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Neutral, non-racemising, catalytic aerobic oxidation of alcohols

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Dedicated with deep respect to Professor Jean Normant

Abstract

A novel procedure for the catalytic aerobic oxidation of alcohols into carbonyl derivatives under neutral, non-racemising conditions, is reported.

Keywords: Catalytic aerobic oxidation; Alcohols; Carbonyl derivatives

1. Introduction

The oxidation of alcohols into aldehydes and ketones is a ubiquitous transformation in organic chemistry. The plethora of reagents available to accomplish this key-reaction stands as a clear testimony to its importance [1]. From an economic and environmental viewpoint, catalytic oxidation processes are extremely valuable [2]. Among these procedures, catalytic protocols based upon molecular oxygen [3] or hydrogen peroxide [4] are particularly attractive since they employ cheap and readily available stoichiometric oxidants (O_2, air or H_2O_2) and only release innocuous H_2O as the sole byproduct[1] [5].

We have recently reported that the inexpensive and readily available complex CuCl·Phen/DBAD (ditert-butyl azodicarboxylate), was a good catalyst for the aerobic oxidation of a wide range of alcohols into carbonyl derivatives (Fig. 1) [6].

Unfortunately, our initial protocol, performed in toluene, required two equivalents of K_2CO_3. Further studies led to the discovery that the amount of potassium carbonate could be reduced by one order of magnitude if the oxidation was effected in fluorobenzene [7]. However, under these slightly basic conditions, partial racemisation of sensitive products, such as Boc-prolinal[2] and competitive catalyst decomposition were noticed.

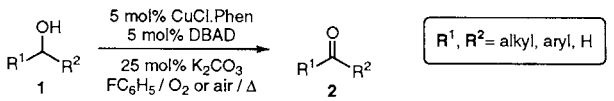

Fig. 1. Copper-catalysed aerobic oxidation of alcohols.

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[1] The harsh conditions typically required to perform aerobic oxidations of alcohols have been a serious impediment for their generalised use in organic synthesis.

[2] Under the previously described conditions, 2% racemisation occured. This small amount of racemisation was missed under the GC conditions employed at the time due to overlap of the overwhelmingly major pic with the minor signal. By slightly modifying the GC conditions and spiking the signal, we can now observe the minor enantiomer which is totally undetectable under this novel, neutral, oxidation protocol.

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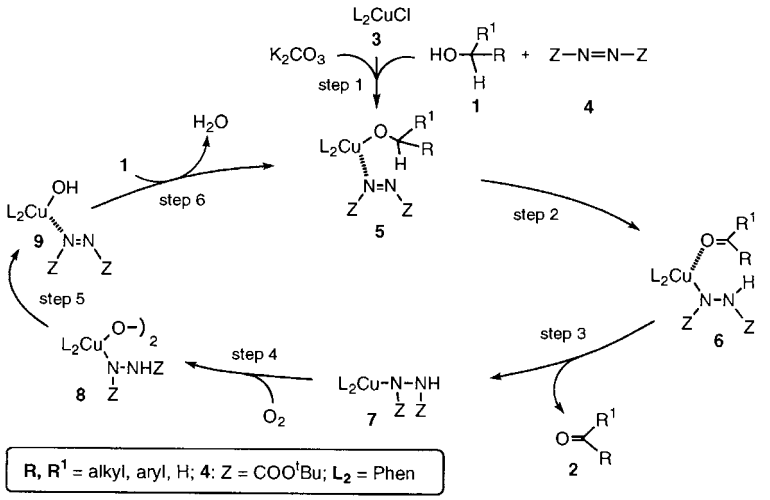


Fig. 2. Proposed mechanism.

2. Results and discussion

In this article, we wish to report a novel 'green' catalytic procedure, which functions under essentially neutral conditions and which is ideally suited for sensitive substrates and products. Furthermore, the absence of solid material in the reaction mixture considerably simplifies the engineering problems associated with the scaling-up of these oxidations.

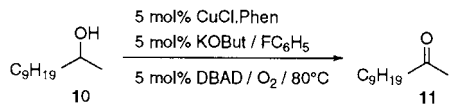
Closer examination of the proposed mechanism of the aerobic, copper-catalysed oxidation revealed that K_2CO_3 was only required for the initial ligand exchange between the alcohol substrate **1** and the chloride substituent of Phen·CuCl (**3**) (Fig. 2, step 1) [8]. After this initial substitution reaction, all the subsequent steps of the catalytic cycle should occur under totally neutral conditions. Therefore, theoretically, only one equivalent (per copper catalyst) of a suitable base should be enough to promote the aerobic oxidation of alcohols.

After screening unsuccessfully a number of different basic additives, we were gratified to find that ^{t}BuOK uniquely satisfied our requirements.

Interestingly, we also noticed that the mode of addition of the various reaction partners played a crucial role in the success of this new procedure (Fig. 3). Thus, it appeared that addition of the base to the pre-formed CuCl·Phen/DBAD complex resulted in strong deactivation of the system, as demonstrated by the poor conversion of 2-undecanol (**10**) into the corresponding ketone (**11**) (Fig. 3, entry 1)[3]. On the other hand, adding ^{t}BuOK to CuCl·Phen, in the presence of 2-undecanol, followed by the addition of DBAD and heating under a gentle stream of oxygen or air led to complete conversion of **10** into **11** (Fig. 3, entry 2). This efficient catalytic procedure was then applied to a range of representative alcohols. Some selected examples are shown in Table 1.

As can be seen from Table 1, secondary aliphatic, allylic and benzylic alcohols are all quantitatively converted into the corresponding carbonyl derivatives. It is interesting to note that no epimerisation of menthone takes place under these conditions (entry 3). Remarkably, both *endo*- and *exo*-borneol are oxidised at the same rate, despite the enormous steric differences between the two alcohol epimers (entry 4). Furthermore, rather hindered decaline derivatives (entry 5) are also smoothly oxidised.

These observations imply that the Cu oxidant is little sensitive to the steric surroundings of the hydroxyl function. The scope of the reaction can be further extended to sensitive cyclopropane and cyclobutane-substituted carbinols (entries 6 and 7) and to protected primary beta-amino alcohols with equal efficiency. Albeit, dibenzyl valinol (entry 8) contains a tertiary nitrogen atom, its oxidation proceeds in excellent yield. Moreover, the involvement of a neutral medium is ideally demonstrated by the complete lack of racemisation of both dibenzyl valinal and Boc-prolinal (entries 8 and 9). Purification of this latter product, which was prepared on a gramme-scale, necessitated only a simple filtration.

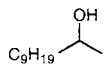
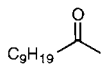
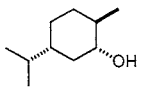
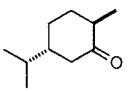
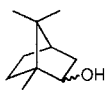
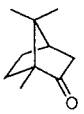
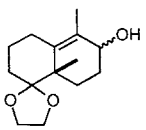
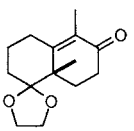
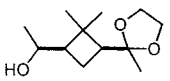
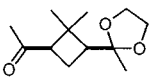
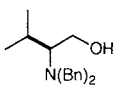
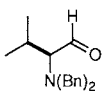
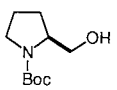
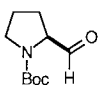


Order of addition	Conversion
CuCl.Phen / DBAD / tBuOK / **10** / Δ	40%
CuCl.Phen / **10** / tBuOK / DBAD / Δ	100%

Fig. 3. Crucial role of the mode of addition.

[3] The deactivation of the catalyst could arise from base-catalysed decomposition of copper-coordinated DBAD.

Table 1
Aerobic oxidation of alcohols [a]

Entry	Substrate	Product	Yield[bc]
1			90%
2			93%
3			92%
4			93%[d]
5			84%[ef]
6			87%
7			78%
8			84%[gh]
9			97%[h]

[a] The reaction conditions are described in Section 3.1.
[b] All yields refer to pure, isolated products. Unless otherwise stated, the products were obtained in an essentially pure form by simple filtration of the crude reaction mixture through a pad of Celigel® (80% Celite® /20% silica gel).
[c] Unless otherwise stated, all the conversions are quantitative.
[d] The oxidation was performed on a 80/20 mixture of borneol and *iso*-borneol. The rate of disappearance of both isomers was monitored throughout the reaction and found to be identical.
[e] The oxidation was affected on a 30/70 mixture of axial and equatorial isomers.
[f] The conversion amounted to 95% in this case.
[g] After silica gel column chromatography.
[h] No racemisation was detected.

3. Experimental

3.1. Typical procedure

3.1.1. Aerobic oxidation of Boc-prolinol

1,10-Phenanthroline (45 mg, 0.25 mmol, 5 mol%) was added to 45 ml of dry FC_6H_5 followed by solid CuCl (25 mg, 0.25 mmol, 5 mol%). After stirring for 5 min at room temperature (r.t.), (L)-Boc-prolinol (1.0 g, 4.97 mmol) was added followed by solid ^{t}BuKO (28 mg, 0.25 mmol, 5 mol%). The resulting yellowish solution was stirred at r.t. for 10 min before DBAD (57.5 mg, 0.25 mmol, 5 mol%) was added. The reaction mixture was refluxed under a gentle stream of O_2 during 4.5 h. After cooling to 20°C, Celigel® (1 g, 80/20 w/w mixture of Celite and silica gel) was added and stirring was continued for 2 min. Filtration, washing off the solid residue with 100 ml of ether and evaporation of the solvents in vacuo afforded pure (L)-Boc-prolinal as a colourless oil (960 mg, 97%). ^{1}H-NMR ($CDCl_3$, 200 MHz). $\delta = 9.55$ (brs, 1H, rotamer 1), 9.45 (brd, $J = 3$ Hz, 1H, rotamer 2), 4.3 (m, 1H, rotamer 1), 4.0 (m, 1H, rotamer 2), 3.6–3.3 (m, 2H), 2.2–1.8 (m, 4H), 1.45 (brs, 9H, rotamer 1), 1.40 (brs, 9H, rotamer 2). ^{13}C-NMR ($CDCl_3$, 75 MHz). $\delta = 199.5$, 199.3, 79.5, 64.4, 46.2, 28.1, 27.6, 24.4, 23.8. The ee was measured by chiral GC (CP-Chiral-Dex CB, 25 m; $F = 0.25$ mm, 130°C for 12 min then 0.8°C min^{-1}) of the derived bis-Boc-prolinol obtained by $LiAlH_4$ reduction of Boc-prolinal followed by derivatisation with Boc_2O (^tR (*R*)-enantiomer, 44.2 min; ^tR (*S*)-enantiomer, 45.1 min).

4. Conclusion

In summary, we have discovered an efficient, catalytic, aerobic procedure for the transformation of alcohols into carbonyl compounds in high yield. The system operates under essentially neutral conditions and is ideally suited for sensitive substrates. Moreover, the purification of most aldehydes and ketones only requires a simple filtration; evaporation of the solvant usually affording pure products. Although much remains to be done in this challenging area, we believe that this novel protocol is a useful and attractive addition to the growing pool of 'green' chemical transformations.

Acknowledgements

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