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A Practical $RuCl_3$-Catalyzed Oxidation Using Trichloroisocyanuric Acid As a Stoichiometric Oxidant under Mild Nonacidic Conditions

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Abstract:

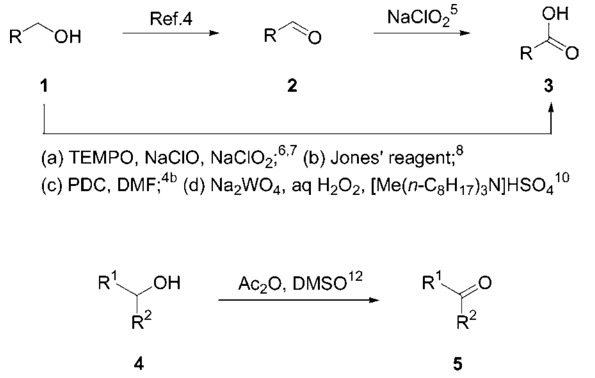
The combined use of catalytic $RuCl_3$ (1.0 mol %) and stoichiometric trichloroisocyanuric acid (TCCA; 1.0 equiv) in the presence of *n*-Bu_4NBr (2.0 mol %) and K_2CO_3 (3.0 equiv) in 1:1 $MeCN/H_2O$ at 25−45 °C allows smooth oxidation of primary alcohols to carboxylic acids. Secondary alcohols can be oxidized to ketones when using the same set of the reagents in 1:1 $MeCN/H_2O$ or 1:1 $AcOEt/H_2O$. By proceeding under the nonacidic biphasic conditions dispensing with hazardous reagents, the oxidation reactions are applicable to structurally diverse alcohols, easy to work up, environmentally benign, and basically high-yielding.

Introduction

With the adjustment of a molecular oxidation state playing a vital role in both total synthesis of natural products[1] and industrial production of organic compounds,[2] intensive effort has been directed towards developing preparative methods to oxidize alcohol groups in multifunctional compounds to carbonyl or carboxylic groups without affecting the other existent functionalities.[3]

Despite a quantum leap in recent synthetic methodologies, oxidation of primary alcohols **1** to carboxylic acids **3** still lacks definitive options, whereas there are different effective tools to oxidize primary alcohols **1** to aldehydes **2** (Scheme 1).[4] Thus, the prevailing method to oxidize primary alcohols **1** to carboxylic acids **3** often depends on discrete two-step procedures involving oxidation of primary **1** alcohols **1** to aldehydes **2**[4] and $NaClO_2$-mediated oxidation of the resulting aldehydes **2** to carboxylic acids **3**,[5] while tandem one-pot procedures have also been developed wherein $NaClO_2$ is used concomitantly with NaClO in the presence of catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[6,7] Indeed, such one-pot procedures are mild enough to find some applications; however, it is the same nature of mildness that has detracted from their practicality as they require a long reaction time when applied to the oxidation of primary alcohols with a relatively complex structure.[6b]

Scheme 1. **Oxidation of alcohols to carboxylic acids or ketones**



When using Jones' reagent,[8] a range of primary alcohols **1** could be oxidized to carboxylic acids **3** in a more expeditious manner (Scheme 1), and it is the reason that no reagent has been more commonly used than Jones' reagent in the laboratory since its advent in 1946[8] despite the fact that this classical method has suffered from two drawbacks: (1) too acidic conditions such that acid-labile functionalities

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(5) (a) Dalancale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567. (b) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskoković, M. R. J. *Org. Chem.* **1993**, *58*, 832.

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cannot survive and (2) use of environmentally demanding toxic chromium(VI) species.

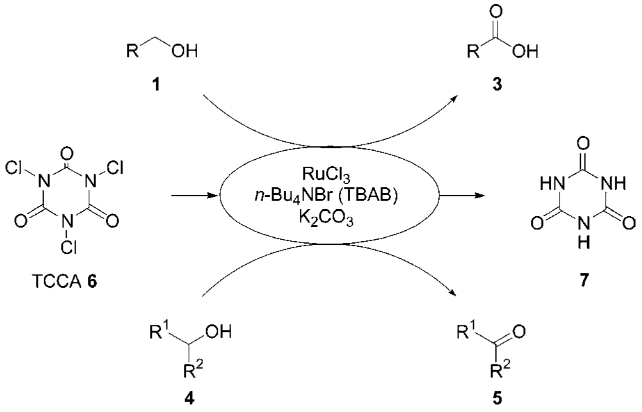
Corey's pyridinium dichromate (PDC) in DMF[4b] could have been used more frequently to oxidize primary alcohols **1** to carboxylic acids **3** because of the neutral nature of the reaction (Scheme 1). However, besides the hazardous nature of the chromium species in PDC, use of the polar solvent of DMF has kept the PDC-mediated oxidation from being practical due to the difficulty in separating the carboxylic acid products **3** from DMF through the extractive workup.[9]

To effect the oxidation of primary alcohols **1** to carboxylic acids **3** in a more environmentally benign manner, Noyori's chromium-free conditions could be applied where aqueous H_2O_2 is used as a stoichiometric oxidant in combination with a catalytic amount of Na_2WO_4 in the presence of $[Me(n\text{-}C_8H_{17})_3N]HSO_4$ as a phase transfer catalyst (Scheme 1).[10] However, this oxidation protocol has found limited use so far because of the severely acidic nature of the reaction media;[10b] thus, the situation seems not to have changed so much from that about half a century ago with respect to practicality, still suffering a tradeoff between applicability and environmental friendliness.[11]

When it comes to oxidation of secondary alcohols **4** to ketones **5**, the standard methods to oxidize primary alcohols **1** to aldehydes **2**[4] are also applicable (Scheme 1). In addition, Albright and Goldman's method using Ac_2O and DMSO is also effective for the oxidation of sterically hindered secondary alcohols **5**.[12] In fact, being so mild and chemoselective, oxidation using activated DMSO has now won renown as a versatile preparative method,[4e,4f] whether the desired products are aldehydes or ketones.[13] However, use of excess DMSO sometimes poses practical problems, such as stench and troublesome product isolation. In particular, the issue of product isolation (separation of polar products from the DMSO used without recourse to silica gel chromatography) can make the DMSO-mediated oxidation less amenable to scale-up when it is applied to the oxidation of polar substrates, such as sugar derivatives.[14]

To overcome the above-discussed limitations of the present methodologies to oxidize primary and secondary alcohols **1** and **4** to carboxylic acids **3** and ketones **5**, respectively, sets of reaction variables were explored based on the literature precedents for a new and improved combination of the relevant reagents that would meet the following requirements: (1) wide applicability owing to sufficient power of oxidation; (2) mild nonacidic milieu in which a range of functionalities can survive unaffected; (3) environmentally benign conditions dispensing with chromium species and halogenated solvents; and (4) facile product isolation due to no use of polar aprotic solvents, such as DMF and DMSO. Experimental effort along these lines has eventually culminated in identification of a practical recipe for the alcohol oxidation that features the combined use of catalytic $RuCl_3$ and stoichiometric trichloroisocyanuric acid (TCCA) in the presence of K_2CO_3 as an acid scavenger under the phase transfer conditions catalyzed by n-Bu_4NBr (Scheme 2).

Scheme 2. **$RuCl_3$/TCCA-mediated oxidation in the presence of TBAB as a phase transfer catalyst**



Results and Discussion

In the course of extensive experimentation designed to address the above-defined issues, $RuCl_3$-catalyzed oxidation[15] turned out promising, while the standard Sharpless protocol has remained less than satisfactory, since it employs expensive $NaIO_4$ as a stoichiometric oxidant and toxic CCl_4 as an essential component of the reaction medium.[15a] Interestingly, $RuCl_3$ proved to work as an effective oxidation catalyst in a heterogeneous system (1:1 MeCN/H_2O) when it was used in combination with stoichiometric trichloroisocyanuric acid (TCCA; 1.0 equiv),[16] an inexpensive oxidant miscible freely with organic solvents of low polarity. Further investigation showed that addition of n-Bu_4NBr (TBAB; 2.0 mol %) as a phase transfer catalyst[4i,17] allowed the usage of $RuCl_3$ to be reduced to no more than 1.0 mol %; and what was better, the progress of the $RuCl_3$/TCCA/TBAB-mediated oxidation

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(9) The workup procedures recommended in ref 4b for the PDC-mediated oxidation of primary alcohols to carboxylic acids in DMF involve pouring the reaction mixture into water followed by extraction with ether or ether/pentane; however, few carboxylic acids of high polarity would be extracted into such solvent(s).

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(11) For the catalytic version of chromium trioxide-mediated oxidation of primary alcohols to carboxylic acids using periodic acid as a stoichiometric oxidant, see: Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.

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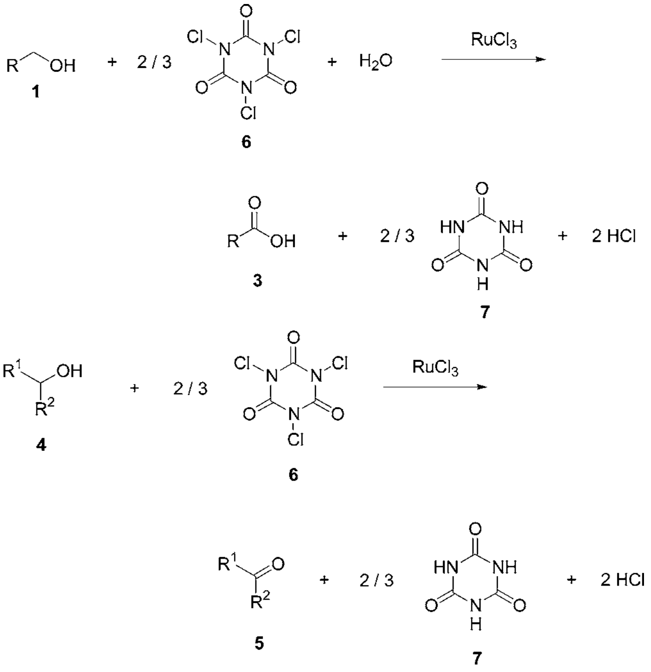
(16) (a) For a comprehensive review on the use of TCCA as an oxidant, see: Tilstman, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384. (b) For the TEMPO (2.0 mol %)-catalyzed oxidation of alcohols to carboxylic acids using TCCA (2.0 equiv) as a stoichiometric oxidant in acetone in the presence of catalytic NaBr (0.2 equiv) and an aqueous $NaHCO_3$ solution, see: Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.

(17) For the $RuCl_3$-catalyzed oxidation with H_2O_2 in a biphasic $Cl(CH_2)_2Cl/H_2O$ system using didecyldimethylammonium bromide as a phase transfer catalyst, see: Barak, G.; Dakka, J.; Sasson, Y. *J. Org. Chem.* **1988**, 53, 3553.

Scheme 3. **Stoichiometry for the $RuCl_3$/TCCA-mediated oxidation**



turned out to be less affected by the presence of an acid scavenger such as K_2CO_3 (3.0 equiv),[18] as discussed in detail below, which should help the oxidation to proceed under mild nonacidic conditions (Scheme 2).[19]

Oxidation of Primary Alcohols. TCCA **6** is converted into cyanuric acid (CNA) **7** with generation of HCl when working as the stoichiometric oxidant for the $RuCl_3$-catalyzed oxidation of alcohols (Scheme 3). Thus, for the oxidation to be compatible with acid-susceptible functionalities, the released HCl and the generated CNA **7** should both be neutralized with a pertinent base that would not affect the oxidation itself. Thus, some common bases were tested for the compatibility with the oxidation of 1-octanol **1a** with $RuCl_3$ (1.0 mol %) and TCCA (1.0 equiv) in the presence of TBAB (2.0 mol %) in 1:1 MeCN/H_2O (Table 1): when the oxidation of 1-octanol **1a** was attempted in the presence of NaOH, $NaHCO_3$, or K_2CO_3 each in 3.0 molar equivalents, it went to completion in 3 h to give octanoic acid **3a** in a GLC yield of 80.6%, 98.4%, and 85.9%, respectively, against an internal standard (*n*-tridecane) without intermediate octanal **2a** being detected.

In contrast, the oxidation running in the presence of pyridine (3.0 equiv) provided **3a** (76%) and **2a** (8%), the product distribution being similar to that for the oxidation in the absence of any base, 69.3:9.9 **3a**/**2a**. Moreover, when the oxidation was attempted in the presence of Et_3N (3.0 equiv), none of **3a** was generated with **1a** being left almost unconsumed. While experimental evidence was lacking, it was assumed that this phenomenon should result from Et_3N diverting the $RuCl_3$/TCCA-mediated oxidation to its *N*-oxide formation because Et_3N has more electron-donating propensity than pyridine.

Table 1. **$RuCl_3$/TCCA-Mediated oxidation of 1-octanol 1a to octanoic acid 3a in the presence of a range of bases[a]**

		product composition (%) after 3.0 h[b]		
entry	base	octanol **1a**	octanal **2a**	octanoic acid **3a**
1	NaOH	0	0	80.6
2	K_2CO_3	0	0	98.4
3	$NaHCO_3$	0	0	85.9
4	pyridine	0	8.2	75.6
5	Et_3N	89.5	0	0
6	none	0	9.9	69.3

[a] A 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of **1a** (0.5 M) and 1:1 MeCN/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and a specified base (3.0 equiv) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h. [b] Determined by GLC using *n*-tridecane as an internal standard after the generated **3a** was converted to the corresponding methyl ester with Me_3SiCHN_2;[23] for the detailed conditions, see procedure 1 in Experimental Section.

Table 2. **Effects of pH on the $RuCl_3$/TCCA-mediated oxidation of 1-octanol 1a to octanoic acid 3a[a]**

		product composition (%) after 3.0 h[b]		
entry	pH	octanol **1a**	octanal **2a**	octanoic acid **3a**
1	5	0	0	82.5
2	7	0	0	83.3
3	9	0	0	100

[a] A 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of **1a** (0.5 M) and 1:1 MeCN/1.0 M potassium phosphate buffer adjusted to a specified pH value in the presence of $RuCl_3$ (1.0 mol %) and TBAB (2.0 mol %) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h during which the pH of the mixture was maintained at an indicated value by adding a 3.0 M aqueous K_2CO_3 solution. [b] Determined by GLC using *n*-tridecane as an internal standard after the generated **3a** was converted to the corresponding methyl ester with Me_3SiCHN_2;[23] for the detailed conditions, see procedure 2 in Experimental Section.

Table 3. **Effects of organic solvent species on the $RuCl_3$/TCCA-mediated oxidation of 1-octanol 1a to octanoic acid 3a[a]**

		product composition (%) after 3.0 h[b]		
entry	organic solvent	octanol **1a**	octanal **2a**	octanoic acid **3a**
1	MeCN	0	0	93.0
2	AcOEt	0	9.4	74.4
3	MeCO*i*-Pr (MIBK)	0	22.4	37.8
4	PhMe	0	0	32.2
5	*n*-heptane	0	1.7	39.5

[a] A 1.0 M solution of TCCA (1.0 equiv) in a specified organic solvent was added dropwise to a stirred mixture of **1a** (0.5 M) and 1:1 the organic solvent/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h. [b] Determined by GLC using *n*-tridecane as an internal standard after the generated **3a** was converted to the corresponding methyl ester with Me_3SiCHN_2;[23] for the detailed conditions, see procedure 1 in Experimental Section.

Now that the highest GLC yield was recorded in the presence of K_2CO_3 (3.0 equiv), it was eventually nominated as the most appropriate acid scavenger for the oxidation in question.

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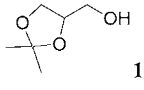
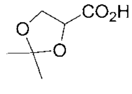
(18) For the kinetics-oriented studies on the $RuCl_3$/TCCA oxidation in acidic media, see: (a) Pati, S. C.; Sahu, A. K.; Sriramulu, Y. *Oxid. Commun.* **1985/86**, *8*, 243. (b) Pati, S. C.; Pathy, H. P.; Dev, B. R. *Oxid. Commun.* **1987**, *10*, 19. (c) Pati, S. C.; Sahu, A. K.; Sriramulu, Y. *Curr. Sci.* **1988**, *57*, 325. (d) Pati, S. C.; Sahu, A. K.; Sriramulu, Y. *Rev. Roum. Chim.* **1988** *33*, 157. (e) Pati, S. C.; Sarangi, C. *Ind. J. Chem.* **1988**, *27A*, 593. (f) Pati, S. C.; Patro, P. S. C. *Proc. Indian Natl. Sci. Acad.* **1989**, *55A*, 75. (e) Mohan, R. V. G. K.; Sondu, S. *React. Kinet. Catal. Lett.* **1997**, *61*, 167.

(19) Ikunaka, M.; Moriya, N.; Yamaoka, H. A patent application submitted.

Table 4. **Best practices for the $RuCl_3$/TCCA-mediated oxidation of primary alcohols to carboxylic acids**[a]

entry	substrate	product	yield (%)
1	octanol **1a**	octanoic acid **3a**	94.9%[b]
2	 **1b**	 **3b**	96.0[c]

[a] A 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of an alcohol substrate (0.5 M) and 1:1 MeCN/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h. [b] An isolated yield. [c] Determined by GLC using *n*-tridecane as an internal standard after the generated **3b** was converted to the corresponding methyl ester with Me_3SiCHN_2;[23] for the detailed conditions, see Experimental Section.

To define the pH range within which the oxidation would proceed uneventfully, the oxidation of **1a** was conducted at pH 5, 7, or 9, each of which was kept constant by the combined use of a 1.0 M potassium phosphate buffer and a 3.0 M aqueous K_2CO_3 solution. As summarized in Table 2, it was presumed that the oxidation at pH 9 provided the highest GLC yield; however, the oxidation seems to proceed smoothly at any pH value tested to give acid **3a** selectively when taking into account the experimental error associated with the quantitative GLC analysis using an internal standard and the complete consumption of the starting alcohol **1a** in each case.

The oxidation was next attempted in a range of organic solvents to see what effect an organic solvent species would have on the course of the oxidation (Table 3): a mixture of 1-octanol **1a** (0.5 M) and 1:1 organic solvent/H_2O containing $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) was treated with a 1.0 M solution of TCCA (1.0 equiv) in the organic solvent at 25−45 °C for 3.0 h, and the product composition was analyzed by GLC quantitatively against an internal standard (*n*-tridecane). When MeCN was used as an organic phase, the GLC analysis indicated that octanoic acid **3a** was produced in 93.0% yield without any octanal **2a** being detected. However, with decreasing polarity of the organic solvents used, the GLC yield of **3a** declined from 74.4% in AcOEt to 32.2% yield in PhMe with complete consumption of **1a**. In contrast, when the oxidation was run in methyl isobutyl ketone (MIBK), its progress was intercepted by the significant formation of aldehyde **2a** (22.4%).

In light of the experimentation discussed above, the best recipe to oxidize primary alcohols to carboxylic acids with TCCA (1.0 equiv) by the catalysis of $RuCl_3$ (1.0 mol %) involves use of the biphasic MeCN/H_2O (1:1) mixture as a reaction medium, TBAB (0.2 mol %) as a phase transfer catalyst, and K_2CO_3 (3.0 equiv) as an acid scavenger at 25−45 °C. In fact, its reliable and versatile nature can be confirmed by Table 4 listing a high isolated yield of **3a** (94.9%) and a successful oxidation of acid-labile solketal **1b** to 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **3b** (GLC yield of 96.0%).

Oxidation of Secondary Alcohols. As a test example, 2-octanol **4a** was treated with TCCA (1.0 equiv) in the presence of $RuCl_3$ (1.0 mol %) and TBAB (2.0 mol %) in 1:1 MeCN/1.0 M potassium phosphate buffer at pH 5, 7, or 9 and at 25−45 °C for 3 h during which the specified pH was maintained by adding a 3.0 M aqueous solution of K_2CO_3. As summarized in Table 5, the oxidation proceeded uneventfully under slightly acidic and neutral conditions as 2-octanone **5a** was obtained quantitatively and in 98.4% yield at pH 5 and 7, respectively, as indicated by quantitative GLC analysis using *n*-tridecane as an internal standard. In contrast, basic conditions proved detrimental to the oxidation of secondary alcohols as GLC analysis showed that **5a** was generated in 78.2% yield at pH 9 with **4a** being left unconsumed in 0.8% yield.

Table 5. **Effects of pH on the $RuCl_3$/TCCA-mediated oxidation of 2-octanol 4a to 2-octanone 5a**[a]

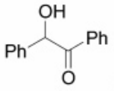
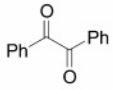
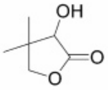
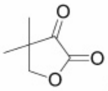
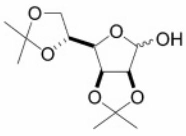
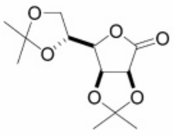
		product composition (%) after 3.0 h[b]	
entry	pH	2-octanol **4a**	2-octanone **5a**
1	5	0	100
2	7	0	98.4
3	9	0.8	78.2

[a] A 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of **4a** (0.5 M) and 1:1 MeCN/1.0 M potassium phosphate buffer adjusted to a specified pH value in the presence of $RuCl_3$ (1.0 mol %) and TBAB (2.0 mol %) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h during which the pH of the mixture was maintained at the indicated value by adding a 3.0 M aqueous K_2CO_3 solution. [b] Determined by GLC using *n*-tridecane as an internal standard; for the detailed conditions, see procedure 3 in Experimental Section.

Interestingly, the $RuCl_3$/TCCA-mediated oxidation of secondary alcohols to ketones would proceed better under slightly basic conditions when compared with that of primary alcohols to carboxylic acids. However, what is noticeable at the moment is that the above-specified procedures have enabled successful oxidation of secondary alcohols to ketones under neutral conditions.

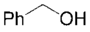
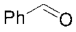
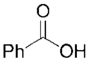
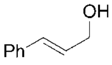
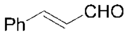
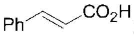
As regards the oxidation of secondary alcohols to ketones, the best procedures for the oxidation of primary alcohols to carboxylic acids also worked well: when a mixture of **4a** (0.5 M) and 1:1 MeCN/H_2O containing $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) was treated with a 1.0 M solution of TCCA (1.0 equiv) at 25−45 °C, **4a** was consumed completely in 1 h to give **5a** in an isolated yield of 98.0%. When the oxidation of **4a** was conducted in AcOEt or MIBK otherwise under the same conditions as mentioned above, **5a** was produced almost quantitatively in 3 h as indicated by quantitative GLC analysis using *n*-tridecane as an internal standard. In contrast, however, use of *n*-heptane

Table 6. **$RuCl_3$/TCCA-Mediated oxidation of diverse secondary alcohols to ketones**[a]

entry	substrate	product	yield (%)	organic phase	base (equiv)
1	2-octanol **4a**	2-octanone **5a**	98.4[b]	MeCN	K_3CO_3 (3.0)
2[c]	cyclopentanol **4b**	cyclopentanone **5b**	89.9[d]	AcOEt	K_3CO_3 (3.0)
3[c]	PhCH(OH)Ph **4c**	PhCOPh **5c**	95.4[b]	AcOEt	K_3CO_3 (3.0)
4[c]	 **4d**	 **5d**	77.7[e]	AcOEt	K_3CO_3 (3.0)
5	 **4e**	 **5e**[20]	97.7[e]	MeCN	AcONa (5.0)
6	 **4f**	 **5f**[21]	52.3[e]	MeCN	AcONa (5.0)

[a] Unless otherwise specified, a 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of an alcohol substrate (0.5 M) and 1:1 MeCN/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h. [b] Determined by GLC using *n*-tridecane as an internal standard; for the detailed conditions, see Experimental Section. [c] A 0.67 M AcOEt solution of TCCA (0.67 equiv) was added to a stirred mixture of an alcohol substrate (0.5 M) and 1:1 AcOEt/H_2O. [d] Determined by GLC using *n*-nonane as an internal standard; for the detailed conditions, see Experimental Section. [e] An isolated yield.

Table 7. **$RuCl_3$/TCCA-Mediated benzyl alcohol 1c and cinnamyl alcohol 1d**[a]

entry	substrate	product distribution (%) after 3.0 h				organic phase
		aldehyde	yield (%)[b]	carboxylic acid	yield (%)[b]	
1	 **1c**	 **2c**	0	 **3c**	93.9	MeCN
2[c]			86.8		0	AcOEt
3	 **1d**	 **2d**	62.5	 **3d**	35.7	MeCN
4[c]			98.5		0	AcOEt

[a] Unless otherwise specified, a 1.0 M MeCN solution of TCCA (1.0 equiv) was added dropwise to a stirred mixture of an alcohol substrate (0.5 M) and 1:1 MeCN/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) at reflux, and the mixture was stirred at the same temperature range for 3 h. [b] An isolated yield. [c] A 0.67 M AcOEt solution of TCCA (0.67 equiv) was added dropwise to a stirred mixture of an alcohol substrate (0.5 M) and 1:1 AcOEt/H_2O in the presence of $RuCl_3$ (1.0 mol %), TBAB (2.0 mol %), and K_2CO_3 (3.0 equiv) at 25−45 °C, and the mixture was stirred at the same temperature range for 3 h.

as the organic phase required as long as 40 h until the oxidation went to completion.

To demonstrate its wide applicability and tunable nature with respect to the organic phase and the acid scavenger, a range of secondary alcohols were subjected to the $RuCl_3$/TCCA/TBAB-based oxidation method under somewhat arbitrarily selected conditions as listed in Table 6. In fact, successful oxidation of benzoin **4d**, α-hydroxy ester (pantolactone) **4e**,[20] and sugar derivatives **4f**[21] should highlight the mild chemoselective nature of the oxidation thus developed.

Oxidation of Unsaturated Alcohols. To complement the scope and limitations studies on the $RuCl_3$/TCCA/TBAB-mediated oxidation, benzyl alcohol **1c** was subjected to the oxidation conditions in question (Table 7). When using MeCN as the organic phase, **1c** was oxidized to benzoic acid **3c** in an isolated yield of 94%. In contrast, when AcOEt was used as the organic phase, the oxidation gave only benzaldehyde **2c** in an isolated yield of 87%.

However, in the case of the oxidation of cinnamyl alcohol **1d**, no such sharp selectivity was observed (Table 7). Indeed, use of AcOEt as the organic phase allowed the selective oxidation of **1d** to cinnamaldehyde **2d** in 98.5% yield. However, when MeCN was used as the organic phase, the

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(20) Ojima, I.; Kogure, T.; Yoda, Y. *Org. Synth.* **1985**, *63*, 18.

(21) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K.; Mocek, U.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 5254.

oxidation ended up giving a mixture of **2d** and cinnamic acid **3d** in an isolated yield of 63% and 36% yield, respectively. Despite a paucity of experimental data, it was presumed that unsaturated primary alcohols could be oxidized selectively to aldehydes when AcOE was used as the organic phase for the $RuCl_3$/TCCA/TBAB-mediated oxidation.

Conclusions

As regards the newly developed biphasic oxidation procedures [$RuCl_3$ (1.0 mol %), TCCA (1.0 equiv), TBAB (2.0 mol %), K_2CO_3 (3.0 equiv); 25−45 °C], comments worth making are itemized as follows: (1) Being essentially neutral, the conditions are compatible with a range of functional groups such as acid-labile acetals and base-labile esters.[22] (2) The pertinent organic phase being less polar organic solvents, such as MeCN and AcOEt, the oxidation product can be isolated in a facile practical manner. (3) The conditions are free of environmentally hazardous toxic reagents, such as chromium species and halogenated solvents including CH_2Cl_2. (4) Primary alcohols are best oxidized to carboxylic acids in 1:1 MeCN/H_2O. (5) Secondary alcohols can be oxidized smoothly to ketones in either 1:1 MeCN/H_2O or 1:1 AcOEt/H_2O. (6) Unsaturated primary alcohols, such as benzyl alcohol **1c** and cinnamyl alcohol **1d**, can be oxidized selectively to aldehydes in 1:1 AcOEt/H_2O.

Experimental Section

Melting points were measured on an Electrothermal 1A8104 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Varian UNITY-400 spectrometer with tetramethylsilane as an internal standard in a solution of $CDCl_3$. FT-IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were recorded on a Hitachi M-8000 mass spectrometer (ESI).

GLC Analysis. (1) *Condition 1* to follow the oxidation of 1-octanol **1a** and 2-octanol **2a**: column, Reoplex 400 (15% Chemosorb AWCS, 2 m × 3 mm ϕ); carrier gas, He, 50 mL/min; injection temperature, 250 °C; column temperature, 120 °C (2 min) → 10 °C/min → 220 °C (8 min); detection, FID at 250 °C; octanoic acid **3a** was converted to the corresponding methyl ester by treatment with Me_3SiCHN_2[23] prior to the analysis: for detail, vide infra. (2) *Condition 2* to follow the oxidation of solketal (2,2-dimethyl-1,3-dioxolane-4-methanol) **1b**, cyclopentanol **4b**, benzhydrol **4c**: column, J & W Scientific DB-624 (30 m × 0.53 mm ϕ); carrier gas, He, 27 cm/s; injection temperature, 260 °C; column temperature, 130 °C (3 min) → 10 °C/min → 210 °C (4 min); detection, FID at 300 °C; 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid **3b** was converted to the corresponding methyl ester by treatment with Me_3SiCHN_2[23] prior to the analysis: for detail, vide infra. To do the analysis quantitatively under each condition, *n*-tridecane or *n*-nonane was used as an internal standard depending on the retention times shown by compounds being analyzed.

Procedures to Assess Effects of Organic Solvent Species and Acid Scavengers on the Oxidation of 1-Octanol (1a) to Octanoic Acid (3a) by the Quantitative GLC Analysis: Procedure 1. A solution of TCCA (700 mg, 3.01 mmol) in an organic solvent (3.00 mL; selected from Table 3) was added dropwise to a stirred mixture of 1-octanol **1a** (472 μL, d 0.827, 3.00 mmol), a base (9.00 mmol; selected from Table 1), $RuCl_3$ (0.10 M aqueous solution; 0.30 mL, 30.0 μmol), TBAB (0.10 M aqueous solution; 0.60 mL, 60.0 μmol), *n*-tridecane (365 μL, d 0.756, 1.50 mmol), and the same organic solvent as that used to dissolve TCCA (3.00 mL) with water-cooling below 40 °C. The mixture was stirred at 30 °C for 3 h. *i*-PrOH (2.0 mL) was added with water-cooling below 40 °C, and the stirring was continued at 30 °C for 30 min to destroy the unconsumed TCCA. A 6.0 M aqueous HCl solution was added at room temperature until the pH of the mixture became 4.0. AcOEt (10.0 mL) was added and the mixture was stirred at room temperature for 10 min. From the organic phase of the mixture was taken an aliquot (0.50 mL) to which was added MeOH (2 drops from a Pasteur pipet). To the mixture was added a 10% solution of Me_3SiCHN_2 in *n*-hexane (purchased from Tokyo Kasei) until the yellow color persisted. A 0.5 μL aliquot of the mixture was injected to a gas chromatograph running under condition 1: t_R 4.4 min for *n*-tridecane, 5.1 min for **2a**, 6.2 min for methyl octanoate, and 7.9 min for **1a**.

Procedures to Assess Effects of pH on the Oxidation of 1-Octanol (1a) to Octanoic Acid (3a) by the Quantitative GLC Analysis: Procedure 2. A solution of TCCA (700 mg, 3.01 mmol) in MeCN (3.00 mL) was added dropwise to a stirred mixture of 1-octanol **1a** (3.00 M solution in MeCN; 1.00 mL, 3.00 mmol), $RuCl_3$ (0.10 M aqueous solution; 0.30 mL, 30.0 μmol), TBAB (0.10 M aqueous solution; 0.60 mL, 60.0 μmol), *n*-tridecane (365 μL, d 0.756, 1.50 mmol), and a 1.0 M potassium phosphate buffer (10.0 mL; pH 5, 7, or 9; Table 2) with water-cooling below 40 °C. In the course of the addition, a 3.0 M aqueous K_2CO_3 solution was added to maintain the same pH as set initially. After the addition was completed, the mixture was stirred at 30 °C for 3 h. The reaction was worked up and analyzed quantitatively according to procedure 1.

Octanoic Acid (3a). To a stirred mixture of 1-octanol **1a** (390 mg, 2.99 mmol) and 1:1 MeCN/H_2O (6.0 mL) were added $RuCl_3 \cdot 3H_2O$ (7.80 mg, 30.0 μmol), TBAB (19.3 mg, 59.9 mmol), and K_2CO_3 (1.24 g, 9.00 mmol) at room temperature. A solution of TCCA (700 mg, 3.01 mmol) in MeCN (3.0 mL) was added dropwise during which the reaction temperature was maintained at 25−45 °C with water-cooling. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (150 μL, 1.97 mmol) was added, and the stirring was continued further for 1 h to destroy the unconsumed TCCA. The mixture was filtered through a short pad of Hyflo Super Cel to remove insoluble materials. To the filtrate was added 5% aqueous HCl solution to adjust its pH to 2.0. The layers were separated, and the aqueous layer was extracted with AcOEt (1.5 mL × 1). The combined organic layers were washed with saturated aqueous NaCl

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[22] While cinnamic alcohol **1d** was oxidized to cinnamaldehyde **2d** with its double bond being unaffected, some preliminary experimentation indicated that isolated double bonds were susceptible to the present oxidation conditions.

[23] Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

solution (2.0 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **3a** (410 mg) in 94.9% yield.

2,2-Dimethyl-1,3-dioxolane-4-carboxylic Acid (3b). Solketal **1b** was subjected to the same conditions as described for the oxidation of **1a** to **3a**. The reaction was worked up and analyzed quantitatively according to procedure 1 except that the GLC analysis was conducted under condition 2: GLC (condition 2) t_R 9.0 min for methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (96.2%; available from Aldrich in enantiomerically pure forms); 7.5 min for **1b** (0%); and 13.3 min for *n*-tridecane.

Procedures to Assess Effects of pH on the Oxidation of 2-Octanol (4a) to 2-Octanone (5a) by the Quantitative GLC Analysis: Procedure 3. 2-Octanol **4a** (391 mg, 3.00 mmol) was subjected to the same oxidation conditions as described for procedure 2. After the reaction mixture was stirred at 30 °C for 3 h, *i*-PrOH (2.0 mL) was added with water-cooling below 40 °C, and the stirring was continued at 30 °C for 30 min to destroy the unconsumed TCCA. AcOEt (10.0 mL) was added, and the mixture was stirred at room temperature for 10 min. A 0.5 μL aliquot of the organic phase was injected to a gas chromatograph running under condition 1: t_R 4.4 min for *n*-tridecane, 5.3 min for **5b**, and 6.4 min for **4a**.

2-Octanone (5a). 2-Octanol **4a** (390 mg, 2.99 mmol) was subjected to the same conditions as those described for the oxidation of **1a** to **3a**. The reaction was worked up and analyzed quantitatively according to procedure 3: t_R 4.4 min for *n*-tridecane, 5.3 min for **5b** (98.4%), and 6.4 min for **4a** (0%).

Cyclopentanone (5b). Cyclopentanol **4b** (860 mg, 9.98 mmol) in 1:1 AcOEt/H_2O (20.0 mL) containing *n*-nonane (640 mg, 4.99 mmol; 0.5 equiv; an internal standard) was treated with TCCA (0.67 M solution in ACOEt; 10.0 mL, 6.71 mmol; 0.67 equiv) otherwise under the same conditions as those described for the oxidation of **1a** to **3a**. The reaction was worked up and analyzed quantitatively according to procedure 3 except that the GLC analysis was conducted under condition 2: GLC (condition 2) t_R 8.8 min for **5b** (89.9%); 8.4 min for **4b** (0%); 10.4 min for *n*-nonane.

Benzophenone (5c). Benzhydrol **4c** (3.86 g, 20.0 mmol) was oxidized in the presence of *n*-tridecane (1.84 g, 10.0 mmol; 0.5 equiv) as an internal standard otherwise under the same conditions as those described for the oxidation of **4b** to **5b**: GLC (condition 2) t_R 6.8 min for **5c** (95.4%); 21.5 min for *n*- tridecane; 22.2 min for **4c** (0%).

Benzil (5d). To a stirred mixture of benzoin **4d** (4.25 g, 20.0 mmol), $RuCl_3 \cdot 3H_2O$ (52.3 mg, 0.20 mmol), TBAB (129 mg, 0.40 mmol), K_2CO_3 (8.29 g, 60.0 mmol), and 1:1 AcOEt/H_2O (40 mL) was added a solution of TCCA (3.09 g, 13.3 mmol) in AcOEt (20.0 mL) with water-cooling at 25−45 °C. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (1.00 mL, 13.1 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. Layers of the filtrate were separated, and the aqueous layer was extracted with AcOEt (10 mL × 1). The combined AcOEt layers were washed with saturated aqueous NaCl solution (10 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **5d** (3.27 g) in 77.7% yield: HPLC [column, YMC-Pack ODS AM-3024 (6 mm ϕ × 150 mm); elution, MeCN/H_2O (60:40), 1.0 mL/min; detection, UV at 254 nm] t_R 8.0 min for **5d** (98.7%); mp 96−98 °C; IR ν_{max} (KBr) 3317, 3064, 3029, 3007, 1660, 1594, 1577, 1450, 1325, 1211, 876, 795, 718, 696, 681, 642 cm^{-1}; ^1H NMR δ 7.99−7.96 (m, 4H), 7.67−7.63 (m, 2H), 7.53−7.49 (m, 4H); ^{13}C NMR δ 194.5, 134.8, 132.9, 129.8, 129.0.

Ketopantoyl Lactone (Dihydro-4,4-dimethyl-2,3-furandione) (5e).[20] To a stirred mixture of pantolactone **4e** [dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone; 2.60 g, 20.0 mmol], $RuCl_3 \cdot 3H_2O$ (52.3 mg, 0.20 mmol), TBAB (129 mg, 0.40 mmol), AcONa (8.20 g, 100 mmol), and 1:1 MeCN/H_2O (40 mL) was added a solution of TCCA (4.64 g, 20.0 mmol) in MeCN (20.0 mL) dropwise with water-cooling at 25−45 °C. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (1.00 mL, 13.1 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. Layers of the filtrate were separated. The aqueous layer was extracted with AcOEt (10 mL × 1). The combined organic layers were washed with saturated aqueous NaCl solution (10 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **5e** (2.50 g) in 97.7% yield: mp 68−70 °C (lit.:[20] 66−67.5 °C); IR ν_{max} (KBr) 3526, 2988, 2971, 2937, 1764, 1460, 1395, 1280, 1043, 1009, 991, 952, 940, 732 cm^{-1}; ^1H NMR δ 4.48 (s, 2H), 1.33 (s, 6H); ^{13}C NMR δ 198.1, 160.4, 77.0, 41.8, 22.0.

2,3:5,6-Di-*O*-isopropylidene-D-mannono-γ-lactone (5f).[21] To a stirred mixture of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **4f** (2.60 g, 9.99 mmol; available from Aldrich), $RuCl_3 \cdot 3H_2O$ (26.2 mg, 0.10 mmol), TBAB (64.4 mg, 0.20 mmol), AcONa (4.10 g, 50.0 mmol), and 1:1 MeCN/H_2O (20 mL) was added a solution of TCCA (2.32 g, 9.98 mmol) in MeCN (10.0 mL) dropwise with water-cooling at 25−45 °C. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (500 μL, 6.57 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. Layers of the filtrate were separated. The aqueous layer was extracted with AcOEt (5.0 mL × 1). The combined organic layers were washed with saturated aqueous NaCl solution (5.0 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **5f** (1.35 g) in 52.3% yield: mp 124−125 °C (lit.:[21] 116 °C); IR ν_{max} (KBr) 2991, 2939, 2893, 1784, 1382, 1259, 1216, 1153, 1121, 1084, 1042, 977, 856 cm^{-1}; ^1H NMR δ 4.90−4.84 (m, 2H), 4.44−4.37 (m, 2H), 4.15 (dd, $J = 5.6$ Hz, 9.2 Hz, 1H), 4.07 (dd, $J = 4.1$ Hz, 9.2 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 173.4, 114.4, 109.8, 78.1, 76.0, 75.8, 72.5, 66.4, 26.9, 26.7, 25.7, 25.1; MS *m/z* 281 $[(M + Na)^+]$.

Benzoic Acid (3c). To a stirred mixture of benzyl alcohol **1c** (2.16 g, 20.0 mmol), $RuCl_3 \cdot 3H_2O$ (52.3 mg, 0.20 mmol), TBAB (129 mg, 0.40 mmol), K_2CO_3 (8.29 g, 60.0 mmol), and 1:1 MeCN/H_2O (40.0 mL) was added a solution of TCCA (4.64 g, 20.0 mmol) in MeCN (20.0 mL) dropwise with heating at reflux. The mixture was stirred and heated at reflux for 1 h. The mixture was allowed to cool to room temperature. *i*-PrOH (1.00 mL, 13.1 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. To the filtrate was added 5% aqueous HCl solution to adjust its pH to 2.0. The layers were separated, and the aqueous layer was extracted with AcOEt (10 mL × 1). The combined organic layers were washed with saturated aqueous NaCl solution (10.0 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **3c** (2.29 g) in 93.9% yield: HPLC [column, YMC-Pack ODS AM-302 (4.6 mm ϕ × 150 mm); elution, $H_2O/MeCN/CF_3CO_2H$ (70:30:0.1), 1.0 mL/min; detection, UV at 254 nm] t_R 5.0 min for **3c** (99.9%).

Benzaldehyde (2c). To a stirred mixture of benzyl alcohol **1c** (2.16 g, 20.0 mmol), $RuCl_3 \cdot 3H_2O$ (52.3 mg, 0.20 mmol), TBAB (129 mg, 0.40 mmol), K_2CO_3 (8.29 g, 60.0 mmol), and 1:1 AcOEt/H_2O (40.0 mL) was added a solution of TCCA (3.09 g, 13.3 mmol) in AcOEt (20.0 mL) dropwise with water-cooling at 25−45 °C. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (1.00 mL, 13.1 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. Layers of the filtrate were separated, and the aqueous layer was extracted with AcOEt (10 mL × 1). The combined AcOEt layers were washed with saturated aqueous NaCl solution (10.0 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **2c** (1.84 g) in 86.8% yield: HPLC [column, YMC-Pack ODS AM-302 (4.6 mm ϕ × 150 mm); elution, $H_2O/MeCN/CF_3CO_2H$ (70:30:0.1), 1.0 mL/min; detection, UV at 254 nm] t_R 8.0 min for **2c** (99.6%).

Cinnamaldehyde (2d). To a stirred mixture of cynnamyl alcohol **1d** (2.68 g, 20.0 mmol), $RuCl_3 \cdot 3H_2O$ (52.3 mg, 0.20 mmol), TBAB (129 mg, 0.40 mmol), K_2CO_3 (8.29 g, 60.0 mmol), and 1:1 AcOEt/H_2O (40.0 mL) was added a solution of TCCA (3.09 g, 13.3 mmol) in AcOEt (20.0 mL) dropwise with water-cooling at 25−45 °C. The mixture was stirred at the same temperature range for 1 h. *i*-PrOH (1.00 mL, 13.1 mmol) was added with water-cooling below 45 °C, and the stirring was continued for 1 h to destroy the unconsumed TCCA. The mixture was filtered by the aid of Hyflo Super Cel to remove insoluble materials. Layers of the filtrate were separated, and the aqueous layer was extracted with AcOEt (10 mL × 1). The combined AcOEt layers were washed with saturated aqueous NaCl solution (10.0 mL × 2), dried ($MgSO_4$), and concentrated in vacuo to give **2d** (2.60 g) in 98.5% yield: HPLC [column, YMC-Pack ODS AM-302 (4.6 mm ϕ × 150 mm); elution, $H_2O/MeCN/CF_3CO_2H$ (70:30:0.1), 1.0 mL/min; detection, UV at 254 nm] t_R 12.0 min for **2d** (95.5%).

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