

Cu^I/TPA/4-乙酰胺基-TEMPO 催化的苄醇与 烯丙基醇氧化反应的研究

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摘要: CuI/TPA(tris(pyridin-2-ylmethyl)amine)/4-乙酰胺基-TEMPO(2, 2, 6, 6-Tetramethylpiperidyl-1-oxyl)催化体系能够在室温下, 以氧气作氧化剂, 乙腈作溶剂, 高效、高选择性地催化一系列苄醇, 烯丙基醇和含杂原子伯醇的氧化, 且在体系中无需添加任何碱作助催化剂.

关键词: 苄醇; 氧化; 碘化亚铜; TPA; TEMPO 衍生物

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醇被选择性地氧化成醛在有机化学中是很经典的一类反应, 在药物合成和精细化工中占有很重要的地位^[1-2]. 传统的醇氧化往往使用铬(VI)氧化物, 锰氧化物及高价碘等无机氧化剂, 但这些方法具有用量大, 毒性强等缺点. 因此, 选择高效, 环保的醇氧化方法, 尤其是以空气或氧气作为氧化剂显得尤为迫切. 近年来, 基于 TEMPO 催化体系的氧化反应受到广泛关注^[3-4]. TEMPO 是一类可以稳定存在的氮氧自由基, 因其催化的醇氧化反应, 条件温和, 选择性高而在工业生产中得到广泛的应用. 在均相催化体系, 分子氧作为氧化剂的 TEMPO 催化醇氧化, 助催化剂基本集中在过渡金属催化剂上, 如钨^[5], 铂^[6], 钨^[7], 钒^[8], 铜^[9-10]等. 铜由于储量丰富、价廉使得铜化合物在氧化反应中得到广泛的研究. 早在 1984 年, Semmelhack 研究小组^[11]就首次报道了以 DMF 为溶剂, CuCl/TEMPO 体系在室温下即可有效地催化分子氧对苄醇和烯丙基醇的氧化. 之后, 有关醇氧化的研究主要集中在铜与含氮配体形成的配合物上, 尤其含两个及多个吡啶基的多齿配体研究更多, 如 2, 2'-联吡啶, 2, 6', 2''-三联吡啶, 1, 10-邻二氮菲等. Stahl 课题组^[12, 25-28]利用 Cu(OTf)-联吡啶/氮甲基咪唑/TEMPO 催化体系在空气或氧气存在的情况下, 在催化氧化苄醇, 烯丙基醇, 脂肪族伯醇及含杂原子的伯

醇方面表现出很高的反应活性和选择性. 该体系的不足之处在于所用铜盐 Cu(OTf)的成本较高, 且需要氮甲基咪唑作为弱碱的参与, 才能使反应顺利进行. 含 3 个吡啶单元的三脚架结构的配体自 1967 年被 Anderegg 和 Wenk^[13]首次报道之后, 现已成为配位化学中的经典配体. TPA 与过渡金属 Mn, Ni, Fe, Cu, Zn 形成的配合物被广泛应用于催化各类反应, 如邻苯二酚的氧化^[14], 烷烃氧化^[18], 烯炔环氧化^[15], 烯炔环胺化^[16], 自由基加成反应^[17]等. 但是, 分子氧参与的铜与 TPA 形成的配合物用于催化醇的氧化反应却没有报道. 基于我们课题组非血红素类四氮配体的铁锰配合物在催化烯炔、烷烃和醇氧化^[19-22]中取得的研究成果, 我们构建了 CuI/TPA/TEMPO 催化体系, 以氧气为氧化剂, 不添加任何碱, 在室温下考察苄醇和烯丙醇的氧化(Scheme 1).

1 实验部分

1.1 试剂与仪器

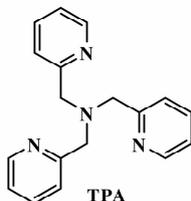
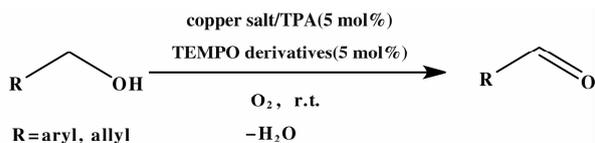
TEMPO 及其衍生物, 醇和溶剂都购买于 Alfa Aesar 和 Aldrich Chemical Co 和国内试剂公司, 且使用前无需处理. 柱层析硅胶: 粒径 0.071 ~ 0.050 mm, 购自烟台江友硅胶公司; 薄板层析硅胶: GF24 plates, 购自烟台江友硅胶公司; 气相色谱仪: Agi-

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图式1 铜盐/TPA/TEMPO 衍生物催化的醇氧化
Scheme 1 Oxidation of alcohols catalyzed by copper salt/TPA/TEMPO derivatives

lent 6820 和 Agilent 7890; 气相色谱仪-质谱联用仪: Agilent 公司 6890N/5973N GC-MS; 核磁共振仪: Bruker Avance III.

1.2 反应条件

1.2.1 配体的合成 TPA 参考文献[23]的方法合成.

1.2.2 氧化反应 在氩气保护下, 向 10 mL 反应管中加入 0.025 mmol 铜盐和 0.025 mmol TPA 配体, 1 mL CH₃CN, 反应 0.5 h. 然后依次加入 0.025 mmol TEMPO, 0.5 mmol 醇, 充入 1.01 × 10⁵ Pa 氧气, 在室温下反应. 通过薄板层析硅胶观察反应

进度, 反应结束后, 以硝基苯或正壬烷为内标, GC 测得反应的转化率和产率, 或者柱分离得到分离收率. 选择性 = 产率/转化率.

2 结果与讨论

以苄醇的氧化为例, 对反应条件进行考察 (Table 1). 首先, 以乙腈为溶剂, 对反应体系的铜盐进行考察 (entries 1-5), 如 CuBr, CuCl, CuI, CuBr₂, CuF₂. 当催化剂量和 TEMPO 量都为 5% 时, 反应 1 h 后, CuI 参与的苄醇氧化反应, 转化率和选择性分别达到 77% 和 97%, 而 CuBr 和 CuCl 参与的氧化反应, 转化率仅 50% ~ 60% 多, 且在该体系中, 2 价铜不能催化苄醇的氧化 (entries 4-5). 此外, 我们还对溶剂进行了考察 (entries 2, 4-7). 在除乙腈之外的体系中, 醇氧化反应都比较差, 转化率仅为 30% 多. 但是, 在质子性溶剂中的活性略大于非质子性溶剂, 如在乙醇和水中反应, 转化率略高于在 CH₂Cl₂ 和 THF 中进行的反应. 显然, 在乙腈中发生的苄醇的氧化, 转化率和选择性最高, 即乙腈为优势溶剂 (entry 2). 除对铜盐和溶剂筛选之外, 我们还对 TEMPO 及其衍生物也进行了考察 (Table 2). 当催化剂用量仍为 5mol% 时, 反应进行 1 h 后, 所有 TEMPO 的衍生物都表现出优于 TEMPO 本身的催化活性 (entries 1-7). 而且 TEMPO 的各种衍生物对苄醇氧化反应表现出相似的催化活

表 1 空气作氧化剂, TEMPO/铜盐/TPA 体系催化的苄醇氧化

Table 1 Oxidation of benzyl alcohol catalyzed by TEMPO/copper salt/TPA using air as the oxidant^a

Entry	Cu salts	Solvent	Selectivity/% ^b	Conv. /% ^b
1	CuBr	CH ₃ CN	97	58
2	CuI	CH ₃ CN	97	77
3	CuCl	CH ₃ CN	91	65
4	CuBr ₂	CH ₃ CN	N. D.	N. D.
5	CuF ₂	CH ₃ CN	trace	trace
4	CuI	CH ₂ Cl ₂	81	31
5	CuI	THF	91	32
6	CuI	H ₂ O	82	33
7	CuI	CH ₃ CH ₂ OH	85	39

a. Reaction conditions; CuX (5 mol%) and TPA (5 mol%) in 1 mL solvent were stirred for 30 min at room temperature in argon atmosphere, then benzyl alcohol (0.5 mmol) and TEMPO (5 mol%) were added and stirred for another 1 h in the air;

b. Conversions and yields are determined by GC using nitrobenzene as the internal standard, and selectivity = yield/conversion.

表2 不同 TEMPO 衍生物催化的苄醇氧化

Table 2 Oxidation of benzyl alcohol catalyzed by different TEMPO derivatives^a

Entry	R-TEMPO	Selectivity/% ^b	Conv. /% ^b
1		97	77
2		97	79
3		95	84
4		93	88
5		96	82
6		96	89
7		93	87

a. Reaction conditions: CuI (5 mol%) and TPA (5 mol%) in 1 mL CH₃CN were stirred for 30 min at room temperature in argon atmosphere, then benzyl alcohol (0.5 mmol) and TEMPO derivatives (5 mol%) were added and stirred for another 1 h in the air;

b. Conversions and yields are determined by GC using nitrobenzene as the internal standard, and selectivity = yield/conversion.

性, 转化率和选择性可达 80% 和 93% 以上, 其中 4-乙酰氨基-TEMPO 表现出最好的催化性能, 转化率和选择性分别可高达 89% 和 96% (entry 6). 之后, 通过电化学表征, 我们测得 TEMPO 本身的电极电势为 0.25 V, 而 TEMPO 衍生物的电极电势值为 0.35 ~ 0.40 V, 由此可见, 接有一定的取代基有利于增加 TEMPO 的氧化性 (Fig. 1). 此外, 由于测得的接有各类取代基的 TEMPO 衍生物电极电势都较为接近, 因此在催化醇氧化反应时表现出相似的活性, 该表征结果与上述的实验结果相吻合.

通过考察反应条件, 我们得到最优的催化条件是: 乙腈作溶剂, CuI/TPA/4-乙酰胺基-TEMPO 作

催化剂.

为了证明该体系在催化醇氧化方面的可行性, 我们对底物进行了拓展 (Table 3). 当苄醇的苯环上接有取代基时, 其反应活性相比苄醇有所降低. 我们推测可能的原因是 Cu-TPA 所形成的配合物是三角双锥结构 (Fig. 2)^[24], 当苯环上接有取代基时, 由于位阻效应, 苄醇很难接近配合物的中心离子, 导致反应的活性降低. 当充入 1.01×10^5 Pa 氧气, 该体系的催化活性明显增强, 且在催化苄醇和烯丙基醇时, 受电子效应的影响不太明显, 当苯环上接有甲氧基、甲基等弱给电子基或者弱吸电子基, 如氯、溴等, 催化剂对这些苄醇的氧化活性没有明显

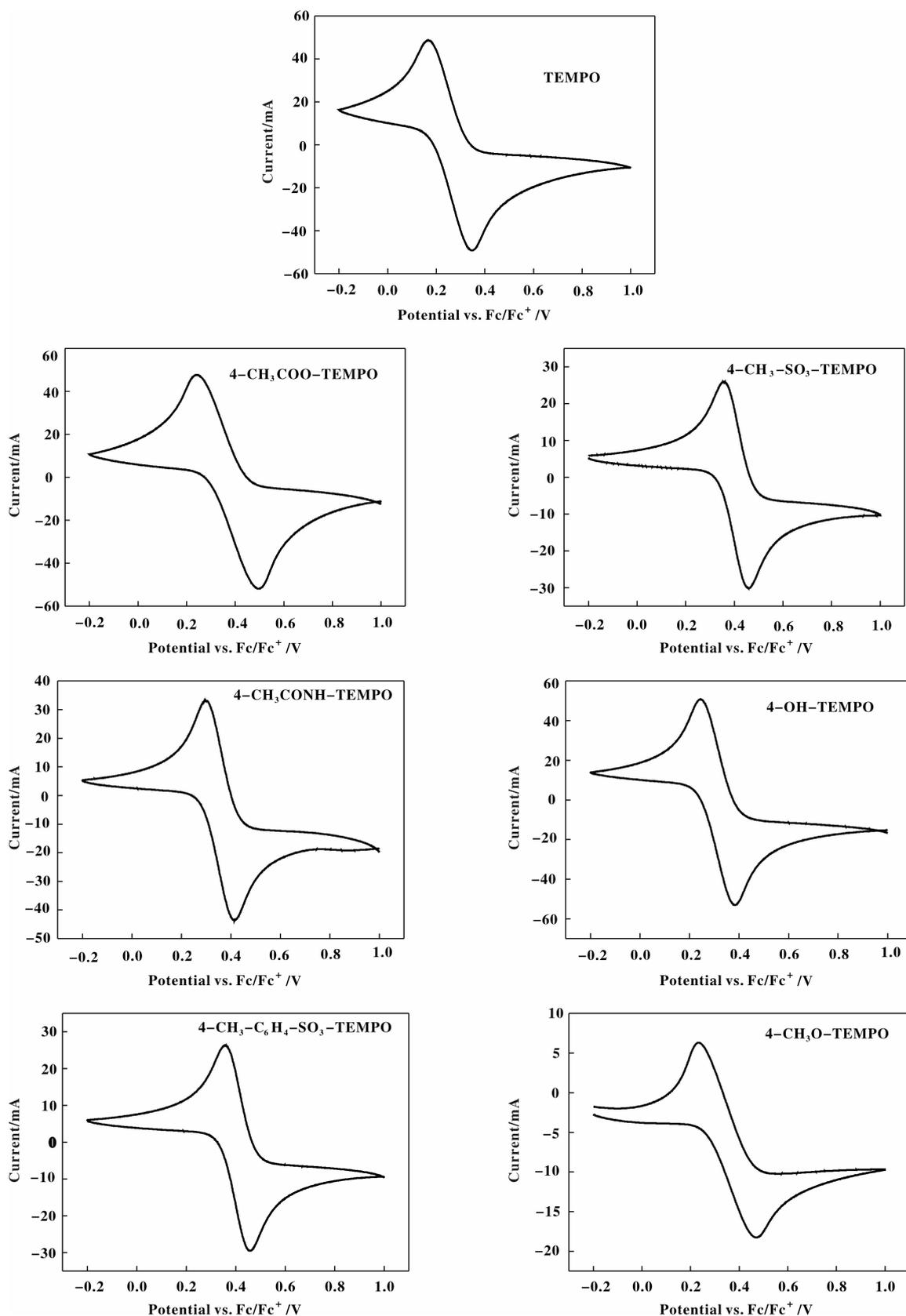


图 1 TEMPO 及其衍生物的循环伏安图. 条件: 0.6 mmol TEMPO 衍生物, 300 mg LiClO₄, 扫描速率: 100 mV/s

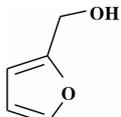
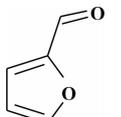
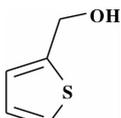
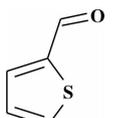
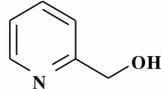
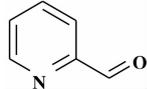
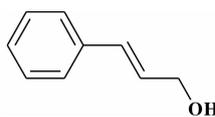
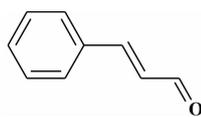
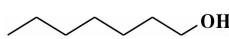
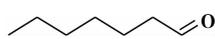
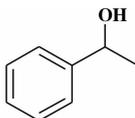
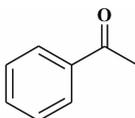
Fig. 1 Cyclic voltammogram of TEMPO and derivatives in acetonitrile under Ar
Conditions: 0.6 mmol TEMPO derivatives, 300 mg LiClO₄, 100 mV/s scan rate.

表3 不同类醇的催化氧化

Table 3 Catalytic Aerobic Oxidation of Various Alcohols ^a

Entry	Substrate	Product	t/h	Yield/% ^b
1			3.5	89
2			3.5	94
3			3.5	92
4			3	87
5			3.5	86
6			3.5	84
7			3.5	88
8			3.5	90
9			3.5	87
10			12	51
11			12	45

续表 3

Entry	Substrate	Product	t/h	Yield/% ^b
12 ^c			10	73
13			10	76
14			24	8
15			10	71
16 ^c			24	40
17			24	trace

a. Reaction conditions: CuI (5 mol%) and TPA (5 mol%) in 1 mL CH₃CN were stirred for 30 min at room temperature in argon atmosphere, then substrates (0.5 mmol) and 4-CH₃-CO-NH-TEMPO (5 mol%) were added and stirred for certain time in the O₂ at room temperature; b. Isolated yield; c. Determined by GC using nonane as the internal standard.

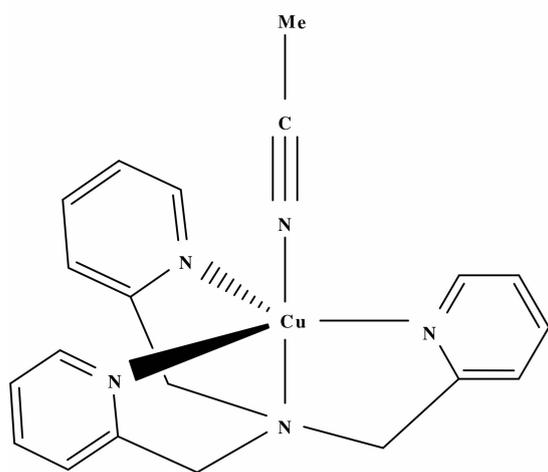


图2 铜-TPA 配合物的三角双锥结构

Fig. 2. The trigonal bipyramidal of Cu-TPA complex

的差别,都表现出很好的催化活性,分离收率和选择性高达85%和95%以上(entries 1-9). 苯环上取代基的位置对苄醇的氧化也几乎没有影响,如2-甲氧基,3-甲氧基,4-甲氧基苄醇的氧化(entries 1-3)和2-溴,3-溴,4-溴苄醇的氧化(entries 7-9)都得到相近的分离收率. 但是,当苯环上接有强吸电子基和羟基的邻位接有位阻较大的取代基时,如4-CF₃-苄醇和2-碘-苄醇,其反应活性明显降低了很多,经反应12 h,所得分离收率分别为51%和45%. 此外,该催化体系还对含有杂原子伯醇的氧化,如噻吩甲醇,糠醇也表现出中等的催化活性和很好的选择性,收率可达到70%以上,而对于吡啶甲醇的催化氧化作用很弱,可能的原因是吡啶氮原子与铜配位,导致了催化剂的失活. CuI/TPA/4-乙酰胺基-

TEMPO 催化体系并不适合催化脂肪族伯醇氧化, 如正庚醇的氧化, 转化率和选择性都较差 (entry 16). 此外, 由于 α -苜醇本身的位阻较大, 该催化体系也并没有表现出很好的催化活性 (entry 17).

3 结论

我们实现了一个高效、高选择性地催化醇氧化反应的 Cu/TPA/TEMPO 体系. 研究发现, 利用乙腈作溶剂, CuI/TPA/4-乙酰胺基-TEMPO 催化体系对苜醇、烯丙基醇, 以及含有杂原子的伯醇具有最优的催化效果. 该催化体系具有环境友好、无其他添加剂参与、底物适应性强、选择性好、产率高等优点.

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The Oxidation of Benzyl, Allyl Primary Alcohols with Cu^I/TPA/TEMPO

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Abstract: The complex generated in situ between CuI and TPA (tris(pyridin-2-ylmethyl) amine) combined with TEMPO can be successfully applied to the aerobic oxidation of benzyl and allyl alcohols in acetonitrile, with more than 90% conversion and yield. Furthermore, the oxidation can be performed at room temperature and any base as additive is needless.

Key words: benzyl alcohol; oxidation; CuI; TPA; TEMPO derivatives