Organocatalytic Oxidative Dimerization of Alcohols to Esters

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Abstract: 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) catalyzes the direct oxidation of primary alkyl alcohols to symmetric esters at 1–2 mol% loadings. These rapid reactions take place at room temperature to afford the products in yields of 55–99%.

Key words: catalysis, dimerization, alcohols, esters, oxidation

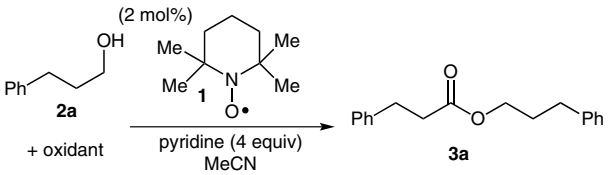
Acylations are one of the most ubiquitous and important processes in organic chemistry,[1] and the development of more efficient ways of preparing esters and amides has been identified as a high priority research goal.[1] Symmetric esters (RCO_2CH_2R) are of importance in, for example, the food and fragrance industries, but commonly require multiple synthetic steps. Oxidative dimerization is an attractive solution to this problem. Although oxidative dimerization has been achieved with stoichiometric oxidants, these protocols often require the use of an excess of expensive and toxic reagent, proceed in low yield, or require unpractical long reaction times.[2,3] Several groups have reported efficient high-temperature transition-metal-catalyzed oxidative dimerization of alcohols to give esters.[4] In contrast, and despite the potential advantages, there are few examples of organocatalytic processes.[5]

Herein, we report an efficient direct 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; **1**)[6] catalyzed oxidative dimerization of alcohols to esters. The reaction uses only 1–2 mol% TEMPO, is complete within 0.5–2 hours, takes place at room temperature, and uses trichloroisocyanuric acid (**7**; TCCA), which is an inexpensive and environmentally benign stoichiometric oxidant.[7]

A particular challenge was that TEMPO-catalyzed oxidation of primary alcohols usually delivers the aldehyde as the major product.[8,9] Bobbitt and Brückner reported that oxidative dimerization of alcohols with an activating β-oxygen substituent could be achieved by using super-stoichiometric amounts of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (2.5 equiv), an oxidized analogue of TEMPO, in the presence of pyridine.[3] We and others had observed in unrelated work that carboxylic acids are formed in preference to aldehydes under Anneli's conditions[9] when the bleach is added slowly to the reaction. Thus, we postulated that ester formation should be favored over aldehyde formation if the oxidant is added slowly to the reaction mixture containing the alcohol, TEMPO, and a base.

Accordingly, we screened a variety of conditions in the TEMPO-catalyzed dimerization of 3-phenylpropanol (Table 1). In all the successful experiments, pyridine was used as a base. Other bases, for example, potassium carbonate, triethylamine, or dimethylaniline inhibited the reaction. The oxidant (2 equiv) was added over one hour as a stock solution. Many standard oxidants including phenyliodonium diacetate, and phenyliodonium dichloride, either failed to give any reaction or afforded only aldehyde (entries 1 and 2). However, promising results were achieved with TCCA (44% yield; Table 1, entry 4) as the oxidant in acetonitrile. Due to the low cost and high ratio of oxidant (Cl^+) to weight in TCCA and its environmentally friendly profile, it was chosen for further optimization. Gratifyingly, reducing the amount of TCCA (0.6 equiv) resulted in complete conversion of the substrate into ester **3a** in an excellent 94% isolated yield (entry 5). No difference in yield was observed using 1 or 2 mol% TEMPO or 2 or 4 equivalent of pyridine. Interestingly, use of NCS (entry 3) afforded the product in lower yield than structurally related TCCA. It should be noted that TCCA is only sparingly soluble in most common organic solvents but dissolves readily in acetonitrile. The solvent requirement is minimal because the reaction can be run at an initial concentration of 1 M of alcohol and is diluted to 0.5 M after complete addition of the oxidant stock solution. The strict exclusion of water is essential to

Table 1 Optimization Study



Entry	Oxidant	Solvent	Yield of **3a** (%)
1	$PhIOAc_2$ (**4**)	CH_2Cl_2	–
2	$PhICl_2$ (**5**)	CH_2Cl_2	[a]
3	NCS (**6**)	MeCN	35
4	TCCA (**7**)	MeCN	44
5[b]	TCCA (**7**)	MeCN	94

[a] A 1:1 mixture of aldehyde and esters was formed.
[b] Reaction conditions: TEMPO (1 mol%), TCCA (0.6 equiv), pyridine (2 equiv).

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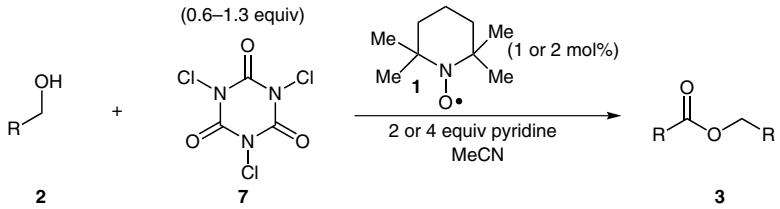
avoid formation of carboxylic acids as side products of the reaction.

Next, we examined the scope of the optimized conditions (Table 2). The method is applicable to a range of primary alcohols. Both unactivated alcohols (entries 9–11 and 13) and alcohols with an activating β-oxygen or nitrogen function (entries 1–8) afforded the products in 55–99% yield.

Table 2 Direct Oxidative Dimerization of Alcohols[a]



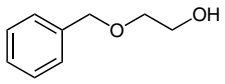
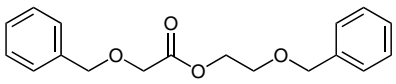
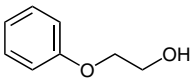
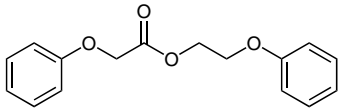
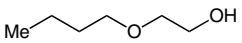
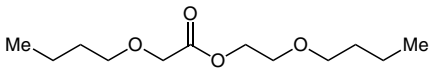
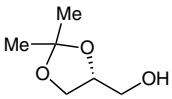
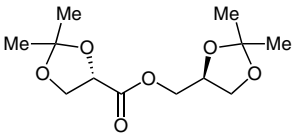
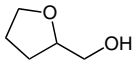
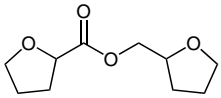
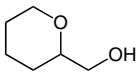
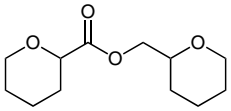
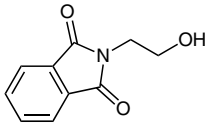
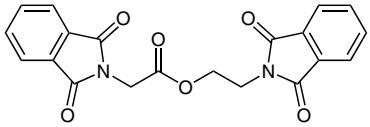
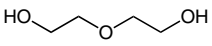
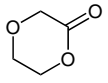
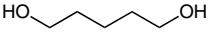
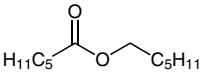
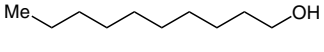
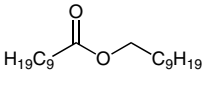
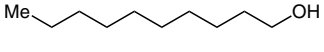
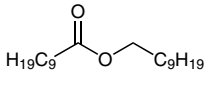
Entry	Id	Starting Material	Product(s)	Yield (%)
1	**b**			86
2	**c**			64
3	**d**			99
4	**e**			55[b]
5	**f**			83[c]
6	**g**			75[c]
7	**h**			82
8	**i**			70–100
9	**j**			86
10	**k**			68[d]
11	**l**			59
12	**l**			75[e]

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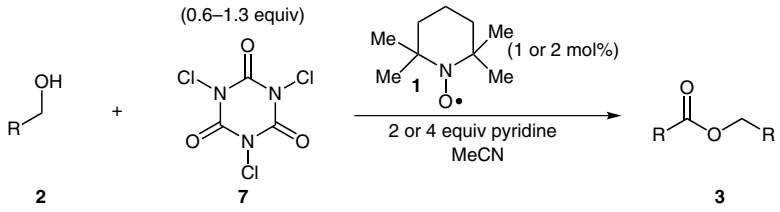
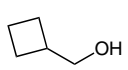
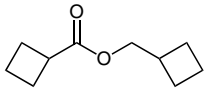
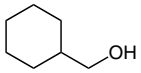
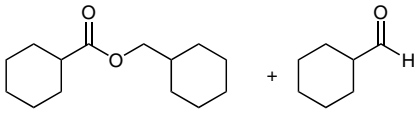
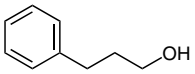
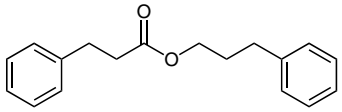
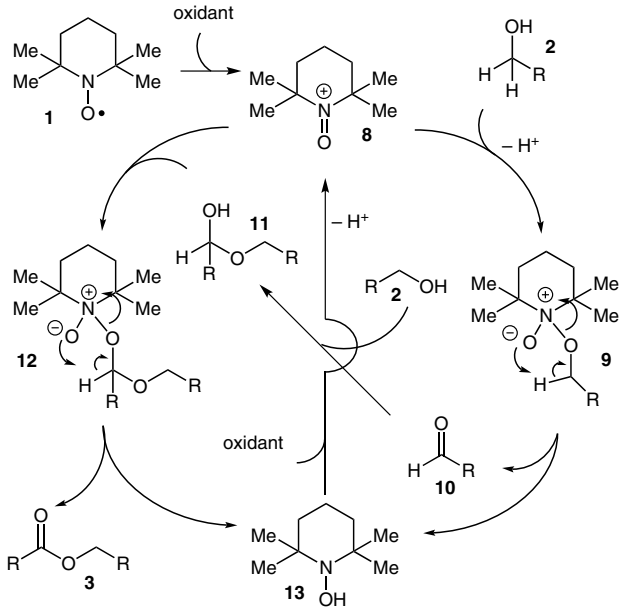
Table 2 Direct Oxidative Dimerization of Alcohols[a] (continued)



Entry	Id	Starting Material	Product(s)	Yield (%)
13	**m**			80
14	**n**			not determined 2:1 mixture
15	**a**			74[e]

[a] See experimental sections for procedure. No difference in yield was observed using 1 or 2 mol% of TEMPO or 2 or 4 equiv of pyridine.
[b] No epimerization was observed.
[c] Mixture of diastereoisomers.
[d] Volatile.
[e] Using *t*-BuOCl (2 equiv) as oxidant.



Scheme 1 Plausible mechanism for the oxidative dimerization of primary alcohols

In the case of hindered unactivated cyclohexylmethanol, both the ester and aldehyde was present in the isolated material (Table 2, entry 14). In contrast, similarly hindered but activated 2-tetrahydropyryl- and 2-tetrahydrofuryl-methanol afforded the esters in high yield (entries 5 and 6). Furthermore, the sensitive and only slightly less hindered cyclobutylmethanol reacted to give the product in a yield of 80%. The method is versatile since it is compatible with a range of functionalities such as acetals (entries 4–6), ethers (entries 1–3), imides (entry 7) and, of course, esters. Of further importance, ester **3e** (entry 4), which is prone to epimerization, was obtained as a single diastereoisomer.

We proceeded to investigate the mechanism. No ester formation was observed in the absence of TEMPO (**1**). The reaction takes place through formation of aldehydes, which could be observed by NMR spectroscopic analysis when the reaction was quenched at low conversions. Notably, despite the presence of pyridine, no aldol condensation product could be observed at the short reaction time required for oxidation.

Two possibilities presented themselves; (1) a Tishchenko type mechanism, and (2) attack by another molecule of alcohol **2** on the incipient aldehyde **10** to form a hemiacetal **11** followed by oxidation to the ester **3** (Scheme 1).[10] In addition, a case could be made for attack by either a derivative of the oxidant, or pyridine upon aldehyde **10** to give a hemi-acetal-like species.[11] If such an intermediate would be oxidized, a reactive acylating reagent would be formed in each case which, upon reaction with a molecule of alcohol **2**, would lead to formation of the observed product **3**.

The possibility that the nucleophile was derived from the oxidant was tested first. It was found that the use of *t*-BuOCl as an alternative oxidant afforded the esters **3** in high yield (compare Table 1, entry 5 and Table 2, entry

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15) under otherwise identical conditions. Since *t*-butanol is an exceedingly poor nucleophile, this ruled out the oxidant as the source of a nucleophile. In certain cases, the use of *t*-BuOCl may be preferable to TCCA in the reaction. Indeed, the oxidation of long chain aliphatic alcohol **2l** proceeded in higher yield with *t*-BuOCl than with TCCA (compare Table 2, entry 11 and 12).

Replacing pyridine with the poorer nucleophile 2,6-lutidine resulted only in the formation of aldehyde. In contrast, when 3-phenylpropanal rather than 3-phenyl-1-propanol (**2a**) was used as the starting material with pyridine as the base, no reaction took place. This experiment also rules out a Tishchenko type mechanism. When 2-propanol was added to this reaction mixture, very slow conversion could be observed. These facts point to the primary alcohol as the nucleophile and indicate a different role for pyridine. In further support, exchanging pyridine for a more nucleophilic reagent i.e., 4-(*N*,*N*-dimethylamino)pyridine (DMAP) or its N-oxide derivative DMAPO inhibited the reaction. Examining the decanal and pyridine mixture in detail by NMR spectroscopic analysis did not indicate the formation of any adducts.

Thus, the most plausible mechanism is that shown in Scheme 1. This mechanism is also analogous to the mechanism postulated for the TEMPO-catalyzed oxidation of aldehydes to carboxylic acids,[12] which is believed to proceed via the hydrated aldehyde. Indeed, benzylic alcohol and sterically encumbered neopentyl alcohol were oxidized to the corresponding aldehydes without any ester formation. These aldehydes form hydrates relatively slowly.[12]

Presently, the role of pyridine in the reaction remains unclear. We believe that, in addition to acting as a base, it may act as a shuttle for chlorine between TCCA and the reduced form of TEMPO (**13**).[13] Mixing two equivalents of pyridine and one equivalent of TCCA in acetonitrile-d_3 led to the rapid formation of an unidentified precipitate. However, the pyridine species remaining in solution had only the characteristic NMR signals of pyridine.

The present method allows for the rapid and convenient synthesis of esters through the dimerization of primary alcohols.[14] Many of the esters prepared in this study are of interest for the chemical industry. We believe that this method is a valuable alternative for the preparation of these compounds.

Acknowledgment

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Chromatographic purification of products (flash chromatography) was performed on silica 32–63, 60 Å. NMR spectra were recorded with a Bruker Avance I 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C acquisitions, respectively, or with Bruker Avance III 400 spectrometers operating at 400 MHz (^{1}H) and 101 MHz (^{13}C) or with a Bruker DPX200 spectrometer operating at 200 MHz (^{1}H) and 50 MHz (^{13}C). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ = 7.26 ppm for ^{1}H, and δ = 77.0 ppm for ^{13}C). IR spectra were recorded with a Bruker FTIR. High-resolution mass spectra APCI were recorded with a Waters Micromass LCT premier instrument operating at 70 eV (acetonitrile–water, 70%; flowrate 0.2 mL). All known pure compounds showed NMR spectra consistent with those reported in the literature.

General Procedure: The alcohol (2 mmol), TEMPO (3.1 mg, 0.02 mmol, 1 mol%) and pyridine (0.322 mL, 4.0 mmol, 2 equiv) were dissolved in acetonitrile (2 mL). A stock solution of TCCA (156 mg/mL, 0.32 mmol/mL, 0.32 equiv/mL) in acetonitrile (3 mL) is added dropwise over 0.5–1 h until no more starting material was observed by TLC (usually 2–3 mL stock solution, 0.65–1.3 equiv of TCCA). Sat. $NaHCO_3$ (25 mL) was added and the reaction was extracted with diethyl ether (4 × 20 mL). The combined extracts were dried over Na_2SO_4 and the product was purified by flash chromatography (EtOAc–hexane).

3-Phenylpropyl 3-Phenylpropanoate (3a):[15] The product was purified by flash chromatography (EtOAc–hexane, 14%) as an oil (252 mg, 94%). R_f = 0.57 (EtOAc–hexane, 20%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23 (m, 10 H), 4.09 (t, *J* = 6.5 Hz, 2 H), 2.96 (t, *J* = 7.6 Hz, 2 H), 2.63 (t, *J* = 7.6 Hz, 4 H), 1.93 (dt, *J* = 13.2, 6.5 Hz, 2 H).

2-(Benzyloxy)ethyl 2-(Benzyloxy)acetate (3b):[3] The product was purified by flash chromatography (EtOAc–hexane, 30%) as an oil (191 mg, 64%). R_f = 0.83 (EtOAc–hexane, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.27 (m, 10 H), 4.66 (s, 2 H), 4.56 (s, 2 H), 4.35 (t, *J* = 4.7 Hz, 2 H), 4.14 (s, 2 H), 3.69 (t, *J* = 9.5 Hz, 2 H).

2-Phenoxyethyl 2-Phenoxyacetate (3c):[3] The product was purified by flash chromatography (EtOAc–hexane, 30%) as an oil (234 mg, 86%). R_f = 0.82 (EtOAc–hexane, 80%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.13 (m, 5 H), 6.90–6.74 (m, 5 H), 4.65 (s, 2 H), 4.56 (t, *J* = 4.8 Hz, 2 H), 4.20–4.12 (t, *J* = 4.5 Hz, 2 H).

2-Butoxyethyl 2-Butoxyacetate (3d):[3] The product was purified by flash chromatography (EtOAc–hexane, 18%) as an oil (250.7 mg, 99%). R_f = 0.51 (EtOAc–hexane, 20%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.25 (t, *J* = 4.5 Hz, 2 H), 4.05 (s, 2 H), 3.59 (t, *J* = 4.9 Hz, 2 H), 3.54–3.36 (m, 4 H), 1.66–1.21 (m, 8 H), 0.87 (td, *J* = 7.1, 1.6 Hz, 6 H).

(*S*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl 2,2-Dimethyl-1,3-dioxolane-4-carboxylate (3e):[3] The product was purified by flash chromatography (EtOAc–hexane, 30%) as an oil (143 mg, 55%). R_f = 0.95 (EtOAc–hexane, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (t, *J* = 7.0 Hz, 1 H), 4.31–3.97 (m, 6 H), 3.69 (dd, *J* = 8.4, 5.9 Hz, 1 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H).

(Tetrahydrofuran-2-yl)methyl Tetrahydrofuran-2-carboxylate (3f):[3] The product was purified by flash chromatography (EtOAc–hexane, 80%) as an oil (166 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (m, 1 H), 4.17 (m, 1 H), 4.05 (m, 3 H), 3.86 (m, 2 H), 3.76 (dd, *J* = 14.3, 7.2 Hz, 1 H), 2.22 (m, 1 H), 1.92 (m, 6 H), 1.58 (m, 2 H).

(Tetrahydro-2*H*-pyran-2-yl)methyl Tetrahydro-2*H*-pyran-2-carboxylate (3g):[3] The product was purified by flash chromatography (EtOAc–hexane, 80%) as an oil (171 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09 (m, 1 H), 3.48 (m, 1 H), 1.96 (m, *J* = 11.6 Hz, 1 H), 1.87 (m, *J* = 7.4 Hz, 1 H), 1.56 (m, 2 H), 1.32 (m, 1 H).

2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl (1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl) Acetate (3h): The product was purified by flash chromatography (EtOAc–hexane, 50%) as a solid (310 mg, 82%). R_f = 0.49 (EtOAc–hexane, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.80 (m, *J* = 6.3, 3.1 Hz, 4 H), 7.77–7.70 (m, 4 H), 4.44–4.38 (m, 4 H), 3.98 (t, *J* = 5.3 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.99, 167.29, 167.16, 134.16, 134.07, 132.08, 131.96, 123.60, 123.47, 62.96, 38.80, 36.65. IR (thin film): 3024, 1763, 1722, 1633, 1520, 1404, 1215, 1014 cm^{-1}. HRMS (APCI): *m*/*z* [M + 1] calcd for $C_{19}H_{12}N_2O_6$: 379.0930; found: 379.0929.

1,4-Dioxan-2-one (3i):[4g] The product was purified by flash chromatography (EtOAc–hexane, 80%) as an oil (103 mg, 100%). Yields varied from 70 to 100% due to the inherent instability of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (t, *J* = 4.7 Hz, 2 H), 4.38 (s, 2 H), 3.87 (t, *J* = 4.7 Hz, 2 H).

Tetrahydro-2*H*-pyran-2-one (3j):[4b] The product was purified by flash chromatography (EtOAc–hexane, 80%) as an oil (86 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (t, *J* = 5.5 Hz, 2 H), 2.56 (t, *J* = 6.9 Hz, 2 H), 2.01–1.79 (m, 4 H).

Hexyl Hexanoate (3k):[2d] The product was purified by flash chromatography (EtOAc–hexane, 20%) as an oil (137 mg, 68%). R_f = 0.5 (EtOAc–hexane, 20%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.03 (t, *J* = 6.7 Hz, 2 H), 2.26 (t, *J* = 7.5 Hz, 2 H), 1.68–1.49 (m, 4 H), 1.37–1.18 (m, 10 H), 0.86 (t, *J* = 6.6 Hz, 6 H).

Decyl Decanoate (3l):[2d] The reaction was carried out using *t*-BuOCl (2 equiv) as the oxidant instead of TCCA. The product was purified by flash chromatography (EtOAc–hexane, 10%) as an oil (234 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (t, *J* = 6.7 Hz, 2 H), 2.29 (t, *J* = 7.5 Hz, 2 H), 1.68–1.55 (m, 4 H), 1.40–1.16 (m, *J* = 13.6 Hz, 26 H), 0.88 (t, *J* = 6.6 Hz, 6 H).

Cyclobutylmethyl Cyclobutanecarboxylate (3m):[16] The product was purified by flash chromatography (Et_2O–pentane, 8%) as an oil (135 mg, 80%). R_f = 0.5 (Et_2O–pentane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (d, *J* = 6.7 Hz, 2 H), 3.07 (pent., *J* = 8.5 Hz, 1 H), 2.55 (sept., 1 H), 2.17 (m, 4 H), 1.98 (m, 2 H), 1.84 (m, 4 H), 1.71 (m, 2 H).

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