

The Oxidation of Alcohols in *N*-Oxyl-Immobilized Silica Gel/Aqueous NaOCl Disperse Systems. A Prominent Access to a Column-Flow System

Hideo Tanaka,* Jingyu Chou, Machiko Mine, and Manabu Kuroboshi

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima-naka 3-1-1, Okayama 700-8530

Received April 20, 2004; E-mail: tanaka95@cc.okayama-u.ac.jp

The oxidation of alcohols was performed successfully in a disperse system with *N*-oxyl-adsorbed or immobilized silica gel as a disperse phase and aqueous NaOCl as a disperse medium. In the disperse system, the oxidation of *sec*-alcohols afforded the corresponding ketones, while *prim*-alcohols were oxidized to aldehydes and/or carboxylic acids depending on their structures and reaction conditions. The *N*-oxyl-immobilized silica gel was recovered and repeatedly used without a significant change in the product yields. A column-flow system was also investigated for the oxidation of alcohols by use of a newly devised column packed with the *N*-oxyl-immobilized silica gel.

The oxidation of alcohols to carbonyl compounds is a fundamental reaction frequently encountered at all levels of organic synthesis.[1] There have been numerous reported methods and reagents for this conversion. Various kinds of oxidants, such as chromium reagents,[2] activated DMSO,[3] Dess–Martin periodinane,[4] manganese(IV) oxide,[5] ruthenium reagents,[6] organobismuth reagents,[7] and osmium(VIII) oxide,[8] have been used as stoichiometric oxidants. These reagents, however, are expensive and/or toxic, frequently producing troublesome wastes. To solve these problems, many combinations of metal catalysts, such as ruthenium,[9] copper,[10] chromium,[11] tungsten,[12] and palladium,[13] with cheap and/or environmentally friendly terminal oxidants, such as oxygen, hydrogen peroxide, hypochlorite, and bromate, have been developed.

On the other hand, stable organic nitroxyl radicals such as 2,2,6,6-tetramethylpiperidin-1-oxyl and its derivatives (*N*-oxyl) as metal-free catalysts have been used to mediate the mild and selective oxidation of alcohols in combination with the appropriate terminal oxidants.[14] Numerous terminal oxidants, such as sodium hypochlorite (NaOCl),[15] *m*-CPBA,[16] sodium bromite,[17] sodium chlorite,[18] *t*-butyl hypochlorite,[19] oxone,[20] NCS,[21] iodine compounds,[22] trichloroisocyanuric acid,[23] and combinations of oxygen with a high-valent metal co-catalyst[24] and hydrogen peroxide with methyltrioxorhenium,[25] have successfully been employed. The *N*-oxyl-mediated electro-oxidation of alcohols has also been investigated as an environmentally benign method.[26]

The *N*-oxyl-catalyzed oxidation of alcohols using NaOCl as a terminal oxidant was first reported by Anelli and co-workers, and has been widely used in organic synthesis.[15] The oxidation of *prim*- and *sec*-alcohols to the corresponding aldehydes and ketones was performed selectively in a two-phase system comprised of a CH_2Cl_2 solution of alcohols containing a catalytic amount of *N*-oxyl and an aqueous solution of NaOCl containing KBr as a co-catalyst with $NaHCO_3$ as a buffer, respectively. Actually, this catalytic process holds much promise for practical applications due to its high catalytic efficiency, mild reaction conditions, and pronounced selectivity.[27]

Anelli's protocol, however, has some disadvantages in a practical sense: (1) environmentally troublesome organic solvents, such as CH_2Cl_2, are mainly used, (2) the presence of a bromide salt is indispensable as a co-catalyst, which sometimes brings about contamination from undesired brominated by-products, (3) the workup process is not simple because the products are always contaminated with *N*-oxyl. To simplify the workup process and to use the *N*-oxyl compound repeatedly, several *N*-oxyl-immobilized solid materials such as polymer particles,[28] MCM-41,[29] and silica gel[30] have been synthesized and employed in Anelli's oxidation. The oxidation of alcohols mediated by thus far reported solid-supported *N*-oxyl compounds is always carried out in an aqueous NaOCl/organic solvent (CH_2Cl_2) two-phase system. These processes are not necessarily satisfactory in terms of environmental stress arising from the use of organic solvents. To avoid the use of troublesome organic solvents, the *N*-oxyl-catalyzed oxidation of alcohols in aqueous NaOCl free from organic solvents was reported, but limited to the oxidation of water-soluble carbohydrate derivatives.[31]

Recently, Bobbitt and co-workers reported that silica gel could significantly facilitate the oxidation of alcohols with a stoichiometric oxoammonium salt.[32] This finding promoted us to develop a newly devised disperse system with silica gel as a disperse phase and water as a disperse medium for the oxidation of alcohols. In a previous paper, we reported a silica gel/water disperse system for the *N*-oxyl-mediated electro-oxidation of alcohols without use of any organic solvent.[33] In our continuing work, we found that the *N*-oxyl-mediated oxidation of alcohols with aqueous NaOCl proceeded smoothly in a similar disperse system free from organic solvents and in the absence of a bromide salt. Herein, we describe that with *N*-oxyl-adsorbed or immobilized silica gel as a disperse phase, the oxidation of alcohols in aqueous NaOCl could be performed successfully without bromide salt. The *N*-oxyl-immobilized silica gel could be recovered and used repeatedly. A

Published on the web September 10, 2004; DOI 10.1246/bcsj.77.1745

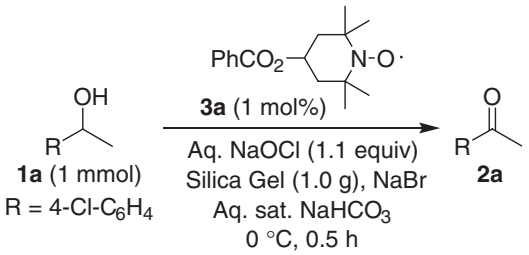
newly devised column-flow system for the oxidation of alcohols using the *N*-oxyl-immobilized silica gel is also described.

Results and Discussion

The Oxidation of Alcohols in an *N*-Oxyl-Adsorbed Silica Gel/Aqueous NaOCl Disperse System. The *N*-oxyl-catalyzed oxidation of alcohols was carried out in a silica gel/water disperse system free from organic solvents, in which *N*-oxyl-adsorbed silica gel was used as a disperse phase and an aqueous NaOCl solution containing NaBr and $NaHCO_3$ was used as a disperse medium. A typical procedure is as follows. A mixture of 1-(4-chlorophenyl)ethanol (**1a**, 1 mmol), 4-benzoyloxy-2,2,6,6-tetramethylpiperidin-1-oxyl (**3a**, 0.01 mmol), and silica gel (1.0 g) in aqueous NaOCl (0.22 M, 1.1 equiv) and aqueous saturated $NaHCO_3$ (2 mL) containing 10 mol% NaBr was stirred at 0 °C (ice bath) for 0.5 h. The mixture was filtered and the disperse phase (silica gel) was washed with acetone. The GC analysis of the washings showed the formation of the corresponding ketone **2a** in 92% yield. Only 1% yield of the ketone **2a** was obtained by extractive workup of the aqueous filtrate with ethyl acetate (Table 1, entry 1). It is interesting to note that no appreciable change of the product yield was observed even in the absence of a bromide salt and/or $NaHCO_3$ (entries 2–4). This fact is in sharp contrast to Anelli's protocol (CH_2Cl_2/aqueous NaOCl two-phase system), in which the reaction does not efficiently proceed in the absence of NaBr and/or $NaHCO_3$ (entries 7 and 8). The presence of a catalytic amount of *N*-oxyl compound **3a** was indispensable. Thus, only a 23% yield of the ketone **2a** was obtained (entry 5) without **3a**.

It is likely that substrate **1a**, product **2a**, and the *N*-oxyl compound **3a** are mainly adsorbed on the silica gel during the course of the oxidation. Indeed, most of **2a** and **3a** were obtained from the washings of the silica gel with acetone.

Table 1. *N*-Oxyl-Mediated Oxidation of Alcohol **1a** with Aqueous NaOCl



Entry	Media	NaBr	$NaHCO_3$	Yield	Recov.
		mol%	mL	%[a]	%[a]
1	SiO_2–H_2O[b]	10	2	93	3
2	SiO_2–H_2O[b]	10	—	90	—
3	SiO_2–H_2O[b]	—	2	88	11
4	SiO_2–H_2O[b]	—	—	96	—
5	SiO_2–H_2O[b,c]	—	—	23	73
6	CH_2Cl_2–H_2O[d]	10	2	89	11
7	CH_2Cl_2–H_2O[d]	—	2	37	62
8	CH_2Cl_2–H_2O[d]	—	—	<1	99

a) Yields were determined by GC. b) Disperse system with silica gel (1.0 g) as a disperse phase and aqueous solution (5–7 mL) as a disperse medium. c) Without **3a**. d) In a two-phase system comprising CH_2Cl_2 (2 mL) and aqueous solution (5–7 mL) (Anelli's protocol).

A plausible reaction mechanism is as follows: The oxidation of *N*-oxyl compound **3a** adsorbed on the silica gel with NaOCl would give the *N*-oxoammonium salt, which would, in turn, react with alcohol **1a** to give the corresponding ketone **2a** and hydroxylamine on the silica gel surface. It has been reported that in Anelli's procedure, the oxidation of the alcohol is very slow at the pH of commercial aqueous NaOCl (pH 12.7), while at pH 8.6 (buffered by $NaHCO_3$) the reaction proceeds smoothly, presumably because at pH 8.6, a significant amount of HOCl (pK_a 7.53) would be distributed between the aqueous and organic phases (Eq. 1).[15,34] The presence of NaBr is also effective for promotion of the oxidation presumably due to the formation of the more powerful oxidant HOBr (Eq. 2).[15,35] In contrast, in the silica gel/aqueous NaOCl disperse system, the oxidation of alcohol **1a** proceeded smoothly without $NaHCO_3$ and NaBr to afford the corresponding product **2a** in good yield. In this case, the oxidation of alcohol **1a** would take place at the interface between the silica gel and the aqueous phase, where NaOCl would partially react with the Si–OH moieties of the silica gel to give HOCl (Eq. 3). Thus, locally formed HOCl would react smoothly with the in situ generated hydroxyamine to afford the *N*-oxoammonium salt. The high concentration of HOCl, **3a**, and alcohol **1a** on the silica gel adsorption layer would facilitate each of the steps of the reaction.

$$NaOCl + NaHCO_3 \rightleftharpoons HOCl + Na_2CO_3 \quad (1)$$

$$HOCl + Br^- \rightleftharpoons HOBr + Cl^- \quad (2)$$

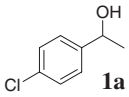
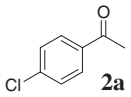
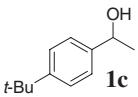
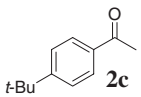
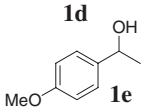
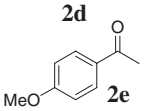
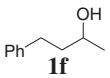
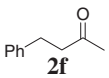
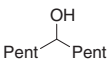
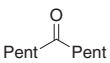
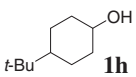
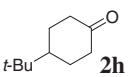
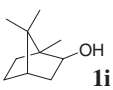
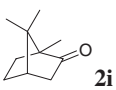
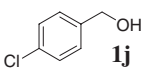
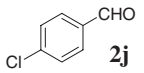
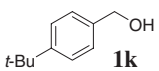
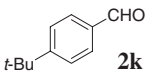
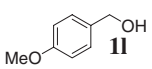
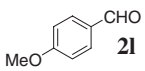
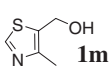
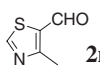
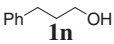
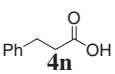
$$NaOCl + \text{—Si—OH} \rightleftharpoons HOCl + \text{—Si—ONa} \quad (3)$$

The newly devised silica gel/aqueous NaOCl disperse system was successfully applied to the oxidation of various alcohols (Table 2). The oxidation of benzylic *sec*-alcohols **1a**–**1d** proceeded smoothly to afford the corresponding ketones **2a**–**2d** in good yields (entries 1–4). The oxidation of 1-(4-methoxyphenyl)ethanol (**1e**) proceeded less effectively (entry 5), presumably due to the electron-donating nature of the *p*-methoxy moiety. An increase in the amounts of NaOCl (3.5 equiv) and the *N*-oxyl compound **3a** (5 mol%) resulted in the formation of the corresponding ketone **2e** in good yield (entry 6).

The oxidation of aliphatic *sec*-alcohols **1f**–**1i** proceeded less effectively. Thus, oxidation of **1f** under similar conditions to those described above afforded the corresponding ketone **2f** in 77% yield together with the recovered alcohol **1f** (10%) (entry 7). The yield of ketone **2f** increased to 93% by use of an excess amount of NaOCl (3.5 equiv) (entry 8). The oxidation of alcohols **1g**–**1i** similarly performed with 2.0–3.5 equiv of NaOCl for 12 h afforded the corresponding ketones **2g**–**2i** in 70–92% yields (entries 9–11).

The benzylic *prim*-alcohols **1j**–**1m** were selectively oxidized in the silica gel/aqueous NaOCl disperse system to give the corresponding aldehydes **2j**–**2m** in 65–92% yields (entries 12–15). The oxidation of 4-methoxybenzyl alcohol (**1l**) gave the corresponding aldehyde **2l** (66%) together with a small

Table 2. Oxidation of Alcohols in an *N*-Oxyl-Adsorbed Silica Gel/Aqueous NaOCl System

Entry	Substrate	*N*-Oxyl **3a** mol%	NaOCl equiv	Time h	Product	Yield %[a]	Recov. %[a]
1	 **1a**	1	1.1	0.5	 **2a**	91	—
2	 **1b**	1	1.1	0.5	 **2b**	82	—
3	 **1c**	1	1.1	0.5	 **2c**	82	—
4	 **1d**	1	2.0	0.5	 **2d**	84[b]	—
5	 **1e**	1	1.1	0.5	 **2e**	30[c]	18
6	**1e**	5	3.5	0.5	**2e**	84	—
7	 **1f**	1	1.1	0.5	 **2f**	77	10
8	**1f**	5	3.5	0.7	**2f**	93	1
9	 **1g**	5	2.0	12	 **2g**	71	27
10	 **1h**	5	2.0	12	 **2h**	92	—
11	 **1i**	5	3.5	12	 **2i**	70	6
12	 **1j**	1	2.0	0.5	 **2j**	92	—
13	 **1k**	1	1.1	0.5	 **2k**	88	1
14	 **1l**	5	1.1	0.5	 **2l**	66[d]	6
15	 **1m**	5	1.1	2	 **2m**	65[e]	5
16	 **1n**	1	1.1	0.5	 **4n**	45[f]	27
17	**1n**	1	3.5	0.5	**4n**	99	—
18	n-$C_{10}H_{21}CH_2OH$ **1o**	5	2.0	2	n-$C_{10}H_{21}C(O)OH$ **4o**	79[g]	—

a) Isolated yields. b) 2,2-Dichloro-1-indanone (**5**, 7%) was obtained. c) 1-(3-Chloro-4-methoxyphenyl)ethanol (**6**, 9%) and 1-(3-chloro-4-methoxyphenyl)-1-ethanone (**7**, 7%) were obtained. d) The corresponding carboxylic acid **4l** (6%) was obtained. e) Refs. 36 and 37. The corresponding carboxylic acid **4m** (11%) was formed. f) The corresponding aldehyde **2n** (12%) and $Ph(CH_2)_2C(O)O(CH_2)_3Ph$ (**8**, 2%) were formed. g) The corresponding aldehyde **2o** (4%) and $CH_3(CH_2)_9C(O)O(CH_2)_{10}CH_3$ (**9**, 2%) were formed.

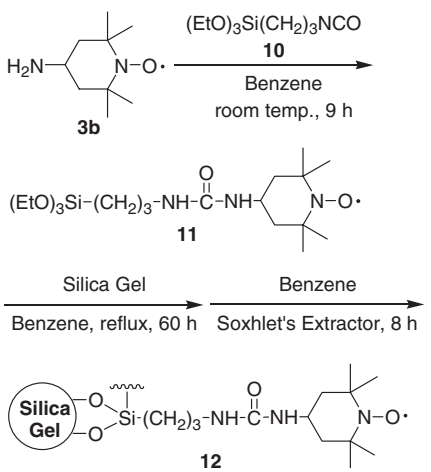
amount of the carboxylic acid **4l** (6%) and the recovered alcohol **1l** (6%) (entry 14). Although the yield of **2l** is not satisfactory, it is interesting to note that this result is much better than Anelli's procedure, in which only a 30% yield of the aldehyde **2l** was obtained (conversion: 62%).[15]

On the other hand, the oxidation of the aliphatic *prim*-alcohol **1n** gave a mixture of the corresponding carboxylic acid **4n** (45%) and aldehyde **2n** (12%) together with the recovered alcohol **1n** (27%) (entry 16). The carboxylic acid **4n** was obtained almost quantitatively when the reaction was carried out with 3.5 equiv of NaOCl (entry 17). 1-Undecanol (**1o**) was oxidized with 2.0 equiv of NaOCl to afford the corresponding carboxylic acid **4o** in 79% yield (entry 18). In Anelli's protocol, a phase transfer catalyst, e.g., Aliquat 336, is indispensable for obtaining carboxylic acids from the corresponding *prim*-alcohols. Otherwise, aldehydes are mainly formed.[15]

The Oxidation of Alcohols in an *N*-Oxyl-Immobilized Silica Gel/Aqueous NaOCl Disperse System. Although a catalytic amount of *N*-oxyl was enough to complete the oxidation of alcohols **1** in the silica gel/aqueous NaOCl disperse system, appropriate isolation and purification procedures were always needed to obtain the products **2** and to recover *N*-oxyl. In order to simplify the workup process as well as to use the *N*-oxyl compound repeatedly, *N*-oxyl-immobilized silica gel was prepared and used as a recyclable catalyst.

The preparation of *N*-oxyl-immobilized silica gel **12** was performed in the manner illustrated in Scheme 1. A mixture of commercially available 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl (**3b**, 10.0 mmol) and silylating reagent **10** (10.5 mmol) in benzene was stirred at room temperature for 9 h to afford the corresponding urea **11**. To this solution was added silica gel (10.0 g), and the whole mixture was heated to reflux for 60 h. Finally, the silica gel was rinsed with hot benzene using a Soxhlet's extractor for 8 h to give the *N*-oxyl-immobilized silica gel **12** as a pale orange solid. In the IR spectrum of **12**, characteristic bands at 2924, 2855 cm^{-1} (ν_{C-H}), and 1570 cm^{-1} ($\nu_{C=O}$) were observed, indicating that the *N*-oxyl moiety (0.64 mmol/g) was immobilized on the silica gel surface through a urea bond.[38]

The oxidation of alcohols **1** was carried out in a disperse



Scheme 1. Preparation of *N*-oxyl-immobilized silica gel **12**.

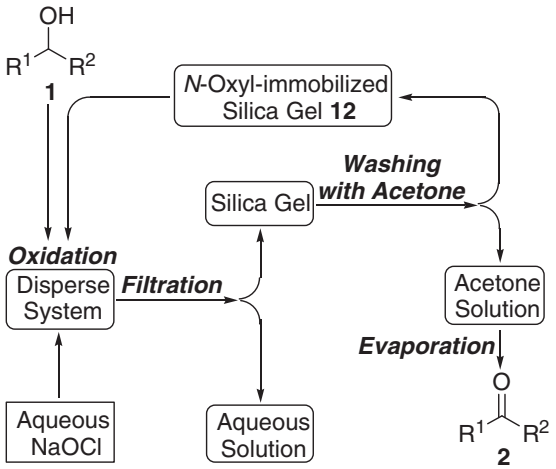


Fig. 1. Oxidation of alcohols in an *N*-oxyl-immobilized silica gel/aqueous NaOCl disperse system.

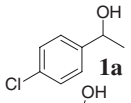
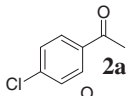
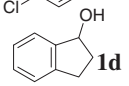
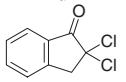
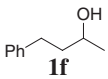
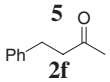
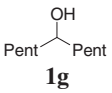
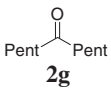
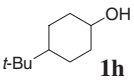
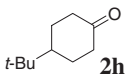
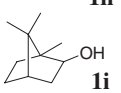
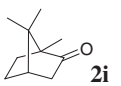
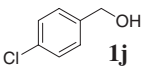
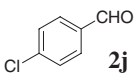
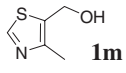
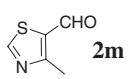
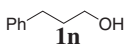
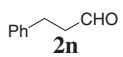
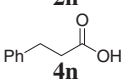
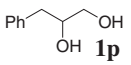
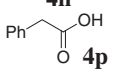
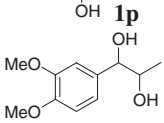
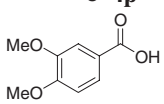
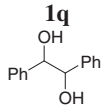
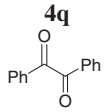
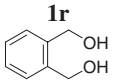
system with *N*-oxyl-immobilized silica gel **12** as a disperse phase and aqueous NaOCl as a disperse medium (Fig. 1). A typical procedure is as follows: A mixture of benzylic alcohol **1a** (0.5 mmol), **12** (0.5 g), and aqueous NaOCl (0.50 M, 1.1 mL, 1.1 equiv) was stirred at 0 °C for 0.5 h. The mixture was filtered, and the disperse phase (the silica gel **12**) was washed with acetone. The washings were concentrated to give the corresponding ketone **2a** as the sole product (>99% pure on GC analysis). Subsequent short-path chromatography (SiO_2, hexane/AcOEt = 5/1) afforded a 92% yield of **2a** (Table 3, entry 1).

The oxidation of 1-indanol (**1d**) with 2.0 equiv of NaOCl afforded a mixture of the corresponding ketone **2d** (37%) and 2,2-dichloro-1-indanone (**5**, 35%) (entry 2). Most likely, the high pH value (pH 12.7) in commercial aqueous NaOCl would facilitate the enolization of 1-indanone (**2d**), and as the result, the chlorination of the α-position of the ketone **2d** would take place competitively to afford **5**. When a buffer solution (aqueous $NaHCO_3$) was used, the oxidation of **1d** proceeded smoothly to give the corresponding ketone **2d** in a 95% yield (entry 3). 2,2-Dichloro-1-indanone (**5**) was mainly obtained (79%) when 1-indanol (**1d**) was treated with an excess amount of NaOCl (3.5 equiv) without $NaHCO_3$ for 12 h (entry 4).

The oxidation of the aliphatic *sec*-alcohol **1f** with an excess of NaOCl (2.0 equiv) for 2 h in a similar disperse system afforded the corresponding ketone **2f** in good yield (97%, entry 5). A longer reaction time for the oxidation of alcohols **1g**–**1i** was needed. The alcohols **1g**–**1i** were oxidized with 2.0 equiv of NaOCl for 12 h to afford the corresponding ketones **2g**–**2i** in 82, 87, and 76% yields, respectively (entries 6–8).

The oxidation of *prim*-alcohols **1j** and **1m** was performed in the *N*-oxyl-immobilized silica gel **12**/aqueous NaOCl disperse system to afford the corresponding aldehydes **2j** and **2m** in 89 and 72% yields, respectively (entries 9 and 10), whereas the oxidation of the aliphatic *prim*-alcohol **1n** in a similar disperse system afforded a mixture of the corresponding aldehyde **2n** (40%), carboxylic acid **4n** (14%), and recovered alcohol **1n** (23%) (entry 11). With an excess amount of NaOCl (3.5 equiv) in the oxidation of alcohol **1n**, the corresponding carboxylic acid **4n** (85%) was obtained selectively (entry 12).

Table 3. Oxidation of Alcohols in an *N*-Oxyl-Immobilized Silica Gel/Aqueous NaOCl Disperse System

Entry	Substrate	NaOCl equiv	Time h	Product	Yield %[a]	Recov. %[a]
1	 **1a**	1.1	0.5	 **2a**	92	—
2	 **1d**	2.0	0.5	 **2d**	37[b]	11
3[c]	**1d**	2.0	0.5	**2d**	95	—
4	**1d**	3.5	12	 **5**	79[d]	—
5	 **1f**	2.0	2	 **2f**	97	—
6	 **1g**	2.0	12	 **2g**	82	17
7	 **1h**	2.0	12	 **2h**	87	12
8	 **1i**	3.5	12	 **2i**	76	9
9	 **1j**	2.0	0.5	 **2j**	89	—
10	 **1m**	2.0	2	 **2m**	72[e]	2
11	 **1n**	1.1	0.5	 **2n**	40[f]	23
12	**1n**	3.5	0.5	 **4n**	85	—
13	 **1p**	4.5	0.5	 **4p**	75	—
14	 **1q**	6	0.5	 **4q**	81	—
15	 **1r**	4.5	6	 **2r**	83	7
16	 **1s**	4.5	0.5	 **2s**	80[g]	—

a) Isolated yields. b) 2,2-Dichloro-1-indanone (**5**, 35%) was obtained. c) Aqueous saturated $NaHCO_3$ (2 mL) was added. d) 1-Indanone (**2d**, 7%) was obtained. e) The corresponding carboxylic acid **4m** (15%) was obtained. f) The corresponding carboxylic acid **4n** (14%) was obtained. g) Phthalic acid (**4s**, 19%) was obtained.

Upon oxidation of 1,2-diols **1p** and **1q** in the *N*-oxyl-immobilized silica gel **12**/aqueous NaOCl disperse system, C–C bond cleavage occurred to afford the corresponding carboxylic acids **4p** and **4q**, respectively (entries 13 and 14), while oxidation of 1,2-diphenyl-1,2-ethanediol (**1r**) gave the corresponding diketone **2r** (83%) (entry 15).[39] Under similar conditions, the diol **1s** was oxidized to afford phthalide (**2s**, 80%) (entry 16).

Recycled Use of *N*-Oxyl-Immobilized Silica Gel. Next, the recycled use of the *N*-oxyl-immobilized silica gel **12** for the oxidation of alcohol **1a** was investigated. Thus, the oxidation of alcohol **1a** in the *N*-oxyl-immobilized silica gel/aque-

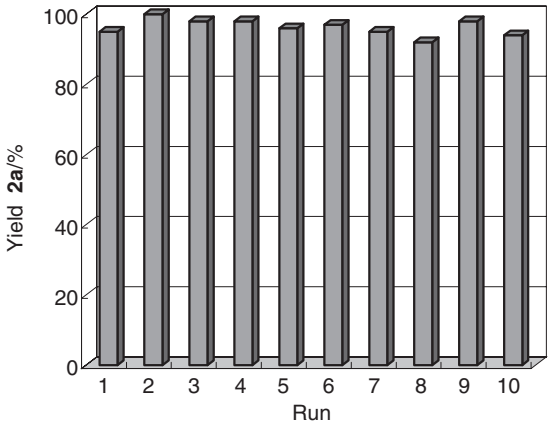


Fig. 2. Recycled use of the *N*-oxyl-immobilized silica gel **12**.

ous NaOCl disperse system was carried out in a similar manner to that described above. After 0.5 h, the disperse phase (silica gel) was separated by filtration and washed with acetone. The GC analysis of the washings showed the formation of the corresponding ketone **2a** in 95% yield. The recovered **12** was used again for the oxidation of **1a**. The same process as for the first run was repeated a total of 10 times. As shown in Fig. 2, the ketone **2a** was obtained in good yields even after 10 times recycled use of **12**, suggesting that the initial catalytic activity of the *N*-oxyl moiety on the silica gel remains intact throughout the recycled uses.

A Column-Flow System for the Oxidation of Alcohols. Reactions with a solid-supported catalyst or reagents have received significant interests in modern organic synthesis, which can be adapted to continuous-flow process, and, hence, used in automated synthesis.[40] The concept of employing solid-phase reagents packed into columns has recently been explored in academic chemistry.[41] The use of the reaction column greatly simplifies the purification of the crude reaction mixture, allowing for shorter production times and thus lower costs under certain circumstances.[41f]

The successful oxidation of alcohols in the *N*-oxyl-immobilized silica gel/aqueous NaOCl disperse system prompted us to investigate a column-flow system in which the *N*-oxyl-immobilized silica gel **12** was packed into the column equipped with a ceramic filter and a three-way cock at the bottom as illustrated in Fig. 3.

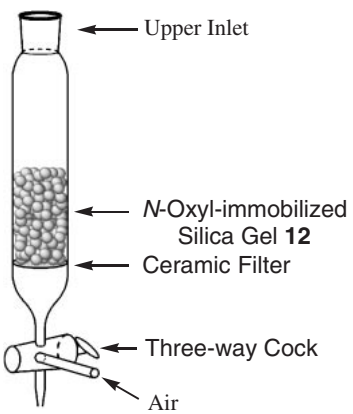


Fig. 3. A column-flow system for the oxidation of alcohols.

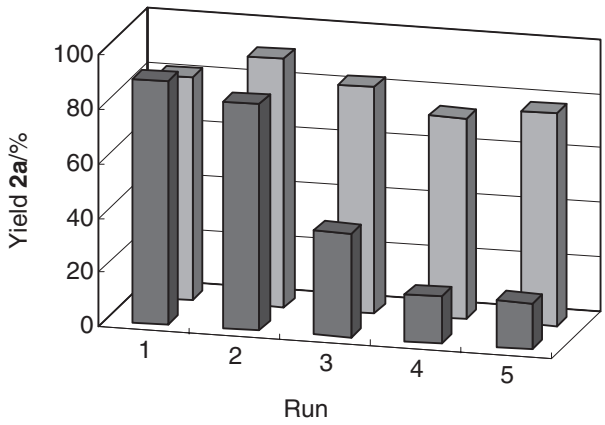


Fig. 4. Oxidation of alcohol **1a** in a column-flow system in the presence of $NaHCO_3$ (back) and in the absence of $NaHCO_3$ (front).

The oxidation of 1-(4-chlorophenyl)ethanol (**1a**) in the column-flow system was carried out as follows. Into a column packed with the *N*-oxyl-immobilized silica gel **12** (1.0 g) was poured a solution of alcohol **1a** (1.0 mmol) in acetone (2 mL). Most of the acetone was removed by passing air through the three-way cock into the column. A mixture of aqueous NaOCl (0.70 M, 5 mL) and aqueous saturated $NaHCO_3$ (2 mL) was passed through the column, and the eluate (aqueous solution) was repeatedly fed to the column for 1 h. Then, most of the aqueous solution was stripped out from the column by passing air from the upper inlet, and the silica gel column was rinsed with acetone. The acetone eluate was concentrated in vacuo and the residue was passed throw a short column to afford the corresponding ketone **2a** in 82% yield. The *N*-oxyl-immobilized silica gel **12** was dried by passing air from the three-way cock, and then alcohol **1a** was loaded again for the second run. The same process was repeated 5 times, affording good to moderate yields of the ketone **2a** in each of the runs (Fig. 4), indicating that **12** packed in the column would be reusable for the oxidation of alcohols.

The presence of $NaHCO_3$ in the aqueous NaOCl solution was indispensable. Thus, when the oxidation of **1a** was carried out in the absence of $NaHCO_3$, a remarkable change of the product yields was observed. The first and second runs afforded the corresponding ketone **2a** in good yields, but in the third run the yield of **2a** significantly decreased to 38%.

The aqueous eluate recovered from the column-flow system includes NaCl. Electro-oxidation of the recovered aqueous NaCl solution would regenerate the aqueous NaOCl solution.[42] Acetone used for loading of the substrates and elution of the products can be recovered and reused. Therefore, one can hope that the present column-flow system can be operated without consumption of any chemicals, thereby offering a formally closed system for the oxidation of alcohols (Fig. 5). Further investigations on the column-flow system are in progress.

Conclusion

Efficient and selective oxidation of alcohols **1** was achieved in a disperse system with an *N*-oxyl-adsorbed or -immobilized silica gel as a disperse phase and aqueous NaOCl as a disperse medium. The oxidation of **1** was performed without the use of

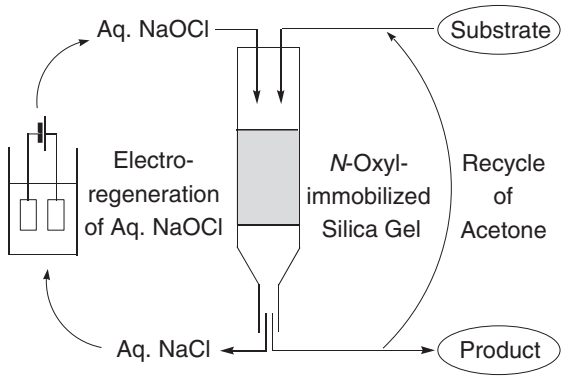


Fig. 5. Formally closed column-flow system.

troublesome organic solvents (CH_2Cl_2), bromide salts (NaBr), and/or a buffer solution ($NaHCO_3$) which are indispensable for Anelli's procedure. The *N*-oxyl-immobilized silica gel can be recovered and used repeatedly for the oxidation of alcohols. The oxidation of alcohol **1a** was performed successfully in the column packed with the *N*-oxyl-immobilized silica gel. Ketone **2a** was afforded in good yield by simple operations involving: (1) loading of the alcohol, (2) passing of aqueous NaOCl containing $NaHCO_3$, and (3) eluting with acetone. A formally closed system is achieved by recycled use of the *N*-oxyl-immobilized silica gel in combination with electrochemical regeneration of NaOCl.

Experimental

General Procedures. All melting points were measured on a Yanaco MP-J3 apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Gemini 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm related to TMS (^{1}H NMR) and the solvent signal (^{13}C NMR), respectively. IR spectra were recorded on a JASCO FT/IR VALOR-III spectrometer in wave number (cm^{-1}). Only major absorption bands were compiled. Gas chromatographic (GC) analysis was performed on a Yanaco G-6800 instrument with a FID using silica glass capillary column type methyl phenyl 5 (25 m, 0.25 μm) (carrier gas N_2 (26 mL/min); column 100 °C, injector 270 °C, detector 270 °C). GC yields were determined using acetophenone as an internal standard. Elemental analysis was executed on a Perkin-Elmer 2400 Series II CHNS/O analyzer. Commercially available reagents were used without further purification. The silica gel for the disperse phase and for the column chromatography was Merck Silica Gel 60 (40–63 μm).

The Oxidation of *sec*-Alcohols in an *N*-Oxyl-Adsorbed Silica Gel/Aqueous NaOCl Disperse System (Table 2, Entry 1). A mixture of 1-(4-chlorophenyl)ethanol (**1a**, 78 mg, 0.5 mmol), 4-benzoyloxy-2,2,6,6-tetramethylpiperidin-1-oxyl (**3a**, 1.4 mg, 0.005 mmol) and silica gel (0.5 g) in acetone (2 mL) was stirred for 10 min, and most of the solvent was evaporated under reduced pressure. To this residue was added an aqueous NaOCl (0.11 M, 5 mL, 0.55 mmol) at 0 °C in one portion, and the mixture was stirred at this temperature for 0.5 h. The disperse phase (silica gel) was separated by filtration and washed with acetone. The acetone washings were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/AcOEt = 5/1) to afford 1-(4-chlorophenyl)-1-ethanone (**2a**, 70 mg, 90%) as a colorless oil:[43] ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 128.8, 129.6, 135.3, 139.4, 196.6. IR (neat) 3062, 3005, 2965, 2928, 2854, 1687, 1590, 1572 cm^{-1}. The disperse medium (aqueous filtrate) was extracted with AcOEt. The extracts were dried (Na_2SO_4) and concentrated in vacuo. This residue was chromatographed (silica gel, hexane/AcOEt = 5/1) to afford **2a** (1 mg, 1%).

In a similar manner, the oxidation of alcohols **1b–1i** was carried out. The reaction conditions and results are compiled in Table 2, entries 2–11.

Acetophenone (2b).[43] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 7.42–7.57 (m, 3H), 7.98 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 128.1, 128.4, 132.9, 136.9, 197.8. IR (neat) 3062, 3006, 2980, 2939, 2862, 1686, 1599, 1583 cm^{-1}.

4′-*t*-Butylacetophenone (2c).[44] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.58 (s, 3H), 7.48 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 31.1, 35.1, 125.4, 128.2, 134.5, 156.7, 197.7. IR (neat) 3056, 2966, 2907, 2871, 1685, 1607, 1563 cm^{-1}.

1-Indanone (2d).[45] White solids; mp 38–40 °C (lit.[46] mp 38–40 °C). ^{1}H NMR ($CDCl_3$) δ 2.67–2.73 (m, 2H), 3.16 (t, J = 6.0 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 25.7, 36.2, 123.6, 126.5, 127.1, 134.4, 136.9, 155.0, 206.9. IR (KBr) 3072, 3034, 2926, 2861, 1713, 1611 cm^{-1}.

2,2-Dichloro-1-indanone (5).[47] Yellow solids; mp 71–73 °C. ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 50.1, 81.5, 126.1, 126.5, 128.9, 130.2, 137.0, 147.1, 191.7. IR (KBr) 3087, 2922, 2864, 1747, 1734, 1713, 1605, 1584 cm^{-1}.

1-(4-Methoxyphenyl)-1-ethanone (2e).[43] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 3.87 (s, 3H), 6.94 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.3, 55.4, 113.6, 130.3, 130.5, 163.4, 196.7. IR (neat) 3076, 3006, 2966, 2938, 2841, 1675, 1602, 1577, 1510 cm^{-1}.

1-(3-Chloro-4-methoxyphenyl)-1-ethanol (6).[48] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.47 (d, J = 6.4 Hz, 3H), 1.84 (br s, 1H), 3.90 (s, 3H), 4.84 (q, J = 6.4 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 1.8, 8.6 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 25.2, 56.2, 69.4, 111.9, 122.3, 124.7, 127.4, 138.9, 154.1. IR (neat) 3650–3100 (br), 3363, 2973, 2930, 2840, 1607, 1505 cm^{-1}.

1-(3-Chloro-4-methoxyphenyl)-1-ethanone (7).[49] White solids. ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 3.98 (s, 3H), 6.98 (d, J = 8.6 Hz, 1H), 7.88 (dd, J = 2.0, 8.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 56.4, 111.2, 122.7, 128.7, 130.6, 135.8, 158.6, 195.6. IR (KBr) 3067, 2923, 2852, 1674, 1597, 1562, 1500 cm^{-1}.

4-Phenyl-2-butanone (2f).[50] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.77 (t, J = 7.5 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 7.16–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 29.6, 29.9, 45.0, 126.0, 128.2, 128.4, 140.9, 207.8. IR (neat) 3061, 3029, 2927, 1718, 1604, 1497 cm^{-1}.

6-Undecanone (2g).[51] A colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 6H), 1.16–1.42 (m, 8H), 1.50–1.66 (m, 4H), 2.39 (t, J = 7.4 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 23.6, 31.5, 42.8, 211.7. IR (neat) 2957, 2933, 2873, 2862, 1717, 1467, 1411, 1377, 1133 cm^{-1}.

4-*t*-Butylcyclohexanone (2h).[52] White solids; mp 46–48 °C (lit.[52] mp 47–49 °C). ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9H), 1.39–1.51 (m, 3H), 2.05–2.18 (m, 2H), 2.23–2.44 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 27.6, 32.5, 41.3, 46.7, 212.6. IR (KBr) 2964, 2945,

2875, 1729, 1473, 1366, 1224, 1162 cm^{-1}.

(−)-Camphor (2i).[53] White solids; mp 175–178 °C (lit.[53] mp 176.9–177.5 °C). ^1H NMR ($CDCl_3$) δ 0.84 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.27–1.47 (m, 2H), 1.59–1.76 (m, 1H), 1.84 (d, J = 18.2 Hz, 1H), 1.91–2.02 (m, 1H), 2.09 (t, J = 4.4 Hz, 1H), 2.29–2.42 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 9.28, 19.2, 19.8, 27.1, 29.9, 43.0, 43.3, 46.8, 57.7, 219.7. IR (KBr) 3440, 2960, 2877, 1744, 1455, 1417, 1386, 1045, 1023 cm^{-1}.

The Oxidation of *prim*-Alcohols in an *N*-Oxyl-Adsorbed Silica Gel/Aqueous NaOCl Disperse System (Table 2, Entry 12). A mixture of 4-chlorobenzyl alcohol (**1j**, 71 mg, 0.5 mmol), 4-benzoyloxy-2,2,6,6-tetramethylpiperidin-1-oxyl (**3a**, 1.4 mg, 0.005 mmol), and silica gel (0.5 g) in acetone (2 mL) was stirred for 10 min, and most of the solvent was evaporated under reduced pressure. To the residue was added an aqueous NaOCl (0.25 M, 4 mL, 1.0 mmol) at 0 °C in one portion, and the mixture was stirred at this temperature for 0.5 h. The disperse phase (silica gel) was separated by filtration and washed with acetone. The aqueous filtrate (disperse medium) was extracted with AcOEt. The extracts and the washings were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/AcOEt = 3/1) to afford 4-chlorobenzaldehyde (**2j**, 65 mg, 92%) as white solids:[54] mp 46–47 °C (lit.[54] mp 48 °C). ^1H NMR ($CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 9.99 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 129.4, 130.8, 134.6, 140.9, 190.7. IR (KBr) 3092, 2927, 2861, 2766, 1699, 1590, 1576 cm^{-1}. The aqueous solution was acidified with 5% aq. HCl (4 mL) and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford no appreciable amount of the corresponding carboxylic acid **4j**.

In a similar manner, the oxidation of alcohols **1k**–**1o** was carried out. The reaction conditions and results are listed in Table 2, entries 13–18.

4-*t*-Butylbenzaldehyde (2k).[55] A colorless oil. ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H), 7.55 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 9.98 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 31.1, 35.4, 125.9, 129.6, 134.0, 158.4, 191.9. IR (neat) 3052, 2969, 1686, 1611, 1570 cm^{-1}.

4-Methoxybenzaldehyde (2l).[56] A colorless oil. ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 9.88 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 55.5, 114.2, 129.8, 131.8, 164.5, 190.6. IR (neat) 3077, 3010, 2938, 2841, 2740, 1683, 1601, 1578, 1511 cm^{-1}.

4-Methoxybenzoic Acid (4l).[57] White solids; mp 185–186 °C (lit.[57] mp 184–185 °C). ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.5, 113.7, 121.6, 132.3, 164.0, 171.4. IR (KBr) 3650–2150 (br), 3028, 2985, 2925, 2851, 1687, 1604, 1578, 1517 cm^{-1}.

4-Methyl-5-thiazolecarboxaldehyde (2m).[36d] White solids; mp 73.5–75 °C (lit.[36d] mp 74 °C). ^1H NMR ($CDCl_3$) δ 2.80 (s, 3H), 8.99 (s, 1H), 10.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.1, 132.6, 158.6, 161.6, 182.1. IR (KBr) 3094, 2966, 2925, 2872, 1661, 1522 cm^{-1}.

4-Methyl-5-thiazolecarboxylic Acid (4m).[58] White solids; mp 235–241 °C (lit.[59] mp 255 °C). ^1H NMR (CD_3OD) δ 2.72 (s, 3H), 8.98 (s, 1H). ^{13}C NMR (CD_3OD) δ 17.0, 99.0, 157.5, 160.5, 164.4. IR (KBr) 3093, 1707, 1545, 1317, 1274 cm^{-1}.

3-Phenylpropanal (2n).[60] A colorless oil. ^1H NMR ($CDCl_3$) δ 2.78 (t, J = 7.4 Hz, 2H), 2.96 (t, J = 7.4 Hz, 2H), 7.12–7.44 (m, 5H), 9.82 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.1, 45.3, 126.2, 128.2, 128.5, 140.2, 201.4. IR (neat) 3063, 3029, 2928, 2725, 1725, 1604, 1497 cm^{-1}.

3-Phenylpropanoic Acid (4n).[61] White solids; mp 46.5–47.5 °C (lit.[62] mp 49 °C). ^1H NMR ($CDCl_3$) δ 2.69 (t, J = 8.0 Hz, 2H), 2.97 (t, J = 8.0 Hz, 2H), 7.17–7.34 (m, 5H), 9.0 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 30.6, 35.6, 126.3, 128.2, 128.5, 140.1, 178.5. IR (KBr) 3700–2200 (br), 3027, 2935, 1711, 1696, 1605, 1574, 1495 cm^{-1}.

3-Phenylpropyl 3-Phenylpropanoate (8).[63] A colorless oil. ^1H NMR ($CDCl_3$) δ 1.93 (quint, J = 6.5 Hz, 2H), 2.63 (t, J = 7.8 Hz, 4H), 2.96 (t, J = 7.8 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H), 7.13–7.33 (m, 10H). ^{13}C NMR δ 30.2, 31.0, 32.2, 35.9, 63.8, 125.9, 126.2, 128.2, 128.3, 128.4, 140.4, 141.1, 172.8. IR (neat) 3063, 3028, 2954, 2929, 2859, 1735, 1604, 1497 cm^{-1}.

Undecanal (2o).[17] A colorless oil. ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.26 (br s, 14H), 1.56–1.70 (m, 2H), 2.42 (dt, J = 1.8, 7.3 Hz, 2H), 9.77 (t, J = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.2, 22.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 43.9, 202.9. IR (neat) 2956, 2929, 2856, 2714, 1732, 1173, 722 cm^{-1}.

Undecanoic Acid (4o).[17] White solids; mp 26–28 °C (lit.[17] mp 28 °C). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.26 (br s, 14H), 1.56–1.70 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 10.5 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 24.7, 29.1, 29.2, 29.3, 29.5, 29.6, 31.9, 34.0, 179.8. IR (KBr) 3570–2330 (br), 2923, 2852, 1697, 1468, 1435, 1411, 1288, 932 cm^{-1}.

Undecyl Undecanoate (9).[17] A colorless oil. ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 6H), 1.26 (br s, 30H), 1.56–1.70 (m, 4H), 2.29 (t, J = 7.3 Hz, 2H), 4.06 (t, J = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 25.1, 26.0, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 34.4, 64.4, 174.0. IR (neat) 2926, 2856, 1739, 1467, 1241, 1172, 722 cm^{-1}.

Preparation of *N*-Oxyl-Immobilized Silica Gel 12. To a solution of 3-(triethoxysilyl)propyl isocyanate (**10**, 2.60 g, 10.5 mmol) in benzene (20 mL) was added a solution of 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl (**3b**, 1.71 g, 10.0 mmol) in benzene (15 mL), dropwise, at room temperature, and the resulting mixture was stirred at room temperature for 9 h to give a benzene solution of the corresponding urea compound **11**. To the solution were added silica gel (10.0 g) and additional benzene (15 mL), and the mixture was heated to reflux for 60 h without stirring. The resulting solids were separated by filtration and rinsed with hot benzene using a Soxhlet's extractor for 8 h. The residual solids were dried under reduced pressure to afford *N*-oxyl-immobilized silica gel **12** (12.8 g) as pale orange solids: IR (KBr) 3420, 2924, 2855, 1636, 1570 cm^{-1}. The content of the immobilized *N*-oxyl moiety was estimated at 0.64 mmol/g by elemental analysis: Found: C, 11.37; H, 1.86; N, 2.74%. Anal. Calcd for 0.64 mmol/g *N*-oxyl-immobilized silica gel **12**: C, 11.53; H, 1.94; N, 2.69%.

The Oxidation of Alcohols in an *N*-Oxyl-Immobilized Silica Gel/Aqueous NaOCl Disperse System (Table 3, Entry 1). A mixture of 1-(4-chlorophenyl)ethanol (**1a**, 78 mg, 0.5 mmol) and *N*-oxyl-immobilized silica gel **12** (0.5 g, 0.32 mmol *N*-oxyl) in acetone (2 mL) was stirred for 10 min, and most of the solvent was evaporated under reduced pressure. To the residue was added aqueous NaOCl (0.11 M, 5.0 mL, 0.55 mmol) at 0 °C in one portion, and the reaction mixture was stirred at this temperature for 0.5 h. The disperse phase (silica gel) was separated by filtration and washed with AcOEt. The washings were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/AcOEt = 5/1) to afford 1-(4-chlorophenyl)-1-ethanone (**2a**, 71.0 mg, 91%) as a colorless oil. The disperse medium (aqueous filtrate) was extracted with AcOEt. The extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/AcOEt = 5/1) to

afford **2a** (1 mg, 1%).

In a similar manner, the oxidation of alcohols **1d**, **1f**–**1j**, **1m**, **1n**, and **1p**–**1s** was carried out in *N*-oxyl-immobilized silica gel **12**/aqueous NaOCl disperse system. The conditions and results are summarized in Table 3. For the oxidation of *prim*-alcohols **1j**, **1m**, and **1n** and diols **1p**–**1s**, after the extractive workup, the aqueous layer was acidified with 5% aq. HCl (4 mL), extracted with AcOEt, dried (Na_2SO_4), and concentrated in vacuo to afford the corresponding carboxylic acids **4j**, **4m**, **4n**, and **4p**–**4s**.

Phenylacetic Acid (4p).[64] White solids; mp 73.5–75 °C (lit.[64] mp 75–77 °C). ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2H), 7.24–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 41.0, 127.3, 128.6, 129.3, 133.2, 177.3. IR (KBr) 3450–2430 (br), 3034, 1703, 1604, 1500 cm^{-1}.

3,4-Dimethoxybenzoic Acid (4q).[65] White solids; mp 176–178 °C (lit.[66] mp 180–181 °C). ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 3.96 (s, 3H), 6.93 (d, $J = 8.6$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.78 (dd, $J = 2.0$, 8.6 Hz, 1H), 9.90 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 55.97, 56.04, 110.2, 112.2, 121.6, 124.5, 148.6, 153.6, 171.9. IR (KBr) 3660–2300 (br), 3005, 2936, 2839, 1680, 1601, 1590 cm^{-1}.

Benzil (2r).[10c] Yellow solids; mp 93.5–95 °C (lit.[67] mp 95–96 °C). ^{1}H NMR ($CDCl_3$) δ 7.47–7.56 (m, 4H), 7.62–7.71 (m, 2H), 7.96–8.02 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 129.0, 129.9, 133.0, 134.8, 194.5. IR (KBr) 3065, 1660, 1594, 1580 cm^{-1}.

Phthalide (2s).[68] White solids; mp 70.5–72.5 °C (lit.[69] mp 69.5–71 °C). ^{1}H NMR ($CDCl_3$) δ 5.34 (s, 2H), 7.49–7.58 (m, 2H), 7.66–7.74 (m, 1H), 7.91–7.95 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 69.6, 122.0, 125.6, 125.7, 129.0, 133.9, 146.4, 171.0. IR (KBr) 3021, 2929, 2865, 1756, 1616, 1596 cm^{-1}.

Phthalic Acid (4s).[70] White solids; mp 202–205 °C (lit.[70] mp 208–209 °C). ^{1}H NMR (CD_3OD) δ 7.40–7.62 (m, 2H), 7.70–7.77 (m, 2H). ^{13}C NMR (CD_3OD) δ 129.7, 131.8, 133.8, 171.1. IR (KBr) 3600–2500 (br), 3077, 3012, 2896, 1695, 1587, 1498 cm^{-1}.

The Recycled Use of *N*-Oxyl-Immobilized Silica Gel. The oxidation of 1-(4-chlorophenyl)ethanol (**1a**, 78 mg, 0.5 mmol) in the *N*-oxyl-immobilized silica gel **12** (0.5 g, 0.32 mmol *N*-oxyl)/aqueous NaOCl (0.11 M, 5.0 mL) disperse system was carried out in a similar manner to that described above. After 0.5 h, the disperse phase (silica gel) was separated by filtration and washed with acetone. The GC analysis of the washings showed the formation of 1-(4-chlorophenyl)-1-ethanone (**2a**) in 95% yield. The recovered *N*-oxyl-immobilized silica gel **12** was dried and reused for the oxidation of **1a**, and the same process as for the first run was repeated 10 times. The results are shown in Fig. 2.

The Oxidation of Alcohol 1a in a Column-Flow System. Reactions were carried out in a glass column ($\Phi = 21$ mm) equipped with a ceramic filter (G3) and a three-way cock at the bottom (Fig. 3). Into the column packed with the *N*-oxyl-immobilized silica gel **12** (1.0 g, 0.64 mmol *N*-oxyl), a solution of 1-(4-chlorophenyl)ethanol (**1a**, 157 mg, 1.0 mmol) in acetone (2 mL) was poured, and most of the solvent was removed by passing air through the three-way cock into the column. A mixed solution of aqueous NaOCl (0.70 M, 5.0 mL, 3.5 mmol) and aqueous saturated $NaHCO_3$ (2 mL) was passed through the column, and the eluate was repeatedly fed onto the column at room temperature for 1 h. Then, most of the aqueous solution was stripped out from the column by passing air from the upper inlet of the column, and the *N*-oxyl-immobilized silica gel **12** was rinsed with acetone. The acetone washings were dried and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/AcOEt = 5/1) to afford 1-(4-chlorophenyl)-1-ethanone (**2a**, 126.9 mg, 82%) together with the recovered **1a** (8.0 mg, 5%). The *N*-oxyl-immobilized silica gel **12** was dried by passing air through the three-way cock and reused for the second run. The same process as for the first run was repeated 5 times. The results are shown in the back column of Fig. 4. A similar process was carried out in the absence of aqueous saturated $NaHCO_3$. The results are shown in the front column of Fig. 4.

References

1 "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 7.

2 a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York (1967), Vol. 1, pp. 142–147, 1059–1064. b) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953). c) W. M. Coates and J. R. Corrigan, *Chem. Ind. (London)*, **1969**, 1594. d) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, **16**, 2647 (1975). For a review, see: e) G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, **1982**, 245.

3 For a review, see: A. J. Mancuso and D. Swern, *Synthesis*, **1981**, 165.

4 a) D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983). b) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, **113**, 7277 (1991).

5 a) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954). b) M. Brink, *Synthesis*, **1975**, 253. For a review, see: c) A. J. Fatiadi, *Synthesis*, **1976**, 65; **1976**, 133.

6 a) L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958). b) H. Tomioka, K. Takai, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **22**, 1605 (1981).

7 D. H. R. Barton, J. P. Kitchin, D. J. Lester, W. B. Motherwell, and M. T. B. Papoula, *Tetrahedron, Suppl.*, **37**, 73 (1981).

8 A. M. Maione and A. Romeo, *Synthesis*, **1984**, 955.

9 a) W. P. Griffith, S. V. Ley, G. P. Whitcombe, and A. D. White, *J. Chem. Soc., Chem. Commun.*, **1987**, 1625. b) S. Giddings and A. Mills, *J. Org. Chem.*, **53**, 1103 (1988). For a review, see: c) S. V. Ley, J. Norman, W. P. Griffith, and S. P. Marsden, *Synthesis*, **1994**, 639. d) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C. J. Urch, and S. M. Brown, *J. Am. Chem. Soc.*, **119**, 12661 (1997).

10 a) I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown, and C. J. Urch, *Science*, **274**, 2044 (1996). b) I. E. Markó, A. Gautier, I. Chellé-Regnaut, P. R. Giles, M. Tsukazaki, C. J. Urch, and S. M. Brown, *J. Org. Chem.*, **63**, 7576 (1998). c) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, A. Gautier, S. M. Brown, and C. J. Urch, *J. Org. Chem.*, **64**, 2433 (1999).

11 M. Zhao, J. Li, Z. Song, R. Desmond, D. M. Tschaen, E. J. J. Grabowski, and P. J. Reider, *Tetrahedron Lett.*, **39**, 5323 (1998).

12 a) K. Sato, M. Aoki, J. Takagi, and R. Noyori, *J. Am. Chem. Soc.*, **119**, 12386 (1997). b) K. Sato, M. Aoki, and R. Noyori, *Science*, **281**, 1646 (1998).

13 a) T. Nishimura, T. Onoue, K. Ohe, and S. Uemura, *Tetrahedron Lett.*, **39**, 6011 (1998). b) G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Science*, **287**, 1636 (2000). c) G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Adv. Synth. Catal.*, **344**, 355 (2002). d) K. Mori, K. Yamaguchi, T. Hara, T. Mizugaki, K. Ebitani, and K. Kaneda, *J. Am. Chem. Soc.*, **124**, 11572 (2002). e) Y. Uozumi and R. Nakao, *Angew. Chem., Int. Ed.*, **42**, 194 (2003). f) S. K. Mandal, D. R. Jensen, J. S. Pugsley, and M. S. Sigman, *J. Org. Chem.*, **68**, 4600 (2003).

14 For reviews, see: a) J. M. Bobbitt and M. C. L. Flores,

Heterocycles, **27**, 509 (1988). b) A. E. J. de Nooy, A. C. Besemer, and H. van Bekkum, *Synthesis*, **1996**, 1153.

15 a) P. L. Anelli, C. Biffi, F. Montanari, and S. Quici, *J. Org. Chem.*, **52**, 2559 (1987). b) P. L. Anelli, S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **54**, 2970 (1989). c) P. L. Anelli, F. Montanari, and S. Quici, *Org. Synth.*, **69**, 212 (1990).

16 a) B. Ganem, *J. Org. Chem.*, **40**, 1998 (1975). b) J. A. Cella, J. A. Kelley, and E. F. Kenehan, *J. Org. Chem.*, **40**, 1860 (1975). c) S. D. Rychnovsky and R. Vaidyanathan, *J. Org. Chem.*, **64**, 310 (1999).

17 T. Inokuchi, S. Matsumoto, T. Nishiyama, and S. Torii, *J. Org. Chem.*, **55**, 462 (1990).

18 a) M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, and P. J. Reider, *J. Org. Chem.*, **64**, 2564 (1999). b) J. E. Dettwiler and W. D. Lubell, *J. Org. Chem.*, **68**, 177 (2003).

19 F. Melvin, A. McNeill, P. J. F. Henderson, and R. B. Herbert, *Tetrahedron Lett.*, **40**, 1201 (1999).

20 C. Bolm, A. S. Magnus, and J. P. Hildebrand, *Org. Lett.*, **2**, 1173 (2000).

21 J. Einhorn, C. Einhorn, F. Ratajczak, and J.-L. Pierre, *J. Org. Chem.*, **61**, 7452 (1996).

22 a) A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, and G. Piancatelli, *J. Org. Chem.*, **62**, 6974 (1997). b) S. S. Kim and K. Nehru, *Synlett*, **2002**, 616. c) K. Sakuratani and H. Togo, *Synthesis*, **2003**, 21.

23 a) L. De Luca, G. Giacomelli, and A. Porcheddu, *Org. Lett.*, **3**, 3041 (2001). b) L. De Luca, G. Giacomelli, S. Masala, and A. Porcheddu, *J. Org. Chem.*, **68**, 4999 (2003).

24 a) M. F. Semmelhack, C. R. Schmid, D. A. Cortés, and C. S. Chou, *J. Am. Chem. Soc.*, **106**, 3374 (1984). b) A. Dijksman, I. W. C. E. Arends, and R. A. Sheldon, *Chem. Commun.*, **1999**, 1591. c) A. Dijksman, A. Marino-González, A. M. i Payeras, I. W. C. E. Arends, and R. A. Sheldon, *J. Am. Chem. Soc.*, **123**, 6826 (2001). d) I. A. Ansari and R. Gree, *Org. Lett.*, **4**, 1507 (2002).

25 W. A. Herrmann, J. P. Zoller, and R. W. Fischer, *J. Organomet. Chem.*, **579**, 404 (1999).

26 a) M. F. Semmelhack, C. S. Chou, and D. A. Cortés, *J. Am. Chem. Soc.*, **105**, 4492 (1983). b) M. F. Semmelhack, C. R. Schmid, and D. A. Cortés, *Tetrahedron Lett.*, **27**, 1119 (1986). c) T. Inokuchi, S. Matsumoto, and S. Torii, *J. Org. Chem.*, **56**, 2416 (1991). d) Y. Kashiwagi, F. Kurashima, C. Kikuchi, J. Anzai, T. Osa, and J. M. Bobbitt, *Chem. Commun.*, **1999**, 1983. e) Y. Kashiwagi, F. Kurashima, C. Kikuchi, J. Anzai, T. Osa, and J. M. Bobbitt, *Tetrahedron Lett.*, **40**, 6469 (1999). f) K. Schnatbaum and H. J. Schäfer, *Synthesis*, **1999**, 864.

27 a) R. Siedlecka, J. Skarżewski, and J. Młochowski, *Tetrahedron Lett.*, **31**, 2177 (1990). b) M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett.*, **33**, 5029 (1992). c) C. Palomo, I. Ganboa, B. Odriozola, and A. Linden, *Tetrahedron Lett.*, **38**, 3093 (1997). d) W. Adam, C. R. Saha-Möller, and P. A. Ganeshpure, *Chem. Rev.*, **101**, 3499 (2001). e) M. Bouktaib, A. Atmani, and C. Rolando, *Tetrahedron Lett.*, **43**, 6263 (2002).

28 a) A. Dijksman, I. W. C. E. Arends, and R. A. Sheldon, *Chem. Commun.*, **2000**, 271. b) T. Siu, S. Yekta, and A. K. Yudin, *J. Am. Chem. Soc.*, **122**, 11787 (2000). c) C. Tanyeli and A. Gümüş, *Tetrahedron Lett.*, **44**, 1639 (2003).

29 M. J. Verhoef, J. A. Peters, and H. van Bekkum, *Stud. Surf. Sci. Catal.*, **125**, 465 (1999).

30 a) C. Bolm and T. Fey, *Chem. Commun.*, **1999**, 1795. b) T. Fey, H. Fischer, S. Bachmann, K. Albert, and C. Bolm, *J. Org. Chem.*, **66**, 8154 (2001).

31 a) A. E. J. de Nooy, A. C. Besemer, and H. van Bekkum, *Tetrahedron*, **51**, 8023 (1995). b) A. Heeres, H. A. van Doren, K. F. Gotlieb, and I. P. Bleeker, *Carbohydr. Res.*, **299**, 221 (1997). c) A. Medgyes, E. Farkas, A. Lipták, and V. Pozsgay, *Tetrahedron*, **53**, 4159 (1997). d) S. Lemoine, C. Thomazeau, D. Joannard, S. Trombotto, G. Descotes, A. Bouchu, and Y. Queneau, *Carbohydr. Res.*, **326**, 176 (2000). e) P. L. Bragd, A. C. Besemer, and H. van Bekkum, *Carbohydr. Res.*, **328**, 355 (2000). f) R. Ciriminna, J. Blum, D. Avnir, and M. Pagliaro, *Chem. Commun.*, **2000**, 1441. g) R. Ciriminna and M. Pagliaro, *Adv. Synth. Catal.*, **345**, 383 (2003). h) R. N. Desai and L. F. Blackwell, *Synlett*, **2003**, 1981.

32 a) J. M. Bobbitt, *J. Org. Chem.*, **63**, 9367 (1998). b) C. A. Kernag, J. M. Bobbitt, and D. V. McGrath, *Tetrahedron Lett.*, **40**, 1635 (1999).

33 H. Tanaka, Y. Kawakami, K. Goto, and M. Kuroboshi, *Tetrahedron Lett.*, **42**, 445 (2001).

34 F. Montanari, M. Penso, S. Quici, and P. Viganò, *J. Org. Chem.*, **50**, 4888 (1985).

35 a) B. E. Douglas and D. H. McDaniel, "Concepts and Models of Inorganic Chemistry," Blaisdell, Massachusetts (1965), Chap. 7.6. b) A. C. Besemer, A. E. J. de Nooy, and H. van Bekkum, 212th ACS National Meeting, Orlando, FL, Augest 25–29, 1996, Abstr., CELL-021.

36 a) C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, **1939**, 443. b) R. L. White and I. D. Spenser, *J. Am. Chem. Soc.*, **104**, 4934 (1982). c) T. Yokoyama, T. Setoyama, N. Fujita, and T. Maki, *Stud. Surf. Sci. Catal.*, **90** (Acid–Base Catalysis II), 47 (1994). d) M. Al Hariri, O. Galley, F. Pautet, and H. Fillion, *Eur. J. Org. Chem.*, **1998**, 593.

37 4-Methyl-5-thiazolecarboxaldehyde (**2m**) is a useful intermediate for the synthesis of a potent cephalosporin family of antibiotics. a) K. Sakagami, K. Atsumi, A. Tamura, T. Yoshida, K. Nishihata, and S. Fukatsu, *J. Antibiot.*, **43**, 1047 (1990). b) Y. Okada, M. Sukegawa, T. Watanabe, H. Iwasawa, Y. Murai, and K. Iinuma, PCT Int. Appl., WO 98 58932 (1998); *Chem. Abstr.*, **130**, 81348x (1999). c) M. Kasai, S. Hatano, K. Nishimura, and N. Kakeya, PCT Int. Appl., WO 98 58933 (1998); *Chem. Abstr.*, **130**, 95424f (1999).

38 Estimated by elemental analysis: Found: C, 11.37; H, 1.86; N, 2.74%. Anal. Calcd for 0.64 mmol/g *N*-oxyl-immobilized silica gel **12**: C, 11.53; H, 1.94; N, 2.69%.

39 Diols **1p**–**1r** were prepared according to the manner of Sharpless AD reaction: K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992); Diol **1s** was prepared according to the reference: W. E. Rosen, V. P. Toohey, and A. C. Shabica, *J. Am. Chem. Soc.*, **80**, 935 (1958).

40 For recent reviews on polymer-supported reagents and catalysts, see: a) S. J. Shuttleworth, S. M. Allin, and P. K. Sharma, *Synthesis*, **1997**, 1217. b) S. J. Shuttleworth, S. M. Allin, R. D. Wilson, and D. Nasturica, *Synthesis*, **2000**, 1035. c) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3815. d) G. Bhalay, A. Dunstan, and A. Glen, *Synlett*, **2000**, 1846. e) A. Kirschning, H. Monenschein, and R. Wittenberg, *Angew. Chem., Int. Ed.*, **40**, 650 (2001). f) B. Clapham, T. S. Reger, and K. D. Janda, *Tetrahedron*, **57**, 4637 (2001).

41 a) S. Itsuno, K. Ito, T. Maruyama, N. Kanda, A. Hirao, and S. Nakahama, *Bull. Chem. Soc. Jpn.*, **59**, 3329 (1986). b) K. Kamahori, K. Ito, and S. Itsuno, *J. Org. Chem.*, **61**, 8321

(1996). c) D. A. Annis and E. N. Jacobsen, *J. Am. Chem. Soc.*, **121**, 4147 (1999). d) A. M. Hafez, A. E. Taggi, H. Wack, W. J. Drury, III, and T. Lectka, *Org. Lett.*, **2**, 3963 (2000). e) A. M. Hafez, A. E. Taggi, T. Dudding, and T. Lectka, *J. Am. Chem. Soc.*, **123**, 10853 (2001). f) K. Ishihara, A. Hasegawa, and H. Yamamoto, *Synlett*, **2002**, 1296.

42 a) G. P. Ponzano, PCT Int. Appl., WO 2001081656 (2001); *Chem. Abstr.*, **135**, 324334z (2001). b) G. E. Itkin, Russ., RU 2153540 (2000); *Chem. Abstr.*, **136**, 44581w (2002). c) V. V. Bannikov, Russ., RU 2162489 (2001); *Chem. Abstr.*, **136**, 157833y (2002). d) V. Zolotarsky, I. A. Ivanter, and M. J. Geusic, PCT Int. Appl., WO 2002061182 (2002); *Chem. Abstr.*, **137**, 146915w (2002). e) K. Yokota, M. Matsushima, J. Morita, and K. Okano, Jpn. Kokai Tokkyo Koho, JP 2002068388 (2002); *Chem. Abstr.*, **136**, 202205h (2002).

43 S. Cacchi, G. Fabrizi, F. Gavazza, and A. Goggiamani, *Org. Lett.*, **5**, 289 (2003).

44 H. B. Kwon, B. H. McKee, and J. K. Stille, *J. Org. Chem.*, **55**, 3114 (1990).

45 Y. Ishii, K. Nakayama, M. Takeno, S. Sakaguchi, T. Iwahama, and T. Nishiyama, *J. Org. Chem.*, **60**, 3934 (1995).

46 P. Ceccherelli, M. Curini, M. C. Marcotullio, and O. Rosati, *J. Org. Chem.*, **55**, 311 (1990).

47 K. Sakai, N. Hida, and K. Kondo, *Bull. Chem. Soc. Jpn.*, **59**, 179 (1986).

48 E. M. Brown, F. H. Fuller, S. C. Hebert, and J. E. Garrett, Jr., U. S. Patent US 5688938 (1997); *Chem. Abstr.*, **128**, 30379j (1998).

49 R. G. Syvret, T. P. Nguyen, V. L. Bulleck, and R. D. Rieth, Eur. Pat. Appl., EP 1138657 A1 (2001); *Chem. Abstr.*, **135**, 272548a (2001).

50 J. Louie, C. W. Bielawski, and R. H. Grubbs, *J. Am. Chem. Soc.*, **123**, 11312 (2001).

51 A. Arase, M. Hoshi, and Y. Masuda, *Bull. Chem. Soc. Jpn.*, **57**, 209 (1984).

52 S. Torii, T. Inokuchi, and T. Sugiura, *J. Org. Chem.*, **51**, 155 (1986).

53 W. L. Meyer, C. E. Capshew, J. H. Johnson, A. R. Klusener, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, **42**, 527 (1977).

54 S. S. Chaudhari and K. G. Akamanchi, *Synthesis*, **1999**, 760.

55 G. Y. Han, P. F. Han, J. Perkins, and H. C. McBay, *J. Org. Chem.*, **46**, 4695 (1981).

56 T. Suzuki, K. Morita, M. Tsuchida, and K. Hiroi, *J. Org. Chem.*, **68**, 1601 (2003).

57 M. Shi and Y.-S. Feng, *J. Org. Chem.*, **66**, 3235 (2001).

58 P. Haake and L. P. Bausher, *J. Phys. Chem.*, **72**, 2213 (1968).

59 J. J. D'Amico and T. W. Bartram, *J. Org. Chem.*, **25**, 1336 (1960).

60 M. Fujii, K. Nakamura, S. Yasui, S. Oka, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **60**, 2423 (1987).

61 M. Kawashima, T. Sato, and T. Fujisawa, *Tetrahedron*, **45**, 403 (1989).

62 V. B. Helavi, S. B. Solabannavar, U. V. Desai, and R. B. Mane, *J. Chem. Res., Symop.*, **2003**, 174.

63 J. Blum and B. Zinger, *J. Org. Chem.*, **43**, 2961 (1978).

64 T. P. Burns and R. D. Rieke, *J. Org. Chem.*, **52**, 3674 (1987).

65 H.-R. Bjørsvik, L. Liguori, and J. A. V. Merinero, *J. Org. Chem.*, **67**, 7493 (2002).

66 P. K. Kachroo, T. K. Razdan, M. A. Qurishi, M. A. Khuroo, S. Koul, and K. L. Dhar, *Phytochemistry*, **29**, 1014 (1990).

67 A. Silveira, Jr. and S. K. Satra, *J. Org. Chem.*, **44**, 873 (1979).

68 Y. Ishii, T. Yoshida, K. Yamawaki, and M. Ogawa, *J. Org. Chem.*, **53**, 5549 (1988).

69 H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, **45**, 1 (1980).

70 M. T. Nuñez and V. S. Martín, *J. Org. Chem.*, **55**, 1928 (1990).