−olefination has been developed. A single and inexpensive copper catalyst provides a large range of olefins from alcohols in good to excellent yields. The reaction exhibits excellent functional group compatibility, and the nonbasic reaction conditions allow the transformation of chiral substrates without racemization.

Multistep processes to perform oxidation followed by olefination reactions are important transformations often employed in syntheses, including the synthesis of natural products.[1] Consequently, there has been much interest in the development of one-pot oxidation−olefination processes.[2,3] This approach is a more green alternative to classical multistep oxidation−olefination through the minimization of the amount of solvent and reagents needed for the reactions and purifications. Furthermore, the isolation of potentially sensitive aldehydes (to overoxidation and/or enolization) is avoided. Nevertheless, available one-pot processes are restricted to benzylic, allylic, and aliphatic primary alcohols and involve the use of stoichiometric oxidants.

Recently, our group has disclosed several efficient catalytic olefination reactions using Rh,[4] Ir,[5] and Cu[6] catalysts.[7] Moreover, these transition-metal-catalyzed transformations have successfully been used in various one-pot procedures.[8] In particular, we have reported the first multicatalytic one-pot palladium-catalyzed oxidation[9]−rhodium-catalyzed me-

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(1) For recent selected examples, see: (a) Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704–13705. (b) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320–3323. (c) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469. (d) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239. (e) Selig, P.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082–5084.

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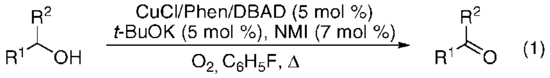
thylenation[4] process.[10,11] Terminal alkenes were obtained in high yields, but two rather expensive catalysts were required. Our recent successes with copper-catalyzed olefination reactions using diazo compounds[6] prompted us to study a novel catalytic oxidation−olefination tandem process. Herein, we describe the use of copper chloride phenanthroline complex in tandem catalysis to efficiently synthesize various alkenes from alcohols.

Copper-catalyzed aerobic oxidation reactions have emerged as a powerful methodology for the transformation of alcohols into carbonyl compounds.[12] Among these methods, Markó et al. have developed the most general and efficient catalytic oxidation of aliphatic, allylic, benzylic, primary, as well as secondary alcohols using CuCl/Phen/DBAB complex (phen = 1,10-phenanthroline, DBAB = di-*tert*-butyl azodicarboxylate) (eq 1).[13−15] The use of such a system in combination with a olefination reaction involving diazo reagents and triphenylphosphine would provide a monocatalytic approach for a one-pot oxidation−olefination process.

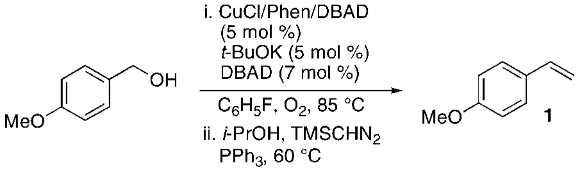


(1)

R^1, R^2 = H, alkyl, vinyl, aryl
Phen = 1,10-phenanthroline
NMI = *N*-methylimidazole
DBAB = di-*tert*-butyl azodicarboxylate

Preliminary studies demonstrated that there was no ligand effect in the copper-catalyzed methylenation reaction, and CuCl/Phen complex provided results similar to those with CuCl. For instance, when the *p*-anisaldehyde was treated with 1.1 equiv of 2-propanol, 1.1 equiv of PPh_3, and 1.4 equiv of $TMSCHN_2$ in the presence of 5 mol % of CuCl/Phen in fluorobenzene at 60 °C, the corresponding styrene was isolated in 74% yield (the same yield was obtained using 5 mol % of CuCl in THF).[6a] Furthermore, the presence of a catalytic amount of either *t*-BuOK, DBAB, or NMI did not inhibit the reaction. These encouraging results led us to explore the one-pot oxidation−methylenation tandem process (Table 1). Treatment of the 4-methoxybenzyl alcohol under standard copper-catalyzed aerobic oxidation, followed by the addition of $TMSCHN_2$, 2-propanol, and triphenylphosphine, led to the formation of the desired styrene **1**, albeit in moderate yields when not using an excess of 2-propanol (entries 1−4). However, in the presence of 5 equiv of 2-propanol and 3 equiv of $TMSCHN_2$ added in two portions, 85% of styrene **1** was obtained (entry 8).[16,17]

Table 1. Copper-Catalyzed Oxidation−Methylenation Tandem Process of 4-Methoxybenzyl Alcohol (eq 2)



(2)

entry	*i*-PrOH (equiv)	$TMSCHN_2$ (equiv)	yield[a] (%)
1	1.1	1.4	36
2	1.1	4.0	54
3	2.0	2.0	29
4[b]	2.0	2.0	45
5	5.0	2.0	52
6[b]	5.0	2.0	72
7	5.0	3.0	71
8[b]	**5.0**	**3.0**	**85**

[a] Isolated yield. [b] $TMSCHN_2$ was added in two portions.

These reaction conditions were general and could be applied to a wide variety of alcohol substrates (Table 2). Terminal alkenes from linear primary alcohols as well as sterically

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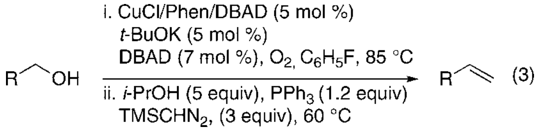
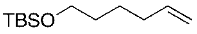
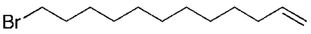
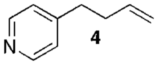
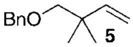
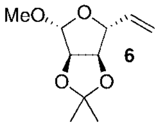
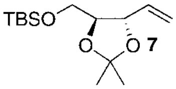
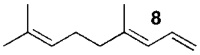
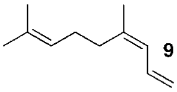
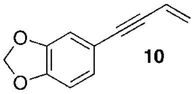
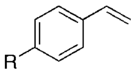
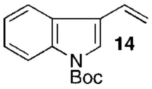
Table 2. Copper-Catalyzed Oxidation−Methylenation Tandem Process of Primary Alcohols (eq 3)

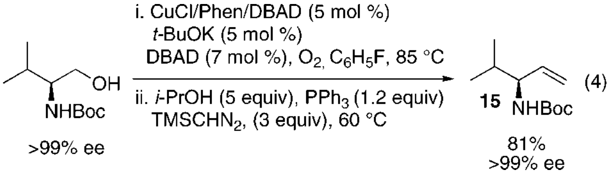


entry	product	yield[a]
1	 **2**	71
2	 **3**	84
3[b]	 **4**	65
4	 **5**	81
5	 **6**	61
6	 **7**	74
7	 **8**	74
8	 **9**	69
9	 **10**	79
10	 R = Br, **11**	78
11	R = NHBoc, **12**	82
12[c]	R = NO_2, **13**	60
13	 **14**	60

[a] Isolated yields. [b] 10 mol % of CuCl/Phen/DBAB. [c] c = 0.05 M.

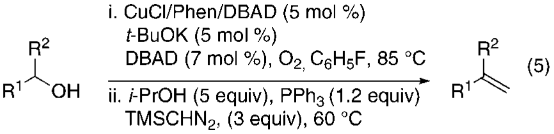
hindered alcohols were isolated in good yields (entries 1−6). Even substrates containing strong coordinating groups such as pyridine were efficiently converted, although the use 10 mol % of catalyst was required (Table 2, entry 3). Geraniol and nerol afforded the expected terminal alkenes without isomerization of the carbon−carbon double bond (Table 2, entries 7 and 8).[18] Other activated alcohols, such as propargylic and benzylic alcohols, were also suitable substrates (Table 2, entries 9−13). Overall, the reaction showed an excellent functional group compatibility and alcohols were reacted in the presence of nitro groups, amides, esters, and halides. Additionally, a wide variety of protecting groups are tolerated (silyl and benzyl ether, acetal, and carbamate).

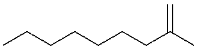
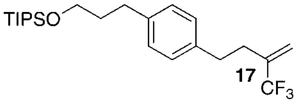
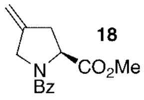
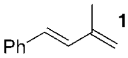
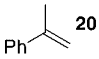
α-Chiral alcohols are converted into olefins without any detectable racemization (Table 2, entries 5 and 6).[19] This was also confirmed with *N*-Boc-valinol substrate (>99% ee). Copper-catalyzed oxidation−methylenation provided the corresponding alkene **15** in 81% yields and 99% ee (eq 4).



To date, no monocatalytic oxidation−olefination one-pot processes starting with secondary alcohols have been reported. We were pleased to find that the copper-catalyzed aerobic oxidation−methylenation process was also compatible with aliphatic, allylic, or benzylic secondary alcohols (Table 3). The corresponding 2,2-disubstituted alkenes were isolated in good yields.

Table 3. Copper-Catalyzed Oxidation−Methylenation Tandem Process of Secondary Alcohols (eq 5)



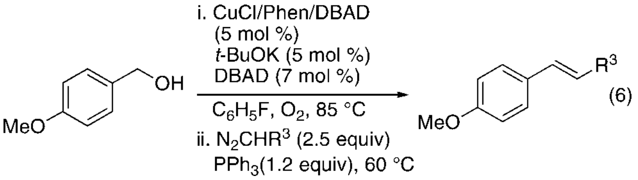
entry	product	yield[a]
1	 **16**	77
2	 **17**	59
3	 **18**	82
4	 **19**	55
5	 **20**	78

[a] Isolated yields.

We have previously observed that copper salts are general catalysts that can be used with a number of diazo reagents,[6c] a significant advantage over other catalyzed olefination reactions. Similarly, the described one-pot process is compatible with various diazocarbonyl reagents (Table 4). It was indeed possible to produce the corresponding α,*β*-unsaturated ester, ketone, or amides from 4-methoxybenzyl alcohol. In all cases, the reaction proceeded in good yields and high *E*-selectivities. Interestingly, in contrast to results in the literature, the addition of a Brønsted acid does not enhance the yield and/or selectivity.[20]

In conclusion, we have disclosed the use of a simple and efficient copper catalyst for a tandem process aerobic

Table 4. Oxidation−Olefination Tandem Process with Various Diazo Reagents of 4-Methoxybenzyl Alcohol (eq 6)



entry	R^3	product	yield[a] (%)	*E*/*Z*[b]
1	CO_2Et	**21**	87	94:6
2	COPh	**22**	70	91:9
3	$CONMe_2$	**23**	74	95:5
4	CON(OMe)Me	**24**	81	97:3

[a] Isolated yields. [b] Determined by ^1H NMR of the crude product.

oxidation−olefination using primary and also secondary alcohols. Some noteworthy attributes of the system include its simple and inexpensive catalytic system, nonbasic reaction conditions, compatibility with sensitive and enolizable substrates, and functional group tolerance for the synthesis of a large variety of alkenes from alcohols.

Acknowledgment. This research was supported by NSERC (Canada), the Canada Foundation for Innovation, and the Université de Montréal. Acknowledgement is also made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. We thank Professors István E. Markó and Freddi Philippart (Catholic University of Louvain) for fruitful discussions.

Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **Typical procedure**: CuCl (5 mg, 0.05 mmol) and 1,10-phenanthroline (9 mg, 0.05 mmol) were placed in a vessel, and anhydrous fluorobenzene was added (10 mL, *c* = 0.1 M). The resulting solution was stirred at room temperature until the solution became green and clear (5 to 10 min). The alcohol (1.00 mmol) was added, followed by solid ^{t}BuOK (5.6 mg, 0.05 mmol). The solution was stirred at room temperature for 10 min, and NMI (120 mg, 1.4 mmol) and DBAD (230 mg, 1 mmol) were added. The reaction mixture was heated at reflux under a gentle stream of O_2 until the reaction was completed as monitored by TLC. The resulting mixture was cooled to 60 °C, and the vessel was backfilled with argon. Triphenylphosphine (315 mg, 1.20 mmol) and 2-propanol (383 μL, 5.00 mmol) were added. Then, 1.50 of trimethylsilyldiazomethane (solution in ether) was added, and the mixture was stirred for 2 h before a second portion of 1.50 equiv of $TMSCHN_2$ was added. The reaction was stirred until the reaction was completed as gauged by GC, ^1H NMR, or TLC analysis. The solvent was removed under reduced pressure, and the crude alkene was purified by flash chromatography on silica gel.

(17) An excess of 2-propanol accelerated the rate of the reaction, whereas the excess of $TMSCHN_2$ is required, as this reagent is destroyed over time in the reaction mixture.

(18) In the palladium-catalyzed aerobic oxidation, only moderate conversions were observed for the allylic alcohols (see ref 11). For modified conditions for the palladium-catalyzed aerobic oxidation of allylic alcohols, see: Batt, F.; Bourcet, E.; Kassab, Y.; Fache, F. *Synlett* **2007**, 1869–1872.

(19) In some cases, racemization was observed during the palladium-catalyzed aerobic oxidation, see ref 11.

(20) For examples of Brönsted acid-catalyzed Wittig reaction, see: (a) Rüchardt, C.; Eichler, S.; Panse, P. *Angew. Chem., Int. Ed.* **1963**, *2*, 619. (b) Bose, A. K.; Manhas, M. S.; Ramer, R. M. *J. Chem. Soc. C* **1969**, 2728–2730. (c) Patil, V. J.; Mävers, U. *Tetrahedron Lett.* **1996**, *67*, 1281–1284. (d) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608–8615.