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Passerini Three-Component Reaction of Alcohols under Catalytic Aerobic Oxidative Conditions

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ABSTRACT

Alcohols instead of aldehydes were used in the Passerini three-component reaction under catalytic aerobic conditions. Mixing alcohols, isocyanides, and carboxylic acids in toluene in the presence of a catalytic amount of cupric chloride, $NaNO_2$, and TEMPO afforded, under an oxygen atmosphere, the P-3CR adducts in good yields.

Tandem oxidative processes (TOP) in which oxidation of alcohols are combined with the subsequent elaboration of the carbonyl intermediates have been developed into powerful synthetic tools.[1,2] Although great progress has been made in developing bimolecular TOP processes, studies on combining alcohol oxidation with a multicomponent reaction (MCR)[3] remain scarce. The difficulties associated with the development of such one-pot oxidation/MCR processes are self-evident due to the presence of mutli-functionalities/multi-intermediates and the complexity of the reaction mechanism intrinsic to MCRs. This is unfortunate since aldehydes are ubiquitous substrates in many powerful MCRs. Therefore, the ability to perform domino oxidation/MCR would widen significantly the versatility and scope of these aldehyde-based MCRs. In this context, we recently reported a Passerini three-component reaction (P-3CR)[4] of primary alcohols using *O*-iodoxybenzoic acid (IBX) as an oxidant.[5,6] In addition to its wide application scope, this protocol proved to be particularly valuable when the desired aldehydes were inaccessible as demonstrated in Wessjohann's elegant synthesis of macrocycles.[7] Although both IBX and its reduced form (IBA) are easily removable by simple filtration, the need to use an excess amount of IBX was nevertheless a drawback of this methodology. As a continuation of this

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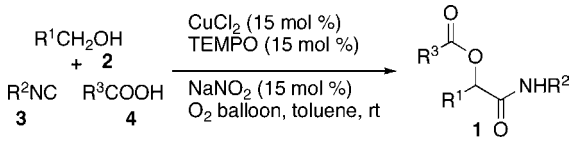
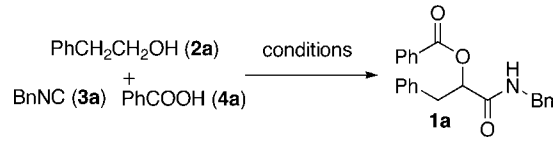
research program, we report here the realization of Passerini three-component reaction starting from alcohols under catalytic conditions using oxygen as terminal oxidant (Scheme 1).

Scheme 1. Passerini Reaction of Alcohols under Catalytic Oxidative Conditions



The catalytic aerobic oxidation of alcohols using molecular O_2 as a terminal oxidant has attracted much attention in recent years.[8] Many efficient catalytic systems have been developed using transition metals alone or in combination with TEMPO as catalysts.[7,9] While a wide range of benzylic alcohols have been successfully oxidized to aldehydes and ketones, primary nonactivated alcohols were known to be poor substrates due to their low reactivities and side reactions such as overoxidation, aldol, or Tishchenko reaction associated with the resulting aldehydes.[8,10−12] In spite of this discouraging observation, we set out to examine the reaction of 2-phenylethanol (**2a**), benzyl isocyanide (**3a**), and benzoic acid (**4a**) under catalytic aerobic oxidation conditions, assuming

Table 1. Optimization of Reaction Parameters[a]



entry	conditions	conversion of (**2a**, %)	yield of **1a**,[b] %
1	A/toluene (0.25 M), O_2, 80 °C	NR	0
2	B/C_6H_5F (0.5 M), O_2, 80 °C	NR	0
3	C/C_6H_5F (0.5 M), O_2, 80 °C	NR	0
4	D/DCM (1 M), O_2, rt	NR	0
5	E/toluene (0.5 M), O_2, rt	100	30
6	F/toluene (0.5 M), O_2, rt	100	35
7	F/toluene (2.5 M), O_2, rt	100	67[c]
8	F/toluene (0.1 M), O_2, rt	75	ND
9	F/toluene (2.5 M), air, rt	50	ND[c]
10	F/toluene (0.5 M), O_2, rt	15	ND[d]

[a] General conditions: **2a**/**3a**/**4a** =1:1:1, 24 h under conditions specified as follows. Method A: TPAP (15 mol %), 4 Å molecular sieves. Method B: CuCl (10 mol %), 1,10-phenantroline (10 mol %), DBAD (10 mol %), *t*BuOK (10 mol %), NMI (15 mol %). Method C: CuBr·DMS (5 mol %), 4,4′-dinonyl-2,2′-bipyridine (5 mol %), TEMPO (10 mol %). Method D: $PyHBr_3$ (20 mol %), TEMPO (5 mol %), $NaNO_2$ (20 mol %). Method E: $FeCl_3{\cdot}5H_2O$ (15 mol %), TEMPO (15 mol %), $NaNO_2$ (15 mol %). Method F: $CuCl_2{\cdot}2H_2O$ (15 mol %), TEMPO (15 mol %), $NaNO_2$ (15 mol %). [b] Yield of isolated product. [c] 2.5 equiv of isonitrile. [d] In the absence of $NaNO_2$. Abbreviations: TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl; TPAP, tetra-*n*-propylammonium perruthenate; DBAB = dibenzyl azodicarboxylate, NMI = *N*-methylimidazole; NR = no reaction; ND = not determined.

that in situ trapping of the aldehyde intermediate by isocyanide could potentially avoid these aforementioned undesired pathways. Initial experiments using ruthenium[13] and copper[14] as metal catalysts (entries 1−3, Table 1) and under metal-free conditions[15] (entry 4) were found to be ineffective, leading only to the complete decomposition of isocyanide **3a**. Gratefully, the Passerini adduct **1a** was isolated in 30% yield using $FeCl_3$−TEMPO−$NaNO_2$ (0.15 equiv each) catalytic system developed by Liang and Hu (entry 5, Table 1).[16] Replacing $FeCl_3$ by $CuCl_2$ gave a cleaner reaction, although the yield remained moderate (enrty 6). By using 2.5 equiv of isocyanide **3a**, the yield of **1a** increased to 65% (c = 2.5 M) under otherwise identical conditions (entry 7, Table 1). On the other hand, replacing oxygen gas by air atmosphere (entry 9, Table 1) diminished significantly the reaction efficiency. Another key factor is the concentration. The reaction had to be performed at high concentration to guarantee the success of the overall domino process

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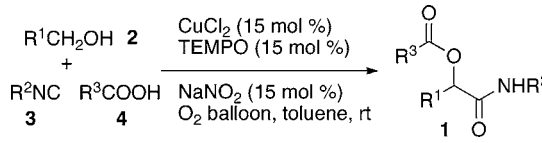
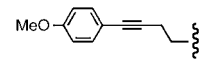
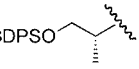
(entries 7 vs 8, Table 1). Other copper sources [$Cu(SO_4)_2$, $CuBr_2$, $Cu(NO_3)_2$, CuF_2, CuI, CuBr], solvents (MeCN, dichloroethane, and trifluorobenzene), and co-oxidants (KNO_2, Bu_4NNO_2, $AgNO_2$, ^{t}BuONO) were also examined (data not shown). However, none of them afforded results superior to those using the conditions shown in entry 7 (Table 1). Control experiments indicated that the use of a ternary system ($CuCl_2$−TEMPO−$NaNO_2$, as well as their ratio (1/1/1, 0.15 equiv each)) was important for the production of **3a**. In the absence of one of them, the domino process became less efficient. For example, in the absence of $NaNO_2$ only a conversion equal to the catalysts loading was observed (entry 10, Table 1). Its role seems to be important in the turnover of the catalytic oxidation. It is worth noting that the Passerini product resulting from over oxidation of alcohol to the corresponding carboxylic acid and its subsequent reaction with aldehyde and isocyanide was formed only in a trace amount (<5%).[17]

Using optimized conditions [$CuCl_2$ (0.15 equiv), TEMPO (0.15 equiv), $NaNO_2$ (0.15 equiv), O_2, **2**/**3**/**4** = 1/2.5/1, in toluene (*C* 2.5 M), room temperature], the scope of the oxidative Passerini reaction was examined with representative primary alcohols, isonitriles, and carboxylic acids (Table 2). Functional groups such as ester (entry 12), benzyl ether (entry 13), silyl ether (entry 17), acetal (entry 16), and double bond (entry 14) were tolerated. The alcohol **2j** afforded the low yield of the P-3CR adduct presumably due to the coordination of alkyne unit to the copper species, consequently blocking the catalytic cycle. Cyclopropylmethanol (**2d**) also participated in the reaction to afford the corresponding adduct in moderate yield (entry 7, Table 2). Finally, β-substituted enantioenriched alcohols such as (*R*)-1,2-*O*-isopropylideneglycerol (**2k**, entry 16) and (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol (**2l**, entry 17, Table 2), whose corresponding aldehydes are known to be sensitive toward racemization,[18] were successfully engaged in this oxidative P-3CR reaction. In both cases, the Passerini adducts were obtained as a mixture (1:1) of two diastereomers in 75% and 60% yields, respectively. The lack of diastereoselectivity in P-3CR is not unexpected.[3,19] To our delight, the chiral HPLC analysis of **1q** and **1r** indicated that no racemization of the transient aldehydes occurred under these conditions. In the case of **2l**, α-hydroxyamide derived from a nucleophilic addition of water to nitrilium intermediate[20] was isolated in about 10% yield together with **1r**. Aromatic and aliphatic isocyanides with different steric properties such as benzyl isocyanide (**3a**), cyclohexyl isocyanide (**3b**), 2,6-dimethylphenyl isocyanide (**3c**), and *tert*-butyl isocyanide (**3d**) participated in the reaction. The domino oxidation/P-3CR process has also been applied to representative carboxylic acids including (*R*)-*O*-methyl mandelic acid (**4c**), cyclopropyl carboxylic acid (**4d**), and α,β-unsaturated carboxylic acid (**4g**), etc. However, *N*-protected amino acids failed to participate in this reaction (data not shown).

Table 2. Scope and Limitation of the Reaction Conditions[a]



entry	R^1	R^2	R^3	product/ yield (%)[b]
1	Bn (**2a**)	Bn (**3a**)	Bn (**4b**)	**1b** / 75
2	Bn (**2a**)	Cy (**3b**)	Ph (**4a**)	**1c** / 43
3[c,d]	$BnCH_2$ (**2b**)	 (**3c**)	(**4c**)	**1d** / 40
4[c,d]	 (**2c**)	 (**3c**)	Ph (**4a**)	**1e** / 76
5[c,d]	 (**2c**)	Bn (**3a**)	Ph (**4a**)	**1f** / 81
6[c,d]	 (**2c**)	 (**3c**)	 (**4d**)	**1g** / 65
7	 (**2d**)	 (**3c**)	*i*-Pr (**4e**)	**1h** / 40
8	*o*-BrC_6H_4 (**2e**)	Bn (**3a**)	Me (**4f**)	**1i** / 80
9	*o*-BrC_6H_4 (**2e**)	*t*-Bu (**3d**)	Me (**4f**)	**1j** / 65
10	*o*-BrC_6H_4 (**2e**)	*t*-Bu (**3d**)	 (**4g**)	**1k** / 61
11	*p*-$CF_3C_6H_4$ (**2f**)	*t*-Bu (**3d**)	Me (**4f**)	**1l** / 60
12	$EtO_2C(CH_2)_4$ (**2g**)	Bn (**3a**)	*i*-Bu (**4h**)	**1m** / 60
13	$BnO(CH_2)_3$ (**2h**)	Bn (**3a**)		**1n** / 65
14	$CH_2{=}CH(CH_2)_3$ (**2i**)	 (**3c**)	Me (**4f**)	**1o** / 60
15[e]	 (**2j**)	Bn (**3a**)	Me (**4f**)	**1p** / 30
16[c,d]	 (**2k**)	Bn (**3a**)	Ph (**4a**)	**1q** / 75
17[c,d]	 (**2l**)	Bn (**3a**)	Me (**4f**)	**1r** / 60

[a] General conditions: 2/3/4 = 1/2.5/1, O_2 balloon, in toluene (c = 2.5 M), 24 h. The oxidation of alcohol was performed in the presence of other reactants (cf. Supporting Information). [b] Yield of isolated product. [c] dr = 1: 1. [d] dr determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e] 0.3 equiv each of $CuCl_2{\cdot}2H_2O$, $NaNO_2$, TEMPO was used instead.

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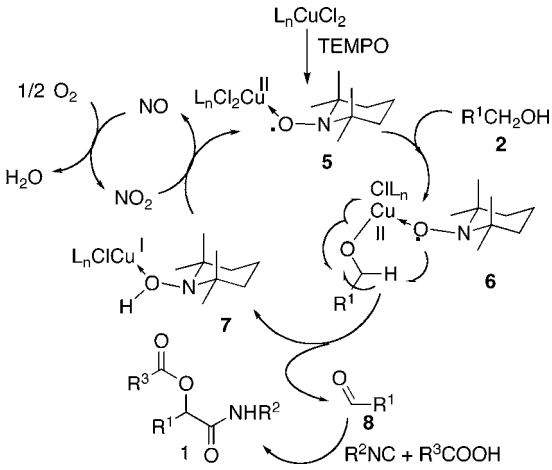
(20) See, for example: Grassot, J.-M.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 947–950.

Scheme 2. Mechanistic Proposal



A possible reaction sequence for this aerobic oxidative P-3CR reaction is shown in Scheme 2. Formation of $CuCl_2$−TEMPO complex **5**[21] followed by ligand exchange with alcohol would lead to a ternary complex **6**. An intramolecular hydrogen abstraction followed by fragmentation would then give the copper(I)−TEMPOH complex and aldehyde **8**. Subsequent reaction of **8** with isocyanide **3** and carboxylic acid **4** afforded the Passerini three-component adduct.[22] On the other hand, oxidation of the copper(I)−TEMPOH species **7** by NO_2, produced from $NaNO_2$ and carboxylic acid,[23] would regenerate the copper(II)−TEMPO complex **5**. Finally, NO_2 is regenerated by oxidation of NO with molecular oxygen, thus completing the dual catalytic cycle. The observation that both $CuCl_2$ and $NaNO_2$ were important for the reaction was in accord with the proposed catalytic cycle. Nevertheless, at the present stage of the development, we cannot exclude the pathway involving oxoammonium intermediate.[14b,24] The fact that cyclopropylmethanol (**2d**) and hex-5-en-1-ol (**2i**) can be converted into their corresponding P-3CR adducts, inferring that the ionic mechanism may also be operating.[25] However, it has to be noted that substrates prone to radical cyclization have been successfully oxidized to aldehydes under metal-catalyzed aerobic conditions that are known to involve a radical mechanism.[26]

In conclusion, we documented the first examples of an efficient Passerini reaction of alcohols under aerobic conditions in the presence of a catalytic amount of a ternary system, $CuCl_2$−$NaNO_2$-TEMPO, using molecular oxygen as a terminal oxidant. We believe that such a process could find useful applications in view of the power of the Passerini reaction and that the concept could be extended to other MCRs involving aldehyde substrates.[27]

Acknowledgment. Financial support from CNRS and ANR is gratefully acknowledged. J.B. thanks ICSN for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) X-ray structure of $CuBr_2$−Tempo complex: (a) Caneschin, A.; Grand, A.; Laugier, J.; Rey, P.; Subra, R. *J. Am. Chem. Soc.* **1988**, *110*, 2307–2309. X-ray structure of $CuCl_2$−Tempo complex: (b) Laugier, J.; Latour, J.-M.; Caneschi, A.; Rey, P. *Inorg. Chem.* **1991**, *30*, 4474–4477. In ref b, the authors proposed that complexation of TEMPO by the copper salt did not involve an electron transfer between the two fragments and that the complex is better formulated as Cu^{2+}(TEMPO$^{\bullet}$) rather than as Cu^{3+}(TEMPO$^-$) or Cu^+(TEMPO$^+$).

(22) Note that isocyanides can undergo a number of competitive reactions in the presence of cupric chloride under aerobic conditions. (a) Oxidation to isocyanate: Saegusa, T.; Kobayashi, S.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 275–276. (b) Conversion to imidocarbonyl chloride: Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Takeda, N. *Can. J. Chem.* **1969**, *47*, 1217–1222. (c) Insertion to alcohol leading to formamidate: Saegusa, T.; Ito, Y.; Kobayashi, S.; Takeda, N.; Hirota, K. *Tetrahedron Lett.* **1967**, 521–524. (d) Polymerization: Saegusa, T.; Ito, Y.; Kobayashi, S. *Tetrahedron Lett.* **1967**, *127*, 3–1275. Control experiments have shown that mixing the benzyl isocyanide and $CuCl_2$ in toluene under oxygen atmosphere led to the complete decomposition of the former after 20 h. Therefore, to guarantee the success of the present domino oxidation/P-3CR, the oxidation of alcohol to aldehyde and its subsequent P-3CR had to be faster than these competitive reactions. We found that polymerization of isocyanide was the main side reaction. However, in initial condition surveys, oxidation of isocyanide to isocyanate was also observed.

(23) Miao, C.-X.; He, L.-N.; Wang, J.-Q.; Wang, J.-L. *Adv. Synth Catal.* **2009**, *351*, 2209–2216.

(24) For mechanistic discussion on the Cu−Tempo-catalyzed aerobic oxidation, see: (a) Semmelhack, M. F.; Schmidt, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376. (b) Semmelhack, M. F.; Schmidt, C. R.; Cortes, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119–1122. (c) Dijiksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232–3237. (d) For a review, see: Galli, C.; Gentili, P.; Lanzalunga, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 4790–4796. See also ref 20.

(25) The reaction of **2a**, **3a**, and **4a** in the absence of $CuCl_2$ [TEMPO (0.15 equiv), $NaNO_2$ (0.15 equiv), O_2, in toluene (*C* 2.5 M), rt] led to 50% conversion of alcohol.

(26) Astolfi, P.; Brandi, P.; Galli, C.; Gentili, P.; Gerini, M. F.; Greci, L.; Lanzalunga, O. *New J. Chem.* **2005**, *29*, 1308–1317.

(27) MCRs of in situ generated isocyanides : El Kaim, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, *7*, 3024–3026.