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4-OH-TEMPO/TCQ/TBN/HCl: A Metal-Free Catalytic System for Aerobic Oxidation of Alcohols under Mild Conditions

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A green and economical catalyst system, 4-OH-TEMPO/TCQ/TBN/HCl, for the aerobic oxidation of a broad range of primary and secondary alcohols to the corresponding carbonyl compounds has been developed. These reactions proceed without transition-metals under mild conditions with excellent yields.

Keywords oxidation of alcohols, transition-metal-free, green and economical

Introduction

The oxidation of alcohols to the corresponding carbonyl compounds is an important class of reactions in chemical synthesis.[1] Recently, interest in developing efficient catalysts for aerobic alcohol oxidation has been burgeoning.[2] During the past several decades, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and its derivatives have been widely used as versatile catalysts for the aerobic oxidation of alcohols to the corresponding carbonyl compounds due to their high efficacy and selectivity.[3] Among them, there is increasing interest in developing transition-metal-free TEMPO-based catalyst systems for aerobic alcohol oxidations. A literature survey showed since Liang and coworkers reported a transition-metal-free, aerobic alcohol oxidation protocol (TEMPO/Br_2/$NaNO_2$) in 2004,[4] more and more efficient metal-free TEMPO-based catalysts for aerobic alcohol oxidation were reported, including TEMPO/TBN/HBr (TBN: *tert*-Butyl nitrite),[5] TEMPO/HCl/$NaNO_2$,[6] TEMPO/KNO_2,[7] TEMPO/NH_2OH,[8] and TEMPO/HCl/PEG-NO_2,[9] AcNHTEMPO/HNO_3/HCl,[10] TEMPO/NaBr-$NaBrO_3$/H_2SO_4,[11] oxidative systems. Especially, Iwabuchi *et al*. reported a highly efficient organocatalytic aerobic oxidation protocol composed of 5-fluoro-2-azaadamantane *N*-oxyl (5-F-AZADO) and $NaNO_2$.[12] It was proved that, 1-methyl-AZADO,[13a,13b] 9-azanoradamantane *N*-oxyl (Nor-AZADO)[13c] and 9-azabicyclo[3.3.1]-nonane *N*-oxyl (ABNO)[13d] can also enhance the efficiency significantly.[13]

This is true especially for laboratory scale operations and fine chemicals manufactures, where the credible, operationally convenient and economical, as well as condition mild oxidation methods are particularly of importance. As such, one key criterion is the use of minimum quantities or total nonuse of auxiliary additives. In 2012, Hu used catalytic amounts of TBN, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), TEMPO, and TFA, as well as O_2 as the terminal oxidant to oxidize alcohols to their corresponding carbonyl compounds.[14] Although it is effective, this TEMPO/TBN/DDQ/TFA catalyst for aerobic alcohol oxidation has two drawbacks, namely: (i) the need for an oxygen partial pressure of 0.2 MPa, which entails the use of an autoclave; (ii) the use of expensive TEMPO (836 RMB/kg) and DDQ (10 000 RMB/kg). We wished to expand this transition-metal-free alcohol oxidation system, and have a clear incentive to develop a cheaper, more efficient protocol that the reaction can proceed under ambient conditions. Specifically, we hope to seek and find cheaper and more efficient alternatives of TEMPO and DDQ, and enable the reaction to proceed at ambient temperature and oxygen partial pressure, thereby dispensing with the need for autoclaves and minimizing the risk of explosions on a preparative scale in industrial organic synthesis.

Results and Discussion

Upon closer investigation of TEMPO/DDQ/TBN/TFA catalyst system for the alcohol oxidation, we found that the requirement of high oxygen partial pressure and elevated reaction temperature is necessary, because TEMPO was not active enough to perform the reaction under ambient oxygen partial pressure. We have recently evaluated a variety of 4-substituted TEMPO derivatives for their ability in the aerobic alcohol oxidation,[3f] and found that 4-OH-TEMPO (51 RMB/kg) was a prominent member in terms of both lower prices and high catalytic activity. Thus we explored the possibility of aerobic alcohol oxidation with 4-OH-TEMPO in place of TEMPO, inexpensive TCQ (tetrachlorobenzo-

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quinone, 810 RMB/kg) in place of DDQ and HCl in place of TFA. Initial investigations of the aerobic oxidation were performed by using benzyl alcohol as the model substrate at room temperature (Table 1). The results showed that the target product was obtained with 76% conversion and 100% selectivity in 4 h when 4-OH-TEMPO, TCQ and HCl were used at room temperature and under 0.1 MPa oxygen partial pressure (Entry 5). The preliminary experimental results strongly suggested that 4-OH-TEMPO, TCQ, and TBN, together with HCl, could synergistically activate molecular oxygen for the oxidation of benzyl alcohols to the aldehydes under 0.1 MPa oxygen partial pressure and at room temperature.

Table 1 Experimental exploration based on the previous[a]

Entry	TEMPO/mol%	DDQ/mol%	HX/mol%	Time/h	Conv.[b]/%
1[c]	4	4	1 (TFA)	12	99
2	4	4	1 (TFA)	4	59
3	2	2	5 (TFA)	4	50
4	2 (4-OH-TEMPO)	2 (TCQ)	5 (TFA)	4	21
5	2 (4-OH-TEMPO)	2 (TCQ)	1 (HCl)	4	76

[a] The aerobic oxidation was carried out with benzyl alcohol (10 mmol), TBN (5 mmol %), O_2 balloon, room temperature. [b] Determined by GC, and all selectivities were 100%. [c] 0.2 MPa of O_2 was used. Referred to *ChemCatChem* **2012**, *4*, 76–80.

Having verified the feasibility of the idea, we turned our attention to the optimization of reaction conditions. The reaction only provided very low conversion in the absence of each one of the 4-OH-TEMPO, TCQ, TBN, and HCl additives (Table 2, Entries 1—4 vs. Entry 5). To our surprise, although 4-OH-TEMPO was decreased to 1 mol%, the reaction could also obtain quantitative yield of benzaldehyde at room temperature for 4 h (Entry 6). Interestingly, when the use of 4-OH-TEMPO was decreased to 0.5 mol%, we still observed both 100% selectivity and conversion by prolonging the reaction time to 8 h (Table 2, Entry 7). A further decrease of 4-OH-TEMPO loading to 0.1 mol% did not reach a satisfying oxidation result even for 12 h reaction (Entry 8). When O_2 balloon was replaced by air, only 42% conversation was achieved (Entry 16). In light of the results shown in Table 2, we found that the catalyst system 4-OH-TEMPO/TCQ/TBN/HCl could be applied to the conversion of benzyl alcohol to the aldehyde with O_2 balloon and ambient temperature.

In addition, we examined the catalytic ability of typical TEMPOs, quinonoids and organic chlorinated cyclic compounds (Table 3, Entries 1—10). Different acids and NO donor $NaNO_2$ were also screened (Table 3, Entries 11 — 14). Although some catalytic system showed high catalytic activity, such as Entries 3, 6, 9, 11, we selected 1 mol% 4-OH-TEMPO, 2 mol% TCQ, 5 mol% TBN and 1 mol% HCl, O_2 balloon at room temperature as the optimal reaction conditions in the viewpoint of green and economic chemistry.

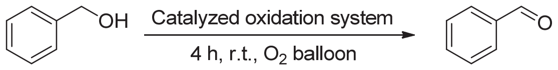
Having established the optimal conditions for the transition-metal-free and solvent-free catalysis, we next examined the range of alcohols for this catalytic aerobic oxidation system. As showed in Table 4, all benzylic alcohols, including 2-thienyl methanol and 3-pyridine methanol, were converted into the corresponding benzaldehydes in high isolated yields (Entries 1—7). Similarly, activated secondary aryl alcohols, such as 1-phe-

Table 2 Oxygen activation in catalytic oxidation of benzyl alcohol at room temperature[a]

Entry	4-OH-TEMPO/mol%	TCQ/mol%	TBN/mol%	HCl/mol%	*t*/h	Conv.[b]/%
1	2	2	—	1	4	1
2	—	2	5	1	4	5
3	2	—	5	1	4	31
4	2	2	5	—	4	14
5	2	2	5	1	4	76
6	1	2	5	1	4	100
7	0.5	2	5	1	8	100
8	0.1	2	5	1	4	47
9	0.5	2	5	0.5	4	39
10	0.5	1	5	0.5	4	32
11	0.5	0.5	5	0.5	4	37
12	0.5	0.5	2.5	0.5	4	18
13	0.5	0.5	1	0.5	4	13
14	1	2	5	0.5	4	42
15	1	2	5	0.1	4	28
16[c]	1	2	5	1	4	42

[a] Reaction conditions: benzyl alcohol (10 mmol), 4-OH-TEMPO, TCQ, TBN, HCl, r.t., O_2 balloon for 4 h. [b] Determined by GC, and all selectivities were 100%. [c] In the presence of air.

Table 3 Further optimization of the oxidation conditions[a]



Entry	X_1-TEMPO/mol%; X_1=4-OH	Q/mol%; Q=TCQ	TBN/mol%	H-X_2/mol%; X_2=Cl	Conv.[b]/%
1	1 (TEMPO)	2	5	1	20
2	1 (MeO-TEMPO)	2	5	1	78
3	1	2 (DDQ)	5	1	100
4	1	2 (BQ)	5	1	68
5[c]	1	2 (BQ)	5	2 (TCCA)	76
6[c]	1	2 (BQ)	5	2 (TCCA)	99
7[c]	1	2 (BQ)	5	2 (NCS)	86
8	1	2 (TCCA)	5	1	38
9	1	2 (TCCA)	5	1	93
10	1	2 (NCS)	5		83
11	1	2	5	1 (HBr)	99
12	1	2	5	0.5 mL (CH_3COOH)	20
13	1	2	5	5 (HBF_4)	20
14	1	2	5($NaNO_2$)	10	35

[a] The reaction was carried out with benzyl alcohol (10 mmol) under solvent-free reaction conditions. [b] Determined by GC, and all selectivities were 100%. [c] TCCA: trichloroisocyanuric acid; TCTA: 4,4',4''-tris(carbazol-9-yl)-triphenylamine; NCS: N-chlorosuccinimide. The three reactions proceed with TCCA, TCTA and NCS in place of acids.

nylethanol, 1-phenyl-1-propanol, could be smoothly oxidized to the corresponding acetophenone, propiophenone respectively by Method A, in nearly quantitative isolated yields (Entries 8, 9). We were pleased to find that primary and secondary aliphatic alcohols, which remain difficult recalcitrant substrates in many aerobic oxidation protocols, were oxidized to the expected aldehydes with high conversions and selectivities. 2-Octanol, 2-ethyl hexanol and cyclohexanol could be smoothly converted to the corresponding carbonyl compounds in high isolated yields under the standard mild conditions (Entries 10—12). Allylic alcohol such as cinnamyl alcohol was smoothly oxidized with high selectivity (Entry 13). In Entry 14, the oxidation reaction was applied to pairs of substrates, both of which bore groups susceptible to oxidation, namely hydroxyl and sulfide groups. To our delight, the oxidation system highly selectively oxidized the hydroxyl group to carbonyl groups, whereas the sulfide groups remained intact.

Despite the efficiency of the oxidation reaction, the substrate scope is limited to liquid alcohols. The solid alcohols are proven to be inefficient substrates for the solvent-free catalytic system.

Conclusions

In conclusion, we have shown that the transition-metal-free and solvent-free catalyst system 4-OH-TEMPO/TCQ/TBN/HCl permits the selective aerobic oxidation of a broad range of primary and secondary alcohols, which may contain N or S heteroatoms or carbon-carbon double bonds at normal temperatures and pressures. This inexpensive and convenient catalytic system could be broadly used in laboratory and in fine chemicals manufacture.

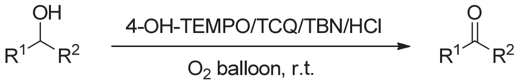
Experimental

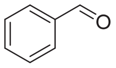
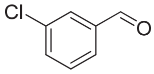
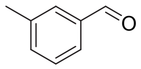
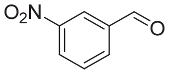
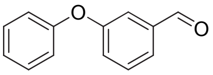
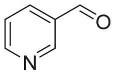
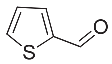
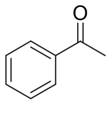
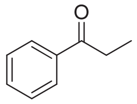
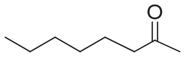
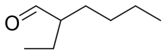
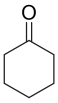
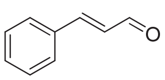
General procedure for the 4-OH-TEMPO/TCQ/TBN/ HCl-catalyzed aerobic oxidation of alcohols

The oxidation of alcohols was carried out in a 50 mL long-necked, round-bottomed flask equipped with a magnetic stirrer. Typically, the alcohol (10.0 mmol), 4-OH-TEMPO (0.10 mmol) and TCQ (0.20 mmol) were located. The flask was evacuated and backfilled with O_2. Concentrated hydrochloric acid (0.10 mmol) was added, followed by TBN (0.50 mmol).

The resulting mixture was stirred at room temperature and atmospheric pressure. The conversion and selectivity of the product were detected by GC. When GC showed the reaction was completed, adequate amounts of hydrochloric acid and saturated $Na_2S_2O_3$ solution were added to the reaction mixture for converting the 4-OH-TEMPO to reduced, easy water-soluble compound. The reaction mixture was extracted three times with ethyl acetate. The organic layer was combined and dried with anhydrous Na_2SO_4, and then concentrated on a rotary evaporator to provide the products. In the case of incomplete substrate conversion (Table 4, Entries 10—13), the desired product was isolated after column chromatography on silica gel.

Table 4 Catalytic aerobic oxidation for various alcohols[a]



Entry	Product	Method	t/h	Conv./%	Select./%	Yield/%
1		A	5	100	100	97
2		A	8	100	100	95
3		A	7	100	100	99
4		A	16	100	100	96
5		A	6	100	100	98
6[b]		A	24	100	100	97
7		A	5	100	100	97
8		A	12	100	100	96
9		A	12	100	100	97
10[c]		B	24	97	93	86
11[c]		C	30	91	90	84
12[c]		D	5	91	94	80
13[c]		D	6	87	100	85
14[d]	PhCHO+ PhSMe	A	8	100	100	—

[a] The aerobic oxidation conditions were as follows: alcohols (10.0 mmol), O_2 balloon, room temperature. Method A: 4-OH-TEMPO (0.1 mmol), TCQ (0.2 mmol), TBN (0.5 mmol), HCl (0.1 mmol); Method B: 4-OH-TEMPO (0.4 mmol), TCQ (0.2 mmol), TBN (0.5 mmol), HCl (0.05 mmol); Method C: 4-OH-TEMPO (0.8 mmol), TCQ (0.2 mmol), TBN (1 mmol), HCl (0.025 mmol); Method D: 4-OH-TEMPO (0.8 mmol), TCQ (0.4 mmol), TBN (1 mmol), HCl (0.05 mmol); conversions and selectivities are based on gas chromatography (GC) analyses with area normalization. [b] In the presence of 1.2 equivalents of HOAc. [c] Isolated yield after column chromatography. [d] PhSMe remains intact after the reaction.

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