of Health for financial support (Grant GM 15997-17). C.-J.F.D. also thanks Dow Chemical Co. and BASF Corp. for fellowship support.

Registry No. 1, 19821-80-8; **6**, 103-64-0; **7**, 15022-93-2; **8**, 583-55-1; **9**, 63262-06-6; **10**, 31604-30-5; *cis*-**11**, 645-49-8; *trans*-**11**, 103-30-0; **12**, 1725-76-4; **13**, 1608-41-9; **14**, 25634-86-0; **15**, 109764-44-5; **16**, 31024-80-3; **17**, 6738-06-3; **18**, 501-65-5; **19**, 109744-41-4; **20**, 13141-36-1; **21**, 19230-28-5; **22**, 13074-99-2; **23**, 25634-84-8; PhC≡CH, 536-74-3.

General Ether Synthesis under Mild Acid-Free Conditions. Trimethylsilyl Iodide Catalyzed Reductive Coupling of Carbonyl Compounds with Trialkylsilanes to Symmetrical Ethers and Reductive Condensation with Alkoxysilanes to Unsymmetrical Ethers[1]

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Facile synthesis of symmetrical ethers is achieved by either trimethylsilyl triflate or trimethylsilyl iodide catalyzed reductive coupling of carbonyl compounds (aldehydes and ketones) with trialkylsilanes. The method was also extended to the trimethylsilyl iodide catalyzed preparation of unsymmetrical ethers by reductive condensation (of carbonyl compounds) with alkoxysilanes. The scope and limitations of the reactions are discussed with emphasis on diastereoselectivity.

Introduction

The formation of carbon–oxygen single bonds is one of the oldest and most widely used functional group transformations in organic synthesis. The reaction of methyl iodide with silver oxide to prepare dimethyl ether was reported by Wurtz in 1856.[2] The Williamson ether synthesis, with its modifications, still a most widely used method, predates Wurtz's report by 6 years.[3] The attack of alkoxides on alkyl halides (Williamson's method), however, is synthetically useful only when the alkyl halide is primary. Low yields are obtained from secondary halides due to competing elimination and tertiary halides yield only elimination products.[3] Methods that involve carbocation intermediates such as the acid-catalyzed (Markovnikov) addition of alcohols to alkenes are plagued by competing rearrangements.[4] Solvomercuration, while fairly rapid, gives complicated mixtures in certain cases.[5]

In a series of papers from 1972–1975 Doyle and coworkers[6] reported acid-promoted reductive coupling of carbonyl compounds with trialkylsilanes as a route to symmetrical ethers. Their original method, however, presents the following major drawbacks: (1) Bronsted acids must be used in several-fold molar excess of the reactants, often as the solvent. Thus, the method cannot be used with acid-sensitive compounds. (2) Under these conditions, the formation of alcohol, alkene, and ester byproducts is unavoidable.

In 1979, Noyori's group reported the related trimethylsilyl triflate catalyzed reaction of acetals with trialkylsilanes.[7] This method is extremely mild and gives nearly quantitative yields of methyl ethers from the corresponding acetals. Mukaiyama et al.[8] reported a similar method from carbonyl compounds using trityl perchlorate as the catalyst. Yields ranged from 64% to 85% and circumvented most of the problems inherent in earlier methods. The use of trityl perchlorate as catalyst, however, is inconvenient and the preparation and handling of perchlorates should be avoided whenever possible.[9]

Since these latter methods overlapped with our own work involving reductive etherification of carbonyl compounds with trialkylsilanes over solid superacid catalysts,[10] we extended our studies to the reductive coupling of carbonyl compounds using trimethylsilyl triflate and trimethylsilyl iodide catalysts. In the latter case the in situ generation of trimethylsilyl iodide from hexamethyldisilane and iodine[11] was considered to provide a convenient mild way to carry out the reductive coupling of carbonyl compounds and also formation of unsymmetrical ethers. In this paper we report our studies of the trimethylsilyl iodide catalyzed preparation of ethers, its scope and limitations, as well as comparison with trimethylsilyl triflate catalyzed reactions.

The use of various alkylsilane reducing agents was also investigated and some unexpected stereochemical consequences observed.

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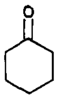
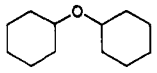
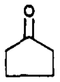
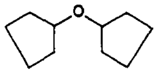
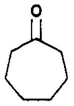
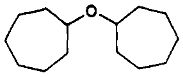
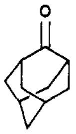
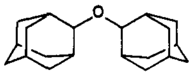
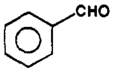
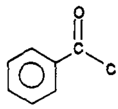
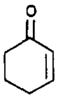
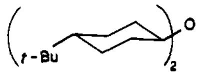
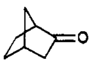
Table I. Symmetrical Ethers. Trimethylsilyl Triflate/Triethylsilane[a,b]

	aldehyde/ketone	ether	
1		 I	
2		 II	
3		 III	
4		 IV	
5	CH_3CH_2CHO	PrOPr	
6		$C_6H_5CH_2OCH_2C_6H_5$ $C_6H_5CH_2OH$	major minor
7		$(CH_3)C_6H_5CHOCHC_6H_5$ CH_2OH	major minor
8		mixture of products	
9			isomers
10		mixture of products	

[a] Products not isolated. [b] Yields quantitative (by ^{13}C NMR) unless otherwise stated.

Scheme I

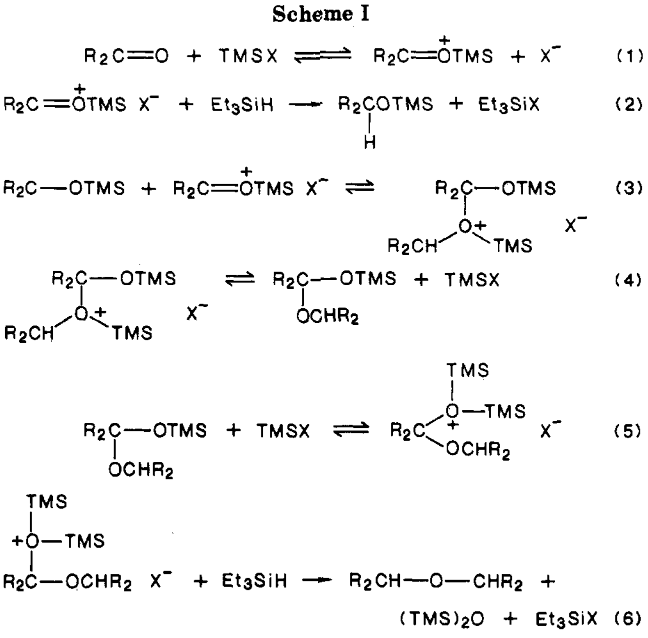
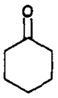
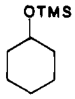
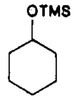
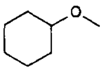
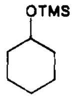
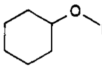
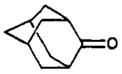
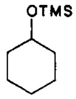
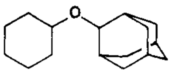
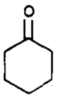
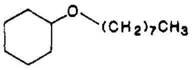


Table II. Symmetrical and Unsymmetrical Ethers. Trimethylsilyl Iodide/Triethylsilane[a,b]

	aldehyde/ketone	alkoxysilane	ether
1			I
2	CH_3CH_2CHO		 VI
3	$CH_3CH_2CH_2CHO$		 VII
4			 VIII
5		$CH_3(CH_2)_7$ OTMS	 IX
6	$CH_3CH_2CH_2CHO$	$CH_3(CH_2)_7$ OTMS	$CH_3(CH_2)_7OBu$ (X)

[a] Products not isolated. [b] Yields quantitative (by ^{13}C NMR).

Results and Discussion

The Catalyst. The addition of an aliphatic ketone or aldehyde to a solution of 1 equiv of triethylsilane in methylene chloride containing 10 mol % trimethylsilyl triflate generally gave quantitative yields of the corresponding symmetrical ethers within several minutes. The reaction mixtures were usually allowed to stir for an additional 2 h at room temperature (initial addition was carried out at 0 °C) before workup. Aromatic aldehydes and ketones gave in addition to their symmetrical ethers, benzylic alcohols as minor byproducts. α,β-Unsaturated ketones gave mixtures of products that included the reduction of the carbon-carbon double bond. Norcamphor gave evidence of some rearranged products (in addition to the expected symmetrical ether) (see Table I). These observations suggest a carboxonium ion intermediate, in keeping with the mechanism proposed by Doyle[6b] for the related Bronsted acid catalyzed system (see Scheme I).

$$2R_2CO + 2R_3SiH \rightarrow (R_2CH)_2O + (R_3Si)_2O$$

The observations that acetals are reductively cleaved to ethers by Noyori[7] and Olah[10] give support to the above mechanism (eq 6, Scheme I) and imply that in the case of mixed acetals, a siloxy group would be cleaved preferentially. We further considered that if an alkylsilyl ether was formed during the course of the reaction, as in eq 2, Scheme I, then the addition of an alkoxytrimethylsilane to a carbonyl compound would provide a route to unsymmetrical ethers. We were, therefore, rather disappointed when the addition of cyclohexoxytrimethylsilane to butyraldehyde, under the reaction conditions, gave a complicated mixture of no less than five products.[12]

We then turned our attention to the system employing trimethylsilyl iodide as the catalyst. While both trimethylsilyl triflate and trimethylsilyl iodide fume in moist air, the latter can be easily generated in situ from equimolar amounts of iodine and hexamethyldisilane[11,13] without any special precautions to exclude air or moisture. We found that for the formation of symmetrical ethers from carbonyl compounds, trimethylsilyl iodide, and trimethylsilyl triflate performed equally well (see Table I).

---

(12) Analysis of the reaction mixture was performed in a somewhat cursory manner by thin layer chromatography (silica gel-hexane). No starting material was detectable; five components giving R_f values at 0.98, 0.77, 0.60, 0.40, and 0.12 in addition to a band at the solvent front were observed, but no attempt to identify any of the components was made.

(13) We found it convenient to generate trimethylsilyl iodide using a slight excess of hexamethyldisilane.

Table III[a]

catalyst/reducing agent	product ether symmetrical	 unsymmetrical
TMSOTf/Et_3SiH	✓	X
TMSI/Et_3SiH	✓	✓
TMSOTf/i-Pr_3SiH	X	-
TMSI/i-Pr_3SiH	X	-
TMSOTf/PMHS	✓	X
TMSI/PMHS	X	X
TMSOTf/Me_3SiH	✓	-
TMSI/Me_3SiH	✓	✓

[a] Key: ✓, applicable; X, not applicable; -, no entry; PMHS = polymethylhydrosiloxane.

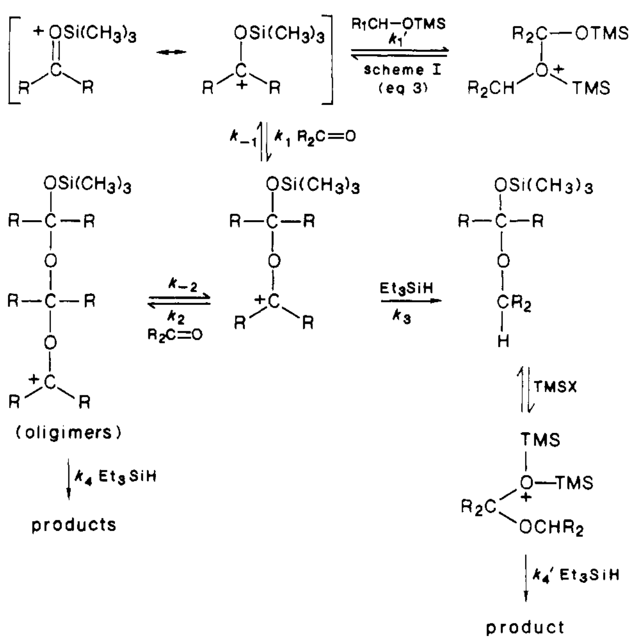
When cyclohexoxytrimethylsilane and butyraldehyde were combined using trimethylsilyl iodide instead of trimethylsilyl triflate, we obtained, much to our delight, quantitative yields of *n*-butyl cyclohexyl ether. Similarly, a variety of carbonyl compounds with alkoxysilanes gave quantitative yields of unsymmetrical ethers (see Tables II and IV). The method could not be extended to include silyl enol ethers or phenoxytrimethylsilane, the former undergoing reductive desilylation to form the parent carbonyl compound, which underwent coupling, and the latter forming phenol as a nonparticipant in the coupling of the carbonyl component in the reaction.

It is apparent that while the mechanism proposed in Scheme I seems to be valid when X = I, there are competing or alternate processes for the triflate catalyst. One possibility, which would account for the large number of products, involves the direct attack of a carbonyl oxygen on a stabilized carbocation *without* preliminary formation of an alkoxysilane.

In this manner, a new cation is generated and opens the pathway for the formation of oligomers (see Scheme II).

The k_2 and k_3 pathways are proportional to the concentrations of ketone and triethylsilane, respectively. In reactions with alkoxytrimethylsilanes, only half the amount of triethylsilane (compared to symmetrical coupling) is consumed. Since the reaction was run with the stoichiometrically determined quantity, the reduced concentration of silane compared to the concentration of ketone, favors k_2 over k_3.

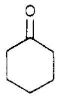
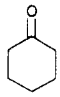
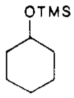
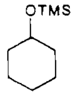
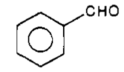
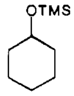
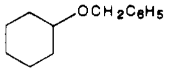
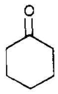
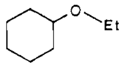
Scheme II



$k_1 > k_1'$ for triflate
$k_1' > k_1$ for iodide
$k_4 \simeq k_4' < k_2$ or k_3
$k_2 \propto [R_2C{=}O]$
$k_3 \propto [Et_3SiH]$

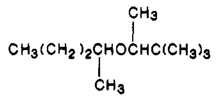
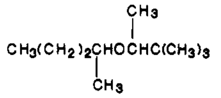
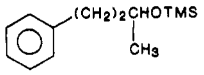
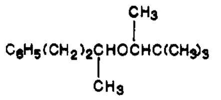
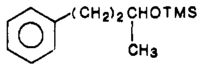
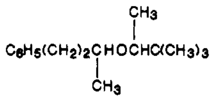
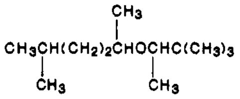
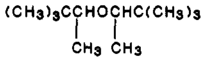
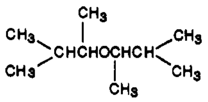
The Reducing Agent. Since triethylsilane enters into the catalytic cycle (eq 2, Scheme I), three disiloxane byproducts are obtained, which, due to the similarities between themselves and the desired products, invariably defy attempts at separation by either fractional distillation or chromatographic methods. We, therefore, entertained the use of alternate alkylsilanes which would yield either very high boiling or very low boiling byproducts. Our results are summarized in Table III. Triisopropylsilane gave a mixture of the symmetrical ether and the corresponding alkoxytriisopropylsilane with either catalyst, a higher proportion of ether being obtained with the triflate. Polymethylhydrosiloxane gave complete conversion with the

Table IV. Symmetrical and Unsymmetrical Ethers. Trimethylsilyl Iodide/Trimethylsilane

	aldehyde/ketone	alkoxysilane	ether	yield,[a] %	boiling point, °C
1			I	88	93-94/2.1 mm
2			I	93	93-94/2.1 mm
3	$CH_3CH_2CH_2CHO$		VII	93	68-70/0.08 mm
4			 XI	98	122-124/0.1 mm
5		C_2H_5 OTMS	 XII	91	141-144
6	$CH_3(CH_2)_5CHO$	C_2H_5 OTMS	$CH_3(CH_2)_6OEt$ (XIII)	90	159-161
7	$EtOC(O)(CH_3)CHC(O)CH_3$	$CH_3(CH_2)_4$ OTMS	$EtOC(O)(CH_3)CHCH(CH_3)O(CH_2)_4CH_3$ (XIV) (diastereomers)	90	

[a] Yields are for isolated products.

Table V. Diastereoselectivity Experiments. Trimethylsilyl Iodide/Trimethylsilane

	aldehyde/ketone	alkoxysilane	temp, °C	ether	diastereomer distribution
1	$CH_3C(O)C(CH_3)_3$	$CH_3(CH_2)_2C(CH_3)H$ OTMS	0	 $CH_3(CH_2)_2CH(CH_3)OCH(CH_3)C(CH_3)_3$ XV	54%/45%[a]
2	$CH_3C(O)C(CH_3)_3$	$CH_3(CH_2)_2C(CH_3)H$ OTMS	−78	 $CH_3(CH_2)_2CH(CH_3)OCH(CH_3)C(CH_3)_3$ XV	54%/45%[a]
3	$CH_3C(O)C(CH_3)_3$		0	 $C_6H_5(CH_2)_2CH(CH_3)OCH(CH_3)C(CH_3)_3$ XVI	
4	$CH_3C(O)C(CH_3)_3$		−78	 $C_6H_5(CH_2)_2CH(CH_3)OCH(CH_3)C(CH_3)_3$ XVI	
5	$CH_3C(O)C(CH_3)_3$	$(CH_3)_2CH(CH_2)_2C(CH_3)H$ OTMS	0	 $(CH_3)_2CH(CH_2)_2CH(CH_3)OCH(CH_3)C(CH_3)_3$ XVII	50%/50%[b]
6	$CH_3C(O)C(CH_3)_3$		0	 $(CH_3)_3CCH(CH_3)OCH(CH_3)C(CH_3)_3$ XVIII	100%[b] (*R*,*S*/*S*,*R*)
7	$CH_3C(O)CH(CH_2)_2$		0	 $(CH_3)_2CHCH(CH_3)OCH(CH_3)CH(CH_3)_2$ IXX	100%[b] (*R*,*R*/*S*,*S*)

[a] Diastereomer ratio determined by ^1H NMR. [b] Diastereomer ratio determined by NOE-suppressed ^{13}C NMR.

iodide catalyst. The desired products, however, became incorporated in the amorphous polymeric byproduct during workup and, thus, could not be separated. The best results were obtained with trimethylsilane.

Either of two methods for introducing trimethylsilane worked equally well. In the first method, a 1 M stock solution of trimethylsilane, (bp 6–7 °C) in dichloromethane was prepared at low temperature (−78 °C) and stored at −20 °C. For reductions, the flask was warmed to 0 °C and the solution transferred with a precooled syringe. Alternatively, with trimethylsilyl iodide as the catalyst, gaseous trimethylsilane was directly bubbled into the reaction mixture with the catalyst providing its own color indicator for the completion of the addition.[14] After aqueous workup, hexamethyldisiloxane (bp 99–100 °C), the single byproduct, was easily removed by rotary evaporation to obtain the pure ether. In some cases, particularly for ethers of lower molecular weight, better isolated yields were obtained by removing the dichloromethane solvent and dissolving the crude product in diethyl ether prior to aqueous workup. A summary of ethers synthesized and isolated by the trimethylsilyl iodide/trimethylsilane system appears in Table IV.

Diastereoselectivity. The slightly uneven diastereomeric distribution in the reaction of 2-pentoxytrimethylsilane with pinacolone (entries 1 and 2, Table V) led us to reflect on the possibilities of enhanced diastereoselectivity in the reaction. We observed no change in distribution when the reaction was run at −78 °C instead of 0 °C. Considering that a preferential approach where bulky alkyl groups on the nucleophile and electrophile avoid one another, we tried extending the terminus of the alkoxysilane. Neither (4-phenyl-2-butoxy)trimethylsilane nor (5-methyl-2-pentoxytrimethylsilane) showed improved selectivity with pinacolone either at 0 °C or −78 °C (see entries 3, 4, and 5, Table V). In fact, they seemed to be less selective. We were, then, surprised to find that the symmetric coupling of pinacolone yielded a single diastereomer (*R*,*S*/*S*,*R* enantiomers) (entry 6, Table V). Realizing that the stereochemical bias results from substitution at the α-carbon, we symmetrically coupled methyl isopropyl ketone to, again, obtain a single diastereomer (*R*,*R*/*S*,*S* enantiomers) (entry 7). This unexpected 100% selectivity seems to be dependent on having di- or trisubstituted α-carbons on both reactants (in addition to a non- or possibly monosubstituted α-carbon). Further studies are currently under investigation to extend the scope of diastereoselectivity.

Scope and Limitations. The method of ether synthesis by reductive coupling is compatible with a number of functional groups.

Under these conditions, esters, amides, acids, acid chlorides, and nitriles are unreactive. With catalytic trimethylsilyl iodide, the reaction of 1-pentoxytrimethylsilane with ethyl 2-methylacetoacetate gave a clean conversion

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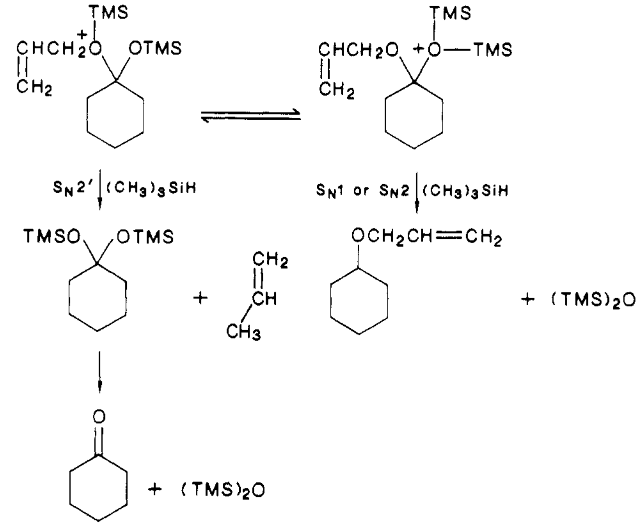
[14] Solution of trimethylsilyl iodide generated in situ is deep violet in dichloromethane. Upon completion of the addition of trimethylsilane, the color rapidly becomes a vivid red-gold, thus providing a convenient internal method for monitoring the reduction.

Scheme III



to a diastereomeric mixture of ethyl 3-*n*-pentoxy-2,3-dimethylpropanoate in 90% (isolated) yield (see entry 7, Table IV). As previously described, silyl enol ethers, α,β-unsaturated carbonyls, and phenoxytrimethylsilanes did not give promising results. Trimethylsilyl iodide gave no evidence of alcoholic byproducts with aromatic carbonyls.

One additional limitation is notable. In the reaction of allyoxytrimethylsilane with cyclohexanone, we obtained mixtures of the expected allyl cyclohexyl ether and the parent ketone. This was unusual in two respects. First, we had never before observed unreacted carbonyl compounds. Under the conditions of the reaction, an excess of the carbonyl component always underwent symmetrical coupling. Secondly, whether the reaction was run with equimolar quantities of starting material or with a 20% excess of allyloxytrimethylsilane, the same product distribution was obtained: a 1.7/1.0 ratio of ether to parent ketone. Our explanation lies in a competing S_N2' process which yields propene and a silyl ketal. The ketal in the presence of the catalyst then spontaneously reverts to the parent ketone with the loss of hexamethyldisiloxane as shown in Scheme III (below).

Summary

Trimethylsilyl triflate and trimethylsilyl iodide are both efficient catalysts for the synthesis of symmetrical ethers by reductive coupling of carbonyl compounds. The latter offers significant advantages in its ease of preparation and handling, and most importantly, in its ability to catalyze the formation of unsymmetrical ethers from carbonyl compounds and alkoxytrimethylsilanes in quantitative yields. The trimethylsilyl iodide/trimethylsilane system (see Experimental Section, method C) has been shown to be a particularly easy general method for ether synthesis, with the catalyst providing its own color indicator for the reduction step.

Experimental Section

All proton and carbon-13 magnetic resonance experiments were performed on a Varian XL-200 NMR spectrometer. Boiling points were determined by simple distillation and are uncorrected. Trimethylsilane was supplied by SCM Specialties, Gainesville, FL. Trimethylsilyl trifluoromethanesulfonate was supplied by Petrarch Systems, Inc., and distilled under argon prior to use. All other chemicals were supplied by Aldrich, Milwaukee, WI, and used without further purification.

With the exception of (allyloxy)trimethylsilane, alkoxy- and (aryloxy)trimethylsilanes were prepared in diethyl ether by treating a solution of the parent alcohol and 1.5 equiv of trimethylsilyl chloride with 1.5 equiv of triethylamine according to the method of Corey and Snides.[15] To avoid aqueous workup, (allyloxy)trimethylsilane was prepared by deprotonation of allyl alcohol with methyllithium in diethyl ether at −78 °C, followed by the addition of trimethylsilyl chloride.

Method A. Symmetrical Ethers by Reductive Coupling of Carbonyl Compounds (Trimethylsilyl Triflate). A solution of 1.0 mmol trimethylsilyl triflate and 20.0 mmol triethylsilane in 20 mL of CH_2Cl_2 is prepared in a three-neck flask equipped with a rubber septum, nitrogen inlet, and magnetic stir bar. After cooling to 0 °C, the aldehyde or ketone (10.0 mmol) in 10 mL of CH_2Cl_2 is slowly added via syringe. The cold bath is then removed and the reaction allowed to stir at room temperature for 2 h. The solvent is removed in vacuo and the product purified by distillation or recrystallization (see main text for explanatory remarks on problems associated with mixed siloxane byproducts).

Method B. Unsymmetrical Ethers. Reaction of Alkoxytrimethylsilanes with Carbonyl Compounds (Trimethylsilyl Iodide). Finely powdered iodine (0.50 mmol) and hexamethyldisilane (0.54 mmol) are combined in 14 mL of CH_2Cl_2 and stirred 10 min at room temperature under nitrogen. The resulting violet solution is then cooled to 0 °C and to it is slowly added the ketone or aldehyde (10.0 mmol) in 10 mL of CH_2Cl_2. After stirring for 10 min, trimethylsilane as a 1.0 M solution in CH_2Cl_2 (11.0 mmol) is added, giving a vivid red-gold solution within several seconds. The reaction is allowed to stir at room temperature two hours and then washed with 10% $Na_2S_2O_3$ (4×30 mL) and H_2O (4 × 30 mL) and dried over $MgSO_4$, and the volatiles are removed under reduced pressure on a steam bath to obtain the uncontaminated product.

Method C. Unsymmetrical Ethers. Reaction of Alkoxytrimethylsilanes with Carbonyl Compounds Employing Gaseous Trimethylsilane (Trimethylsilyl Iodide). In a 100-mL three-neck flask equipped with a rubber septum, thermometer, magnetic stirring bar, and nitrogen inlet are placed finely powdered iodine (0.50 mmol) and hexamethyldisilane (0.54 mmol) in 14 mL of CH_2Cl_2. The violet solution is stirred 10 min at room temperature and cooled to 0 °C and a solution of the carbonyl compound (10.0 mmol) and the alkoxytrimethylsilane (10.0 mmol) in 10 mL of CH_2Cl_2 is introduced via syringe. The reaction is stirred 10 min more at 0 °C, after which trimethylsilane is added directly from a gas cylinder by means of Tygon tubing attached to a hypodermic needle inserted through the rubber septum. The gas is allowed to slowly bubble through the solution until the color changes from violet to red-gold. During this time the internal temperature rises from 0 °C to 15 °C. The cold bath is then removed and stirring is continued at room temperature for 2 h. The reaction is worked up as in method B.

Dicyclohexyl ether (I): ^{13}C NMR 74.6, 33.3, 25.4, 24.5; bp 93–94 °C/2.1 mm (lit.[16a] bp 97–98.5 °C/8 mm); 93% yield.

Dicyclopentyl ether (II): ^{13}C NMR 79.1, 32.3, 23.3.

Dicycloheptyl ether (III): ^{13}C NMR 76.8, 39.4, 27.9, 22.7.

Diadamantyl ether (IV): ^{13}C NMR 79.3, 37.1, 36.0, 32.9, 30.6, 26.9, 26.6.

Dipropyl ether (V): ^{13}C NMR 72.4, 22.9, 10.4.

Cyclohexyl propyl ether (VI): ^{13}C NMR 77.0, 69.5, 32.4, 26.4, 24.5, 24.0, 10.8.

Cyclohexyl butyl ether (VII): ^{13}C NMR 77.2, 67.4, 32.4, 32.2, 25.9, 24.1, 19.4, 13.7; bp 68–70 °C/0.08 mm (lit.[6b] bp 193.5–194.5 °C/734 mm).

Cyclohexyl octyl ether (IX): ^{13}C NMR 77.0, 67.6, 32.1, 31.7, 30.1, 29.3, 29.1, 26.1, 25.7, 23.9, 22.4, 13.7.

Octyl butyl ether (X): 70.7, 70.3, 30.0, 29.6, 29.5, 26.4, 22.7, 19.4, 13.8, 13.7.

Benzyl cyclohexyl ether (XI): ^{13}C NMR 139.9, 127.9, 127.0, 76.3, 69.3, 31.1, 26.0, 23.8, bp 122–124 °C/0.10 mm (lit.[16c] bp 146 °C/17 mm), 98% yield.

Ethyl cyclohexyl ether (XII): ^{13}C NMR 76.8, 63.0, 32.6, 26.4, 24.2, 15.9; bp 141–144 °C (lit.[16d] bp 149.6 °C); 91% yield.

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Ethyl heptyl ether (XIII): ^{13}C NMR 70.6, 65.8, 31.7, 29.7, 29.0, 26.0, 22.4, 15.0, 13.8; bp 159–161 °C (lit.[16e] bp 166 °C); 90% yield.

(*R*,*S*/*S*,R)-Bis[3,3-dimethyl-2-butyl] ether (XVIII): ^{13}C NMR 75.4, 26.2, 25.3, 17.7.

(*R*,*R*/*S*,*S*)-Bis[3-methyl-2-butyl] ether (IXX): ^{13}C NMR 78.2, 77.0, 33.4, 32.9, 18.7, 18.5, 17.8, 17.5, 16.8, 16.2.

Ethyl 3-pentoxy-2,3-dimethylbutanoate (diastereomeric mixture) (XIV): ^{13}C NMR 173.4, 173.1, 76.1, 75.8, 68.4, 68.2, 59.1, 59.0, 45.3, 44.8, 29.5, 28.2, 22.1, 16.0, 15.7, 13.7, 13.4, 11.8, 11.5.

2-(3,3-Dimethyl-2-butoxy)pentane (diastereomeric mixture) (XV): ^{13}C NMR 81.0, 79.3, 74.4, 72.2, 39.9, 39.4, 35.3, 34.7, 26.3, 26.0, 25.8, 20.9, 19.5, 18.9, 18.8, 16.0, 14.3, 14.2.

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Ruthenium-Catalyzed Oxidative Transformation of Alcohols and Aldehydes to Esters and Lactones

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Primary alcohols undergo oxidative condensation upon treatment with $RuH_2(PPh_3)_4$ catalyst to give esters and molecular hydrogen. Similarly, 1,4- and 1,5-diols can be converted into the corresponding γ- and δ-lactones, respectively. The lactonization is greatly enhanced by accepting hydrogen with an appropriate hydrogen acceptor such as acetone. Primary alcohols are oxidized chemoselectively in the presence of secondary alcohols to give the corresponding lactones. These reactions are operationally simple and highly efficient for synthesis of esters and lactones from alcohols. The principle of the oxidative condensation of alcohols can be extended to ester formation from aldehydes and alcohols. The ruthenium-catalyzed reaction of aldehydes with water gives esters, while the same reaction in the presence of a hydrogen acceptor gives carboxylic acids. The key step of these reactions is the oxidative addition of ruthenium into the OH bonds of alcohols and subsequent β-elimination of (RuH) species to give the corresponding carbonyl compounds.

The development of a novel catalytic process that simulates the enzymatic function of alcohol dehydrogenase[1] is of synthetic and biological interest. The reported methods for such an oxidation of alcohols by dehydrogenation with homogeneous catalysts are limited to few reactions that involve formation of aldehydes along with molecular hydrogen evolution,[2] alkylation of amines with alcohols,[3] and condensation of phenylacetonitriles[4] with alcohols, although hydrogen-transfer reactions of alcohols to ketones are well documented.[5]

During the course of our study on the simulation of the function of alcohol dehydrogenase[1] with metal catalysts, we found an efficient method for the oxidative condensations of alcohols to give esters and lactones catalyzed by dihydridotetrakis(triphenylphosphine)ruthenium ($RuH_2(PPh_3)_4$, 1) as shown in eq 1.[6]

$$2RCH_2OH \xrightarrow{RuH_2(PPh_3)_4\ (1)} RCO_2CH_2R + 2H_2 \qquad (1)$$

Many methods for the preparation of esters[7] and lactones[8] by the oxidative condensation of alcohols have been performed by using various stoichiometric oxidants. Heterogeneous metal-catalyzed transformations of alcohols to esters and lactones have been reported; however, these reactions require extremely high temperature and proceed nonselectively.[9] Homogeneous catalysts such as $Pd(OAc)_2$ and $Ru_3(CO)_{12}$ catalyze oxidative condensation of alcohols in the presence of a stoichiometric amount of bromobenzene[10] and diphenylacetylene,[11] respectively. Our

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