

Update 1 of: Protection (and Deprotection) of Functional Groups in Organic Synthesis by Heterogeneous Catalysis

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1. Introduction

Fine chemicals are complex and multifunctional molecules, often characterized by low volatility and limited thermal stability, whose manufacture generally is based on multistep synthesis performed in the liquid phase and frequently involving protection–deprotection steps. The use of blocking functions in organic synthesis, developed for nearly 100 years, makes more complex the entire synthetic plan since it requires at least two additional steps. At the same time, environmental and economic considerations have created interest, in both academic and industrial research, in designing synthetic procedures that are clean, selective, high-yielding, and manipulatively easy.

In fact, as clearly recognized by Sheldon, "...traditional concepts of process efficiency are changing from an exclusive focus on chemical yield to one that assigns economic value to eliminating waste..."¹

An extensive application of heterogeneous catalysis in synthetic chemistry can help to achieve new selective reactions, to lower the waste production, and, finally, to render more attractive the synthetic process from both the environmental and also the economic point of view, in agreement with some parameters of the "ideal synthesis" recently presented by Wender.²

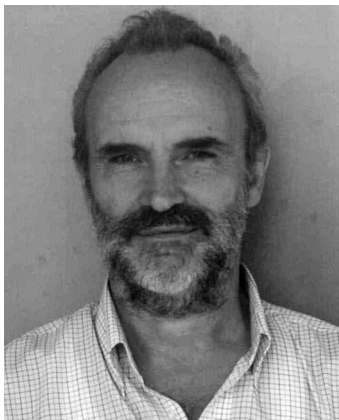
Indeed, solid catalysts can be easily separated from the reaction products by simple filtration and quantitatively recovered in the active form. They can be recycled, making less expensive the preparation of sophisticated fine chemicals and, at the same time, avoiding contamination of the products by trace amounts of metals.

The heterogeneous catalysis that was originally studied and applied in bulk chemistry with particular interest to petrochemical industry was more recently extended to synthetic organic chemistry for production of fine chemicals and pharmaceuticals.³ Among the first reactions performed under heterogeneous catalysis are the hydrogenations and, in general, the redox processes which are extensively applied in synthetic organic chemistry. Acid–base heterogeneous catalysis was successively developed by exploiting the physicochemical properties of zeolites,⁴ clays,⁵ and metal oxides.⁶

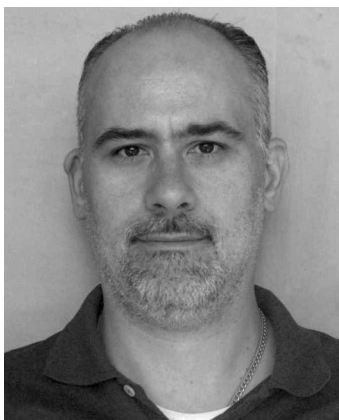
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Giovanni Sartori was born in Casalmaggiore, Italy, in 1944. He studied chemistry at the University of Parma, where he obtained his laurea degree under the guidance of Prof. Giuseppe Casnati in 1971. In 1972, he began his career at the University of Parma, working in the group of Prof. Casnati on the regio- and stereoselective functionalization of ambidental reagents. He was promoted to Associate Professor of Organic Chemistry in 1985 and Full Professor in 1994. He is currently the Head of the "Clean Synthetic Methodologies Groups" of the University of Parma. His research interests include all aspects of the heterogeneous catalysis applied to fine chemicals and pharmaceuticals production, with particular attention to the preparation and use of supported organic (chiral) catalysts. A special area of extensive interest is also the development of new eco-compatible synthetic methods, mainly based on the exploitation of solvent-free and multicomponent reactions. **The more recent research topics concern the continuous-flow processes with heterogeneous catalysts including application of sequentially linked column reactors.** He has published about 150 original studies, **written 11 chapters of books**, and filed approximately 20 patents.



Raimondo Maggi was born in Parma, Italy, in 1963. He graduated from the University of Parma in 1989 (working with Prof. Giuseppe Casnati), and he received his Ph.D. in organic chemistry (under the direction of Prof. Giovanni Sartori) from the same University in 1992. In 1995, he carried out his postdoctoral research with Prof. Manfred Schlosser at the Lausanne University. He began his career at the University of Parma in 1997 as Researcher, and in 2002 he was promoted to Associate Professor of Organic Chemistry. His research interests include the preparation and use of heterogeneous (chiral) catalysts for the environmentally friendly synthesis of fine chemicals and pharmaceuticals **and the setup of microstructured catalytic flow reactors.** He has published about 100 original studies, **written 11 chapters of books**, and **filed 1 patent.**

However, many of these materials present some limitations when large reactants are involved, especially in liquid-phase systems, as frequently occur in the synthesis of fine chemicals. Attempts to improve the diffusion of reactants to catalytically active sites have so far focused on increasing the catalyst pore sizes, such as in the mesoporous MCM⁷ and ITQ⁸ type materials. Finally, application of catalysts to manufacturing technologies, such as grafting and tethering combined with special copolymerization procedures, origi-

nally addressed to materials chemistry, made accessible a large number of (chiral) organic catalysts as well as (chiral) metal complexes covalently bound to the surface of both organic and inorganic supports.^{9,10}

These materials are excellent catalysts for organic synthesis since they combine the properties of a stable organic or inorganic backbone with the flexibility of the organic derivatives; moreover, they are also characterized by higher thermal stability in comparison with their homogeneous counterparts. The application of all these large families of solid catalysts in liquid-phase synthetic chemistry has attracted a lot of interest. They also form the basis of some new industrial processes which have been developed to replace traditional problematic synthetic methods.¹¹ As a consequence of the extensive application of heterogeneous catalysis in synthetic organic chemistry, a large number of articles describing the advantages of performing protection–deprotection reactions over solid catalysts have been published. However, these studies examined only marginally some crucial aspects of the heterogeneous catalysis, such as the quantitative and correct evaluation of catalyst efficiency in terms of the turnover number (TON) and turnover frequency (TOF) values; it is more frequently evaluated through the product yield as a function of each cycle. Similarly, direct and quantitative determination of the amount of recovered catalyst and leaching phenomena were scarcely taken into consideration.^{12,13} On the other hand, these articles were focused on synthetic organic chemistry, and their major goal was to point out the advantages of performing protection–deprotection reactions over heterogeneous catalysis, quantified as yield, easy workup, and, in particular, selectivity when multifunctional compounds are utilized.

Due to the great interest in protecting group chemistry, many books^{14,15} and reviews^{16,17} have been published on this topic. Moreover, updated reviews are published yearly by Kociński¹⁸ and Spivey,¹⁹ describing selected important applications. Several reviews have also touched on more specialized fields, such as enzymatic protecting group techniques²⁰ and protecting groups in solid-phase organic synthesis.²¹ However, until now, a full collection of the applications of heterogeneous catalysis to protecting group chemistry, highlighting the advantages related to the easier workup of the reaction mixture and purification of products as well as the high level of selectivity frequently achieved, has not been published. In this review we describe the application of heterogeneous catalysis in protecting group chemistry, focusing mainly on that developed during the past decade.

The various reactions and procedures reported within this review are sorted into categories based on the functional group, according to Kociński's typical classification. Significant examples for every class of compounds are collected in Tables 2–28, accompanied by the reference, the number of examples reported in the paper, the yield range, and information on the catalyst reusability **when available.**

To provide the reader with rapid and easy information about the large number of catalysts described in the review, Table 1 summarizes the name (and/or the abbreviation) of every catalyst, accompanied by a short description of its availability.

Some of the catalysts are commercially available (CA), such as many clays, zeolites, and metal oxides. In some instances, due to their insufficient acidity, prolonged reaction times or a large quantity of them are usually necessary, and,

Table 1. Heterogeneous Catalysts Utilized

entry ^{ref}	catalyst [abbreviation]	type ^z	preparation
1	bentonite (Mexican)	CA	
2	kaolin	CA	
3	montmorillonite K10	CA	
4	montmorillonite KSF	CA	
5	Sepiolite (Spanish)	CA	
6	Tonsil	CA	
7	Envirocat EPZ10	CA	
8	Envirocat EPZG	CA	
9 ^a	montmorillonite/Ce ³⁺	SA	treatment of Na ⁺ -montmorillonite with Ce(NO ₃) ₃ in aqueous acetone
10 ¹⁰²	montmorillonite K10/FeCl ₃	SA	treatment of montmorillonite K10 with FeCl ₃ in H ₂ O
11 ¹⁴¹	montmorillonite K10/Fe(NO ₃) ₃	SA	treatment of montmorillonite K10 with Fe(NO ₃) ₃
12 ^b	montmorillonite K10/Fe(NO ₃) ₃ [clayfen]	SA	treatment of montmorillonite K10 with Fe(NO ₃) ₃ in acetone
13 ²⁰⁰	montmorillonite K10/K ₂ FeO ₄	SA	treatment of montmorillonite K10 with K ₂ FeO ₄
14 ¹⁴⁰	montmorillonite K10/(Me ₃ Si) ₂ CrO ₄	SA	treatment of montmorillonite K10 with Me ₃ SiOSiMe ₃ and CrO ₃ in CH ₂ Cl ₂
15 ⁹⁸	montmorillonite K10/NH ₄ NO ₃ [clayan]	SA	treatment of montmorillonite K10 with NH ₄ NO ₃ in H ₂ O
16 ³⁰⁴	montmorillonite K10/(NH ₄) ₂ S ₂ O ₈	ISP	mixing of montmorillonite K10 with (NH ₄) ₂ S ₂ O ₈
17 ²¹¹	montmorillonite K10/POCl ₃	SA	treatment of montmorillonite K10 with POCl ₃ in CH ₂ Cl ₂
18 ¹⁸²	montmorillonite/Ti ⁴⁺	SA	treatment of Na ⁺ -montmorillonite with TiCl ₄ in H ₂ O
19	beta zeolite [BEA]	CA	
20 ^c	ferrierite zeolite [FER]	SA	mixing of sodium silicate, aluminum sulfate hexadecahydrate, and pyrrolidine in acidic H ₂ O
21	mordenite zeolite [MOR]	SA	
22	Y zeolite	CA	
23	USY zeolite	CA	
24	ZSM-5 zeolite [MFI]	CA	
25 ⁶⁹	delaminated zeolite ITQ-2	SA	treatment of MCM-22 with CH ₃ (CH ₂) ₁₅ N(CH ₃) ₃ Br, (CH ₃ CH ₂ CH ₂) ₄ NOH, and HCl
26 ¹⁴⁹	Cu-pentasil borosilicate/Cu(NO ₃) ₂	SA	treatment of Cu-pentasil borosilicate with Cu(NO ₃) ₂
27 ²⁷⁴	Y zeolite/KMnO ₄	SA	treatment of Y zeolite with KMnO ₄ in H ₂ O
28 ^d	ZSM-5 zeolite/Fe(NO ₃) ₃ ·9H ₂ O [Zeofen]	SA	treatment of ZSM-5 zeolite with Fe(NO ₃) ₃ ·9H ₂ O
29 ^e	LaY zeolite	SA	treatment of NaY zeolite with LaCl ₃ in H ₂ O
30	NaY zeolite	CA	
31 ⁹¹	molecular sieves/FeCl ₃	SA	shaking powdered Linde 3-Å molecular sieves with FeCl ₃
32 ^{f,g}	Si-MCM-41	SA	mixing of sodium silicate solution, tetramethylammonium hydroxide, and cetyltrimethylammonium chloride in H ₂ O
33 ^h	Si/Al-MCM-41	SA	mixing of CH ₃ (CH ₂) ₁₅ N(CH ₃) ₃ Br, pseudoboehmite, and Aerosil
33b ^{hb}	Al-SBA-15	SA	mixing of TEOS, aluminum isopropoxide, and copolymer EO ₂₀ PO ₇₀ EO ₂₀
34 ⁱ	TS-1	SA	mixing of a source of silicon oxide and a source of titanium oxide
35 ³¹	M-ETS-10	SA	treatment thrice of ETS-10 with a metal chloride solution
36 ^j	SiO ₂ /Al ₂ O ₃	SA	mixing of Al(NO ₃) ₃ with colloidal silica solution (30 wt % SiO ₂) and then NH ₄ OH
37	SiO ₂	CA	
38 ¹⁰⁹	SiO ₂ /Al ₂ (SO ₄) ₃	SA	treatment of silica gel with Al ₂ (SO ₄) ₃
39 ¹¹¹	SiO ₂ /BF ₃	SA	treatment of silica gel with BF ₃ ·Et ₂ O
40 ^k	SiO ₂ /Ce(SO ₄) ₂	SA	treatment of silica gel with Ce(SO ₄) ₂ in H ₂ O
41 ^l	SiO ₂ /[(CH ₃) ₃ SiO] ₂ CrO ₄ [SiO ₂ /BTSC]	SA	treatment of silica gel with (CH ₃) ₃ SiOSi(CH ₃) ₃ and CrO ₃ in CH ₂ Cl ₂
42 ²⁰⁴	SiO ₂ /[(CH ₃) ₃ SiO] ₂ SO ₂ [SiO ₂ /BTS]	ISP	mixing of silica gel with [(CH ₃) ₃ SiO] ₂ SO ₂ in CH ₂ Cl ₂
43 ²⁰⁵	SiO ₂ /CoBr ₂	SA	treatment of silica gel with anhydrous CoBr ₂
44 ^m	SiO ₂ /Cu(NO ₃) ₂	SA	treatment of silica gel with Cu(NO ₃) ₂ ·1.5H ₂ O
45 ²⁰⁷	SiO ₂ /Cu(OTf) ₂	SA	treatment of silica gel with Cu(OTf) ₂
46 ⁿ	SiO ₂ /CuSO ₄	SA	treatment of silica gel with CuSO ₄ in H ₂ O
47 ⁴⁸	SiO ₂ /Et ₃ N	SA	treatment of silica gel with Et ₃ N
48 ²⁸⁴	SiO ₂ /Fe(ClO ₄) ₃ ·6H ₂ O	SA	treatment of silica gel with Fe(ClO ₄) ₃ ·6H ₂ O
49 ²²⁵	SiO ₂ /Fe(NO ₃) ₃ ·9H ₂ O	SA	treatment of silica gel with Fe(NO ₃) ₃ ·9H ₂ O
50 ¹¹³	SiO ₂ /GeCl ₄	SA	treatment of silica gel with GeCl ₄
51 ⁷²	SiO ₂ /H ₂ SO ₄	SA	treatment of silica gel with H ₂ SO ₄ in acetone
51b ^{254b}	SiO ₂ /H ₂ SO ₅	SA	treatment of silica gel with H ₂ SO ₅
51c ^{32b}	SiO ₂ /HClO ₄	SA	treatment of silica gel with HClO ₄
51d ^{32c}	SiO ₂ /HBF ₄	SA	treatment of silica gel with HBF ₄
52 ^o	SiO ₂ /K ₂ FeO ₄	ISP	treatment of silica gel with K ₂ FeO ₄ in cyclohexane

Table 1. Continued

entry ^{ref}	catalyst [abbreviation]	type ^z	preparation
52b ^{ob}	SiO ₂ /K ₂ Na	SA	treatment of silica gel with K ₂ Na liquid alloy
53 ^{106,107}	SiO ₂ /NaHSO ₄	SA	treatment of silica gel with NaHSO ₄ ·H ₂ O
54 ¹²⁶	SiO ₂ /(NH ₄) ₂ Ce(NO ₃) ₆ [SiO ₂ /CAN]	SA	treatment of silica gel with (NH ₄) ₂ Ce(NO ₃) ₆ in H ₂ O
55 ^p	SiO ₂ /PBGSiCl	SA	treatment of silica gel with a preformed trimethyloxysilane-polyalkylguanidinium ion
55b ^{234b}	SiO ₂ /PPA	SA	treatment of silica gel with PPA
56 ³³	SiO ₂ /P ₂ O ₅	SA	treatment of silica gel with P ₂ O ₅
57 ¹¹²	SiO ₂ /rare earth chloride	SA	treatment of silica gel with selected chloride in dry methanol
58 ^q	SiO ₂ /SOCl ₂ [silica chloride]	SA	treatment of silica gel with SOCl ₂
59 ⁷⁴	SiO ₂ /TaCl ₅	ISP	shaking silica gel with TaCl ₅
60 ^r	SiO ₂ /Yb(OTf) ₃	SA	treatment of silica gel with Yb(OTf) ₃ in CH ₃ CN
61 ²⁰⁶	SiO ₂ /ZrCl ₄	SA	treatment of silica gel with anhydrous ZrCl ₄
62 ²³⁴	SiO ₂ -(CH ₂) ₃ NH ₃ Cl [APSG·HCl]	SA	treatment of SiO ₂ -(CH ₂) ₃ NH ₂ with HCl in methanol
62b ^{73b}	SiO ₂ -SO ₃ H	SA	treatment of TEOS with 3-mercaptopropyltriethoxysilane and successive oxidation of the SH groups by H ₂ O ₂
62c ^{245c}	SiO ₂ -OSO ₃ H	SA	treatment of silica gel with ClSO ₃ H
63	Al ₂ O ₃	CA	
64 ¹⁴⁵	Al ₂ O ₃ /CrO ₃	SA	treatment of neutral alumina with H ₂ O and CrO ₃
65 ¹³³	Al ₂ O ₃ /KF	SA	treatment of basic alumina and KF in H ₂ O
66 ¹⁴⁶	Al ₂ O ₃ /KMnO ₄	SA	treatment of neutral alumina with KMnO ₄
67 ¹³⁴	Al ₂ O ₃ /Oxone	SA	treatment of neutral alumina with Oxone in H ₂ O
67b ^{245d}	Al ₂ O ₃ /P ₂ O ₅	SA	treatment of alumina with P ₂ O ₅
68 ⁷⁵	Al ₂ O ₃ /ZnCl ₂	ISP	mixing of alumina with a THF solution of ZnCl ₂
69	Amberlyst 15	CA	
70	Amberlyst A-21	CA	
71	Amberlite IR-120	CA	
72	Dowex 50WX2	CA	
73	Dowex 50WX8	CA	
74	IRA-400(OH ⁻)	CA	
75	Nafion	CA	
76 ¹⁵⁶	D001/AlCl ₃	SA	treatment of D001 with AlCl ₃ in EtOH
77 ¹⁵⁷	salicylic acid resin/FeCl ₃	SA	treatment of salicylic acid resin with FeCl ₃ in CHCl ₃
78 ^s	polymeric dicyanoketene acetal [(P)-DCKA)]	SA	copolymerization of monomeric DCKA bearing styrene moiety with ethylene glycol dimethacrylate
79 ⁸³	poly- <i>p</i> -styryldiphenylacetonylphosphonium bromide [(P)-ATPB]	SA	multistep synthesis from <i>p</i> -bromobenzaldehyde, styrene, and divinylbenzene
80 ³⁰⁸	polystyrene-1-hydroxybenzotriazole [(P)-HOBT]	SA	multistep synthesis from polystyrene-divinylbenzene copolymer, 3-nitro-4-chlorobenzyl alcohol, hydrazine monohydrate, and ethylene glycol monoethyl ether
80b ^{137b}	PS-barbituric acid/Pd(Ph ₃) ₄	SA	multistep synthesis from aminomethylpolystyrene, PrNCO and malonic acid and subsequent treatment with Pd(Ph ₃) ₄
81 ²⁴⁹	poly(vinyl chloride)/FeCl ₃ [PVC/FeCl ₃]	SA	treatment of poly(vinyl chloride) with FeCl ₃ in CH ₂ Cl ₂
81b ^{134c}	poly(4-vinylpyridine)/FeCl ₃ [PVP/FeCl ₃]	SA	treatment of poly(4-vinylpyridine) with FeCl ₃
82 ¹³⁷	sulfonated cross-linked polystyrene	SA	treatment of cross-linked gel-type polystyrene with H ₂ SO ₄
83 ¹⁵⁹	Celite/CsF	SA	treatment of Celite 521 with CsF in H ₂ O
83b ^{318b}	HAP/Pd	SA	treatment of hydroxyapatite with PdCl ₂ (PhCN) ₂
84 ²⁴⁸	expansive graphite	SA	treatment of graphite with H ₂ SO ₄ , HNO ₃ , and KMnO ₄ in H ₂ O
85 ^r	sulfonated charcoal	SA	treatment of active charcoal with fuming H ₂ SO ₄
86	Pd/C	CA	
87	PdO hydrate	CA	
88 ^u	hydrated zirconia	SA	mixing ZrOCl ₂ ·8H ₂ O and NaOH in H ₂ O
89	sulfated zirconia [ZrO ₂ /SO ₄ ²⁻]	CA	
90 ¹⁸⁷	yttria-zirconia [Y ₂ O ₃ /ZrO ₂]	SA	mixing Y(NO ₃) ₃ ·6H ₂ O, ZrO(NO ₃) ₂ ·xH ₂ O, and NH ₃ in H ₂ O
91 ⁴⁰	WO ₃ /ZrO ₂	SA	treatment of ZrO _x (OH) _{4-2x} with (NH ₄) ₂ WO ₄ in H ₂ O
92 ¹⁵⁴	MoO ₃ /ZrO ₂	SA	addition of (NH ₄) ₆ Mo ₇ O ₂₄ ·4H ₂ O oxalic acid aqueous solution to Zr(OH) ₄
93 ¹⁹⁰	Pt/MoO ₃ /ZrO ₂	SA	addition of (NH ₄) ₆ Mo ₇ O ₂₄ ·4H ₂ O aqueous solution to Zr(OH) ₄ ; after calcination, addition of hexachloroplatinic acid

Table 1. Continued

entry ^{ref}	catalyst [abbreviation]	type ^z	preparation
94 ^w	Zr(KPO ₄) ₂	SA	titration of exfoliated α -zirconium phosphate with a (KCl + KOH) 0.1 M aqueous solution
95 ²³¹	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8}	SA	decomposition of Zr(IV) fluorocomplexes in a solution of <i>m</i> -sulfophenyl phosphoric acid and methanephosphonic acid
96 ^w	Al ₂ O ₃ /AlPO ₄	SA	mixing alumina with AlCl ₃ ·6H ₂ O, H ₃ PO ₄ , and NH ₃ in propylene oxide
97 ^x	AlPO ₄	SA	mixing AlCl ₃ ·6H ₂ O, Al(NO ₃) ₃ ·9H ₂ O, Al ₂ (SO ₄) ₃ ·18H ₂ O
97b ^{247b}	AlPW ₁₂ O ₄₀	SA	mixing of dodecatungstophosphate with Al(NO ₃) ₃
98	H ₃ PW ₁₂ O ₄₀	CA	H ₃ PO ₄ , and NH ₃
99 ⁶⁰	K ₅ CoW ₁₂ O ₄₀ ·3H ₂ O	SA	treating (CH ₃ CO ₂) ₂ Co with Na ₂ WO ₄ ·2H ₂ O in CH ₃ COOH and H ₂ O, then with KCl, and finally with K ₂ S ₂ O ₈ in H ₂ SO ₄
99b ¹⁰⁰	SiPW	SA	mixing of TEOS, Na ₂ WO ₄ , Na ₂ HPO ₄ , and copolymer EO ₂₀ PO ₇₀ EO ₂₀
100 ^y	sulfated SnO ₂	SA	treating Sn(OH) ₄ with H ₂ SO ₄
101 ²⁵⁵	sulfated TiO ₂ [TiO ₂ /SO ₄ ²⁻]	SA	mixing Ti(OH) ₄ with H ₂ SO ₄ in H ₂ O
102 ¹⁵⁵	MgSO ₄ /H ₂ SO ₄	ISP	mixing MgSO ₄ with concentrated H ₂ SO ₄

^a Tateiwa, J.; Horiuchi, H.; Hashimoto, K.; Yamauchi, T.; Uemura, S. *J. Org. Chem.* **1994**, 59, 5901. ^b Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909. ^c Ahedi, R. K.; Kotasthane, A. N. *J. Porous Mat.* **1997**, 4, 171. ^d Heravi, M. M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *J. Chem. Soc., Chem. Commun.* **1999**, 833. ^e Yang, S.; Navrotsky, A. *Microporous Mesoporous Mater.* **2000**, 37, 175. ^f Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, 359, 710. ^g Beck, J. S.; Vartuli, J. C.; Roth, W. J.; Leonowicz, M. E.; Kresge, C. T.; Schmitt, K. D.; Chu, W.; Olson, D. H.; Sheppard, E. W.; McCullen, S. B.; Higgins, J. B.; Schlenker, J. L. *J. Am. Chem. Soc.* **1992**, 114, 10834. ^h Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C. U.S. Patent 5 098 684, **1992**; *Chem. Abstr.* **1992**, 117, 72621. ^{hb} Zhao, D.; Feng, J.; Huo, Q.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, 279, 548. ⁱ Taramasso, M.; Perego, G.; Notari, B. U.S. Patent 4 410 501, 1981; *Chem. Abstr.* **1981**, 95, 206272. ^j Matsumoto, Y.; Mita, K.; Hashimoto, K.; Tokoroyama, T. *Appl. Catal. A: General* **1995**, 131, L1. ^k Nishiguchi, T.; Kamio, C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 707. ^l Lee, J. G.; Lee, J. A.; Yun Sohn, S. *Synth. Commun.* **1996**, 26, 543. ^m Nishiguchi, T.; Asano, F. *Tetrahedron Lett.* **1988**, 29, 6265. ⁿ Caballero, G. M.; Gros, E. G. *J. Chem. Res. (S)* **1989**, 320. ^o Delaude, L.; Laszlo, P. *J. Org. Chem.* **1996**, 61, 6360. ^{ob} Dye, J. L.; Cram, K. D.; Urbin, S. A.; Redko, M. Y.; Jackson, J. E.; Lefenfeld, M. *J. Am. Chem. Soc.* **2005**, 127, 9338. ^p Gauthier, P.; Gros, P.; Le Perche, P.; Senet, J. P. U.S. Patent 5 348 923, 1993; *Chem. Abstr.* **1993**, 119, 203156. ^q Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *Synlett* **2000**, 263. ^r Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* **1997**, 38, 7583. ^s Masaki, Y.; Tanaka, N.; Miura, T. *Tetrahedron Lett.* **1998**, 39, 5799. ^t Patney, H. K. *Tetrahedron Lett.* **1991**, 32, 413. ^u Patil, M. L.; Jnaneshwara, G. K.; Sabde, D. P.; Dongare, M. K.; Sudalai, A.; Deshpande, V. H. *Tetrahedron Lett.* **1997**, 38, 2137. ^v Costantino, U.; Curini, M.; Marmottini, F.; Rosati, O.; Pisani, E. *Chem. Lett.* **1994**, 2215. ^w Campelo, J. M.; García, A.; Luna, D.; Marinas, J. M.; Martinez, M. I. *Mater. Chem. Phys.* **1989**, 21, 409. ^x Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Catal.* **1988**, 111, 106. ^{yo} Shi, C.; Wang, R.; Zhu, G.; Qiu, S.; Long, J. *Eur. J. Inorg. Chem.* **2005**, 4801. ^y Chavan, S. P.; Zubaidha, P. K.; Dantale, S. W.; Keshavaraja, A.; Ramaswamy, A. V.; Ravindranathan, T. *Tetrahedron Lett.* **1996**, 37, 233. ^z CA, commercially available; ISP, in situ prepared; SA, simply added.

consequently, they are often modified by treatment with Lewis acids or protic acids (SA) to increase their catalytic activity. Similar procedures can be utilized to prepare catalysts displaying special redox properties. Unfortunately, the majority of the more attractive catalysts, such as many metal phosphates, polyoxometalates, and catalysts immobilized on solid supports, are not commercially available and must be prepared by tricky methodologies.

In some cases, the catalysts are prepared in situ (ISP) by mixing convenient reagents (i.e., Lewis or protic acids with metal oxides) with the reaction mixture. Even though, in these circumstances, there are still many doubts about the effective heterogeneity of the catalysts, we report the application since the authors showed that use of these combinations affords cleaner and more efficient synthetic procedures.

Similarly, rather sophisticated and useful catalysts are represented by active molecules immobilized through covalent bonds on the surface of polymeric supports. In spite of the exciting results frequently obtained by applying these catalysts to various areas of organic synthesis, further detailed information is needed to achieve their optimum performance in reproducible experiments and to better understand the interaction of the reactants and solvent molecules with the surface of the catalyst.

2. Hydroxy Protecting Groups

Protection and deprotection of alcohols have received attention in recent years not only because of their fundamental importance, but also for their role in multistep synthesis. High selectivity is frequently requested for a given

hydroxy group in polyol chemistry, as well as simplicity and mildness in preparing and removing the specific function. Moreover, even when a substrate protects and deprotects efficiently, the reaction frequently needs quenching and products must be isolated from the reaction mixture and purified by suitable methods. For substrates that are particularly labile, these operations can cause further degradation. In these situations, the use of solid catalysts allows all the above-described operations to be performed in a more efficient way.

2.1. Esters

2.1.1. Protection

The **acylation** of alcohols represents an important reaction for the synthetic organic chemist; it is frequently used for derivatization and characterization of alcohols as well as for further transformations. The reaction is usually performed by using acyl chlorides or the corresponding anhydrides in the presence of a base such as triethylamine or pyridine; faster reaction rates can be achieved by adding 4-(dimethylamino)pyridine (DMAP) as cocatalyst. Under these conditions, base-sensitive substrates may undergo decomposition. To avoid this drawback, protic and Lewis acids can be utilized, such as *p*-toluenesulfonic acid, zinc chloride, cobaltous chloride, and scandium triflate.

Different solid acids have also been successfully utilized to promote the reaction.

Thus, the acetylation of alcohols and phenols was performed at room temperature using acetic anhydride as acylating reagent in the presence of montmorillonites KSF and K10. No selectivity between primary and secondary

hydroxy groups was observed, whereas the tertiary alcohols were recovered unchanged (Table 2, entry 1).^{22,23} Fully acetylated sugars, which are inexpensive and very useful intermediates for the synthesis of many naturally occurring glycosides, oligosaccharides, and glycoconjugates, could be prepared by reaction of several disaccharides and trisaccharides with acetic anhydride; under these conditions, partial anomerization and acetolysis may occur (Table 2, entry 2).²⁴

A more attractive route for the protection of alcohols as esters from the environmental and economic standpoints is represented by their direct reaction with carboxylic acids. By using natural montmorillonite itself or exchanged with Na^+ cations, a wide variety of primary, secondary, benzylic, allylic, homocyclic, and heterocyclic alcohols has been acetylated with acetic acid (Table 2, entry 3).²⁵ In addition, upon increasing the chain length of the carboxylic acid, an increase of the reaction rate was observed, probably due to the fact that a long carbon chain carboxylic acid is more hydrophobic and drives away, from the clay active sites, the water formed during the reaction more effectively than the hydrophilic lower chain acids.

Chavan et al. exploited the surface acidity of different types of zeolites to perform the acetylation of alcohols and phenols under solventless conditions using acetic anhydride. In the presence of a catalytic amount of FER zeolite, several alcohols and phenols, including those containing chiral centers and acid-sensitive groups (acetal, tetrahydropyranyl ether, C–C double and triple bonds), were transformed into the corresponding acetates under mild reaction conditions (Table 2, entry 4).²⁶ More conveniently, Sartori et al. described the acetylation of alcohols and phenols with acetic anhydride in the presence of the commercially available Y zeolite HSZ-360. Functionalities such as double and triple bonds, ketals, and chiral centers survive under the reaction conditions (Table 2, entry 5).²⁷ Of particular interest is the efficient acylation of β -nitro alcohols which, very often, produce nitroolefins upon treatment with acids.²⁸ As expected, the bulkiness of the reagents represents a crucial factor in the process: for example, complete conversion of α - and β -naphthols to the corresponding acetates needs 1.5 h, whereas that of binaphthol takes 12 h. In this particular case, the bulkiness of the reagent limits or completely inhibits its diffusion through the pores of the catalyst, and the reaction probably occurs only on the external surface or on the external acidic sites. Zeolites were also utilized for the protection of sugars. Beta zeolite represented an efficient catalyst for the per-*O*-acetylation of monosaccharides, disaccharides, and alkyl glycosides (Table 2, entry 6).²⁹ Partial anomerization and ring modification occurred under these conditions; no acetolysis was observed with disaccharides.

Acetylation of alcohols with acetic acid was performed in the presence of metal-exchanged zeolites. By using LaY zeolite, different primary and secondary alcohols were acetylated in almost quantitative yield (Table 2, entry 7).³⁰ The same reaction was claimed to be catalyzed by metal-exchanged titanosilicalite M-ETS-10 (Table 2, entry 8).³¹ In contrast to the report for the reaction carried out in the presence of montmorillonite,²⁵ increasing the chain length of the carboxylic acid led to a decrease in the rate of the acylation, together with the formation of byproducts.

Protic and Lewis acids adsorbed on different organic and inorganic polymeric materials can be prepared easily by mixing the reagents and the supports. Despite the lively and deep discussion on the real nature of the active sites, with

particular emphasis on the possible leaching of acidity into solution, these materials have been extensively utilized as heterogeneous catalysts in different fields of synthetic organic chemistry, including their use in the protection–deprotection of hydroxylated compounds.

Various metal oxides and oxide-supported reagents were employed in the protection of hydroxy groups. Usually, the direct reaction of a carboxylic acid with an alcohol results in an equilibrium which requires the use of excess reagent or elimination of water through azeotropic distillation or addition of dehydrating agents. Rezende described the use of sulfuric acid supported on silica gel in chloroform as an efficient catalyst to irreversibly convert carboxylic acids and alcohols into the corresponding esters in high yield (Table 2, entry 9).³² It must be stressed that no reaction was observed when the reagents were stirred in the same solvent in the absence of silica, even if drops of concentrated sulfuric acid were added; in addition, the use of silica gel without the addition of sulfuric acid failed to promote the acylation process. The method is restricted to short-chain aliphatic acids, probably due to the fact that the long-chain lipophilic acids drifted away from the solid support into the nonpolar solvent. This observation, together with the fact that the reaction was not reversible, points to a process that takes place on the surface of the solid catalyst: the acid and the alcohol, both adsorbed on the polar silica gel, react to give the less polar ester, which returns to the nonpolar dichloromethane.



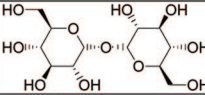
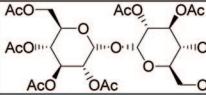


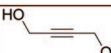







































Perchloric acid adsorbed on silica gel efficiently catalyzed the acylation of structurally diverse phenols and alcohols (Table 2, entry 9b).^{32b} The reaction can be carried out with an equimolecular amount of acetic anhydride at room temperature in 5–30 min. Optically active substrates were acetylated without any detrimental effect on the optical purity. Results confirm that the catalyst was superior in the acylation over the metal triflates. The acetylation of alcohols directly with acetic acid can be similarly performed in high yield.

A great variety of phenols and alcohols were protected as acetic acid esters by reaction with acetic anhydride catalyzed by silica-supported fluoroboric acid ($\text{SiO}_2/\text{HBF}_4$) (Table 2, entry 9c).^{32c} The reaction was best carried out at room temperature under neat conditions. Electron-poor and electron-rich phenols were similarly *O*-acetylated in high yields; similar high activity was observed with alcohols including tertiary ones.

A study was published concerning the high-yielding acetylation of phenols with acetic anhydride catalyzed by sulfated titania ($\text{TiO}_2/\text{SO}_4^{2-}$) (Table 2, entry 9d).^{32d} The reaction was performed in cyclohexane or methylene chloride, and the catalyst can be recovered and reused without significant loss of activity. Esterification of phenols with carboxylic acids has also been reported in combination with phosphorus pentoxide supported on silica gel as catalyst (Table 2, entry 10).³³

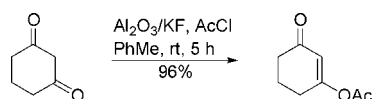
Transesterification of primary alcohols and diols with ethyl acetate used as solvent reagent has been performed in the presence of cerium sulfate-supported silica gel (Table 2, entry 11).³⁴ The corresponding (di)acetates were obtained in very high yield, whereas phenols carrying electron-donating groups were not acetylated; their protection as esters could, however, be achieved by using methyl benzoate in the presence of iron(III) sulfate-supported silica gel.³⁴

Table 2. Protection of Hydroxylated Compounds as Acetates

entry ^{ref}	catalyst ^a (experimental conditions)	hydroxylated compound	acetate	yield (%)	n. ex. (yields %)
1 ^{22, 23}	Mont. KSF (Ac ₂ O, neat, rt)			98	21 (78-98)
2 ²⁴	Mont. K10 (Ac ₂ O, neat, rt, 16 h)			98	14 (86-99)
3 ²⁵	Natural montmorillonite (AcOH, neat, 116 °C, 9 min)			98	13 (65-99)
4 ²⁶	FER zeolite ^a (Ac ₂ O, neat, 75 °C, 2 h)			91	12 (85-99)
5 ²⁷	Y zeolite HSZ-360 ^{a(7)} (Ac ₂ O, neat, 60 °C, 2 h)			89	21 (84-100)
6 ²⁹	Beta zeolite ^a (Ac ₂ O, neat, rt, 5 h)			99	14 (85-99)
7 ³⁰	LaY zeolite ^{a(4)} (AcOH, 80 °C, 12 h)			95	13 (86-99)
8 ³¹	M-ETS-10 ^{a(3)} (AcOH, neat, 120 °C, 8 h)			98	9 (70-99)
9 ³²	SiO ₂ /H ₂ SO ₄ (AcOH, CH ₂ Cl ₂ , rt, 4 h)			90	19 (70-91)
9b ^{32b}	SiO ₂ /HClO ₄ (Ac ₂ O, rt, 15 min)			90	38 (80-100)
9c ^{32c}	SiO ₂ /HBF ₄ ^a (Ac ₂ O, neat, rt, 15 min)			95	33 (75-100)
9d ^{32d}	TiO ₂ /SO ₄ ^{2-a} (Ac ₂ O, cyclohexane, 81 °C, 10 min)			98	15 (95-99)
10 ³³	SiO ₂ /P ₂ O ₅ (AcOH, neat, rt, 6 h)			75	12 (65-84)
11 ³⁴	SiO ₂ /Ce(SO ₄) ₂ (AcOEt, neat, 80 °C, 15 min)			97	7 (97-99)
12 ³⁵	SiO ₂ /TaCl ₅ (Ac ₂ O, CH ₂ Cl ₂ , rt)			79	9 (74-88)
12b ^{35b}	SiO ₂ /SOCl ₂ (Ac ₂ O, hexane, rt, 5 min)			92	17 (80-90)
13 ³⁶	Al ₂ O ₃ ^a (Ac ₂ O, Pyridine, MW 300W, 4 min)			100	13 (54-100)
14 ³⁸	Al ₂ O ₃ /KF (AcCl, neat, rt, 15 min)			98	16 (93-98)
15 ³⁹	α-Zr(O ₃ PCH ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} (Ac ₂ O, CH ₂ Cl ₂ , rt, 15 h)			80	22 (67-99)
16 ⁴⁰	WO ₃ /ZrO ₂ ^{a(1)} (Ac ₂ O, neat, Δ, 2 h)			97	6 (89-97)
17 ^{41, 42}	K ₃ CoW ₁₂ O ₄₀ ·3H ₂ O ^{a(7)} (AcOH, neat, Δ, 2 h)			85	23 (70-99)
18 ⁴³	Expansive graphite ^{a(4)} (Ac ₂ O, CH ₂ Cl ₂ , 40 °C, 3 h)			94	18 (92-99)
19 ⁴⁵	Nafion ^{®a(4)} (Ac ₂ O, CH ₂ Cl ₂ , rt, 4 h)			92	27 (68-99)

^a The catalyst has been recycled (number of recycles).

Scheme 1



The activation of acetic anhydride for conversion of alcohols (phenol and α -naphthol) into the corresponding acetates could be accomplished with **tantalum** chloride-supported silica gel (Table 2, entry 12).³⁵ The only limitation of the method was represented by the fact that, with tertiary alcohols, the production of olefins was strongly competitive.

Primary, secondary, tertiary, and very hindered alcohols and diols were efficiently acetylated with acetic anhydride in the presence of silica chloride (Table 2, entry 12b).^{35b} The reactions were performed in hexane at room temperature for 5 min.

Basic alumina was a versatile catalyst for acetylation of phenols under solvent-free conditions and microwave irradiation in the presence of pyridine. Using acetic anhydride, phenyl acetates were isolated after a very short irradiation time (1–6 min) in high yields (Table 2, entry 13),³⁶ with the sole exception of α - and β -naphthols, whose esters were prepared in 65% and 62% yield, respectively. The method represents an environmentally friendly procedure since acetic acid (byproduct) remains adsorbed over the basic alumina and there is no evaporation into the atmosphere.

Potassium fluoride supported on alumina, earlier used for the *O*-alkylation of alcohols and phenols,³⁷ has been successfully applied by Yadav et al. to protect primary and secondary alcohols in the presence of tertiary ones and phenols. The reaction, carried out with acetyl chloride in toluene, afforded the corresponding acetates in almost quantitative yield (Table 2, entry 14),³⁸ diacetates were obtained from diols, and, interestingly, 1,3-diketones, which do not exist in cyclic hydrogen-bonded structures, underwent monoacetylation (Scheme 1).

The reaction showed an enormous rate enhancement in the absence of the solvent; for example, the acetylation of β -naphthol (90% yield) required 30 h in toluene, whereas in the absence of diluent the reaction was complete within 30 min.

Inorganic–organic layered solids belonging to the class of metal(IV) phosphonates and bearing suitable functional groups are excellent catalysts for organic synthesis, since they combine the properties of a stable inorganic backbone with the flexibility of the organic derivatives. Thus, zirconium methanesulphophenyl phosphonate was able to catalyze the acetylation of not only primary, secondary, benzylic, and acetylenic alcohols but also tertiary alcohols and phenols with the use of acetic anhydride (Table 2, entry 15);³⁹ under these conditions, sugars were peracetylated. In a similar way, WO_3/ZrO_2 was utilized as catalyst for production of acetates of various alcohols and phenols (Table 2, entry 16).⁴⁰

Heteropoly compounds provide a good basis for the design of mixed oxide catalysts with high capability for practical uses. Their catalytic performance could be conveniently tailored on the basis of chemical and physical properties, molecular and bulk composition, structure, and method of synthesis.

Esterification of alcohols with acetic acid was reported by Habibi et al. to be performed in the presence of potassium dodecatungstocobaltate trihydrate ($\text{K}_5\text{CoW}_{12}\text{O}_{40} \cdot 3\text{H}_2\text{O}$). It is important to mention that bulky tertiary alcohols could also be acetylated in high yield (Table 2, entry 17).^{41,42} The

reaction could also be performed efficiently with the use of ethyl acetate as acetylating agent⁴¹ or in the presence of a solvent, namely acetonitrile, isolating the corresponding acetates in good yields and with shorter reaction times.⁴²

Expansive graphite represents a good heterogeneous catalyst for the protection of primary and secondary alcohols and phenols as acetates; polyhydroxylated compounds (i.e., salicylic alcohol, hydroquinone, and benzene-1,3,5-triol) are also converted into their polyacetates (Table 2, entry 18).⁴³ Finally, the commercially available Nafion, a solid acid catalyst commonly used in organic synthesis,⁴⁴ was utilized for the acetylation of primary and secondary alcohols with acetic anhydride (Table 2, entry 19);⁴⁵ monosaccharides underwent peracetylation with the use of acetic anhydride as solvent reagent. Acid-sensitive groups such as ketal, acetal, tetrahydropyranyl (THP) ether, and cyclopropane units survived under these reaction conditions.

2.1.2. Deprotection

The regeneration of alcohols from their esters can be carried out under heterogeneous conditions by using some solid catalysts, such as zeolites, silica, alumina, and acidic resins.

Neutral alumina combined with microwave irradiation was utilized by Varma et al. to promote selective de-esterification of aryl acetates and alkyl acetates under solventless conditions (Table 3, entry 1),⁴⁶ whereas ZSM-5 zeolite alone promoted the deacetylation of alkyl acetates in an aqueous medium (Table 3, entry 2).⁴⁷ Due to the pore dimension of this type of zeolite (5.1–5.6 Å), no reaction in the case of cyclododecanol acetate was observed, ascribable to the nondiffusibility of this reagent into the pores of the solid catalyst. A typical reactant shape selectivity was observed when competitive deacetylation reactions were carried out: for example, by treating a 1/1 mixture of α -methylbenzyl acetate/diphenylcarbinol acetate, the corresponding alcohols were isolated in a 100/21 molar ratio.

A very simple and efficient method for the full deprotection of bistrifluoroacetates of diols could be performed with a silica gel-based catalyst upon treatment with triethylamine (Table 3, entry 3).⁴⁸

A facile cleavage of aryl acetates can be performed in the presence of Amberyst-15 as catalyst (Table 3, entry 3b).^{48b} The reactions were performed at room temperature for 2–6 h in methanol. Aliphatic alcohol acetates were unaffected by the catalyst under the present reaction conditions. Amberyst-15 was inert toward aryl acetates bearing electron-withdrawing groups such as aldehyde, ketone, benzoate, *N*-acetyl, and tosylate.

Finally, the de-esterification of sugar and nucleoside acetates has been accomplished by using IRA-400(OH^-) resin. Complete *O*-deacetylation was observed upon treating peracetylated sugar/nucleosides dissolved in methanol (Table 3, entry 4).⁴⁹

2.2. Silyl Ethers

2.2.1. Protection

Protection of hydroxy groups through the formation of silyl ethers has been extensively utilized in organic synthesis. Silyl ethers are easily prepared, they show resistance to oxidation, good thermal stability, and low viscosity, and they are easily recoverable from their parent compounds. Moreover, numer-

Table 3. Deprotection of Acetates

entry ^{ref}	catalyst ^a (experimental conditions)	protected alcohol	hydroxylated compound	yield (%)	n. ex. (yields %)
1 ⁴⁶	Al ₂ O ₃ (neat, MW 800W, 4 min)			91	14 (82-96)
2 ⁴⁷	ZSM-5 zeolite (H ₂ O, Δ)			94	9 (62-100)
3 ⁴⁸	SiO ₂ /Et ₃ N (neat, rt)			95	7 (95-100)
3b ^{48b}	Amberlyst 15 ^a (MeOH, rt, 4 h)			87	18 (85-95)
4 ⁴⁹	IRA-400(OH) (MeOH, rt, 45 min)			71	6 (70-91)

^a The catalyst has been recycled.**Table 4. Protection of Hydroxylated Compounds as Silyl Ethers**

entry ^{ref}	catalyst ^a (experimental conditions)	hydroxylated compound	silyl ether	yield (%)	n. ex. (yields %)
1 ⁵⁰	Kaolin ^{a(5)} (HMDS, CCl ₄ , rt, 2 h)			94	6 (85-95)
2 ⁵¹	Mont. K10 (HMDS, CH ₂ Cl ₂ , rt, 30 min)			86	17 (76-98)
3 ⁵²	Envirocat EPZG [®] (HMDS, MeCN, 85 °C, 30 min)			97	8 (70-97)
4 ⁵³	α-Zr(O ₃ PCH ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} (HMDS, CH ₂ Cl ₂ , rt, 20 h)			95	10 (71-95)
5 ⁵⁴	Al ₂ O ₃ /KF (SEMCl, DME, rt, 2 h)			96	6 (88-96)

^a The catalyst has been recycled (number of recycles).

ous silylating methods can be utilized today; among them, trimethylsilylation is one of the most often used.

Alcohols and phenols could be conveniently converted into the corresponding silyl ethers by treatment with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of a natural kaolinitic clay treated with 2 M hydrochloric acid (Table 4, entry 1)⁵⁰ or montmorillonite K10 (Table 4, entry 2).⁵¹ The latter procedure was quite general, as a wide range of hydroxy-containing compounds, including some highly bulky ones, were protected. A small substituent effect was observed (Table 5, compare entries 1, 2, 3, 4, and 6). Phenols carrying electron-releasing groups afforded the products in nearly quantitative yield in shorter reaction times.

Silylation of alcohols and phenols with HMDS has been also performed by using Envirocat EPZG (Table 4, entry

Table 5. Protection of Phenols as TMS Ethers

entry	R	time (h)	yield (%)
1	H	1	95
2	3-CH ₃	0.6	90
3	4-OCH ₃	0.75	94
4	2-OH	0.35	92
5	3-OH	1	85
6	2-Cl	5	96
7	2,3-CH=CH-CH=CH	1.5	92
8	3,4-CH=CH-CH=CH	6	76

3).⁵² The reaction tolerates the presence of amines and thiols. Similarly, good results of trimethylsilylation of alcohols and phenols, including *tert*-butyl alcohol, have been achieved by using zirconium sulfophenyl phosphonate [α-Zr(O₃PCH₃)_{1.2}(O₃PC₆H₄SO₃H)_{0.8}] (Table 4, entry 4).⁵³

Table 6. Deprotection of Silyl Ethers

entry ^{ref}	catalyst ^a (experimental conditions)	silyl ether	hydroxylated compound	yield (%)	n. ex. (yields %)
1 ⁵⁸	Mont. K10 (MeOH/H ₂ O 1/1, 75 °C, 12 h)			94	12 (75-97)
2 ⁵¹	Mont. K10 (MeOH, rt, 21 min)			93	17 (89-98)
3 ⁵⁹	Mont. K10 (neat, MW 900W, 1 min)			98	12 (88-100)
4 ⁶⁰	K ₃ CoW ₁₂ O ₄₀ ·3H ₂ O ^a (MeCN, rt, 15 min)			100	17 (96-100)
5 ⁶¹	Al ₂ O ₃ (neat, MW 800W, 11 min)			75	7 (68-93)
6 ⁵⁴	Al ₂ O ₃ /KF (DME, rt, 4 h)			100	6 (88-96)
7 ⁶²	Zr(KPO ₄) ₂ ^a (Me ₂ CO/H ₂ O 9/1, 60 °C, 8 h)			83	11 (76-93)
7b ^{62b}	LL-ALPS-SO ₃ H ^a (H ₂ O, 40 °C, 12 h)			89	15 (76-99)
7c ^{62c}	SiO ₂ -SO ₃ H ^{a(7)} (MeOH, 35 °C, 9 h)			88	16 (48-99)

^a The catalyst has been recycled.

Phenolic 2-(trimethylsilyl)ethoxymethyl (SEM) ethers could be prepared by reaction with SEMCl in the presence of potassium fluoride supported on alumina (Al₂O₃/KF) in order to replace tertiary amine bases. The method is simpler than most of those available, as it avoids aqueous workup and the products are isolated after filtration and removal of the solvent (Table 4, entry 5).⁵⁴ The method is effective for both electron-rich and electron-poor phenols, but alcohols cannot be converted into the alkyl-SEM ethers.

2.2.2. Deprotection

The deprotection of trimethylsilyl (TMS) ethers is commonly carried out in the presence of catalysts such as iron(III) or tin(II) chlorides, copper(II) or cerium(III) nitrates, citric acid, and sodium hydroxide^{55,56} or various fluoro derivatives.⁵⁷

Removal of the silyl protecting group from hydroxy functions of carbohydrates and nucleosides in aqueous methanol has been performed by Arakura et al. with montmorillonite K10. Thus, 3',5'-di-*O*-*tert*-butyldimethylsilyl-2'-deoxyuridine could be efficiently deprotected to 2'-deoxyuridine (Table 6, entry 1).⁵⁸ Differently protected nucleoside derivatives **1**, **2**, and **3** (Figure 1) afforded the completely deprotected compounds in high yield upon treatment with montmorillonite K10 in methanol/water.

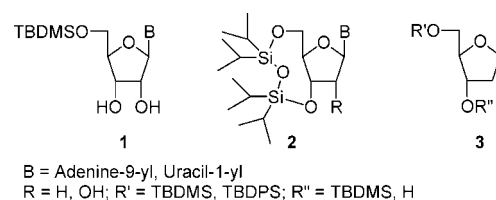


Figure 1.

The authors showed also the applicability of the present catalyst for deprotection of acetal and dimethoxytrityl (DMTr)-protected sugars.

The same catalyst was utilized for the desilylation of primary and secondary alcoholic and phenolic trimethylsilyl ethers. Complex molecules, such as betulin bistrimethylsilyl ether, could be completely desilylated (Table 6, entry 2),⁵¹ but the sterically crowded trimethylsilyloxy triphenylmethane was desilylated only in 40% conversion after 4 h, probably due to the steric hindrance which hampers the access to the active sites of the catalyst. The reaction can be carried out in shorter reaction times by combining the use of clay with microwave irradiation under solvent-free conditions (Table 6, entry 3).⁵⁹

Similarly, TMS ethers of alcohols could be efficiently cleaved by potassium dodecatungstocobaltate trihydrate (K₃CoW₁₂O₄₀·3H₂O) (Table 6, entry 4).⁶⁰ Phenolic TMS ethers were resistant toward deprotection with this catalyst.



Figure 1b.

The *tert*-butyldimethylsilyl (TBDMS) group, one of the most widely used protecting groups in organic synthesis for hydroxy functionality, was removed by a manipulatively easy and solvent-free method. The reaction was performed in high yield and in a short time on an alumina surface under microwave irradiation (Table 6, entry 5).⁶¹ The microwave effect is not purely thermal, as it is borne out by the fact that longer reaction periods are required for similar yields using alternative heating modes at the same temperature. Some drawbacks are related to the great amount of inorganic support required to adsorb the organic compound to be deprotected (i.e., 35 g of alumina for 2 mmol of TBDMS ether). The reaction could be performed with good results by using silica instead of alumina as the support, but in the case of nucleoside analogues, cleaner products are obtained only with basic alumina.

Blass et al. reported the use of potassium fluoride supported on neutral alumina to efficiently and selectively remove a variety of silyl protecting groups from phenols. It was possible to differentiate between electron-rich and electron-poor phenolic ethers on the basis of the strong solvent effect. For example, TMS-4-bromophenol was readily deprotected with neutral $\text{Al}_2\text{O}_3/\text{KF}$ in 1,2-dimethoxyethane (DME) or 1,4-dioxane after only 4 h at 25 °C, whereas TBDMS-4-bromophenol was found to be stable after 16 h in DCE. Switching the solvent to DME facilitated the cleavage of the TBDMS group, which was accomplished only after 4 h at 25 °C (Table 6, entry 6).⁵⁴

Potassium-exchanged layered zirconium phosphate represents another solid, not commercially available, base catalyst that is useful to deprotect phenolic silyl derivatives. The catalyst was efficiently applied for the cleavage of particularly hindered compounds such as TBDMS, triethylsilyl (TES), and *tert*-butyldiphenylsilyl (TBDPS) ethers of phenols (Table 6, entry 7).⁶²

Low-loading polystyrene and alkylated supported sulfonic acid ($\text{LL} \cdot \text{ALPS} \cdot \text{SO}_3\text{H}$, Figure 1b) was utilized by Kobayashi et al. as a hydrophobic heterogeneous sulfonic acid to deprotect TBS ethers (Table 6, entry 7b).^{62b} The reaction proceeded in high yield for primary, secondary, and aromatic TBS ethers, in water under mild conditions. The catalyst gave high to excellent yields not only for silyl ethers such as triisopropylsilyl (TIPS) and TBDPS, but also for trityl (Tr) and methoxymethyl (MOM) ethers.

A high-loading sulfonic acid-functionalized nanoporous silica ($\text{SiO}_2\text{--SO}_3\text{H}$) was utilized as heterogeneous catalyst to perform the deprotection of a variety of TBDMS protected alcohols in methanol (Table 6, entry 7c).^{62c} The method is general for the cleavage of TBDMS ethers of primary, secondary, allylic, and hindered, acid-sensitive secondary TBDMS ethers; in addition, the reaction conditions are mild enough to allow a $\text{C}=\text{C}$ double bond to remain unaffected. The catalyst was recycled seven times for the deprotection of TBDMS-protected benzyl alcohol, giving an average yield of 92.5%.

2.3. Alkoxyalkyl Ethers

2.3.1. Protection as THP Ethers

THP ethers have found extensive use in organic synthesis; they can be easily synthesized from a variety of hydroxy-containing compounds by acid-catalyzed reaction with 3,4-dihydro-2H-pyran (DHP). They are stable to bases, but the protection is removed through acid hydrolysis. It is important to point out that the introduction of the THP ether onto a chiral molecule results in the formation of diastereoisomers because of the additional stereogenic center present in the tetrahydropyran ring, which can make both the NMR spectra interpretation and the handling of the reaction crude somewhat troublesome.¹⁴

Some inexpensive and readily available naturally occurring clays, often utilized as efficient and versatile catalysts for organic reactions⁶³ and already mentioned in this review, were utilized for the tetrahydropyranlation of hydroxy compounds. For example, the protection of a large variety of hydroxy compounds was performed under very mild reaction conditions with DHP in the presence of K10 clay (Table 7, entry 1)⁶⁴ or Spanish sepiolite clay (Table 7, entry 2).⁶⁵ Both procedures gave nearly quantitative yields for most primary, secondary, tertiary, allylic, and polyfunctional alcohols, as well as for phenols. More efficiently, a natural kaolinitic clay, preactivated by washing with 2 M hydrochloric acid, was applied in the reaction with alcohols, including tertiary ones (Table 7, entry 3).⁵⁰ The activity of the catalyst was attributed to the presence of the surface protic and Lewis acid sites due to the disordered Al^{3+} and Fe^{3+} ions and surface water molecules.

Envirocat EPZG, which exhibits both Brønsted and Lewis acid characteristics, could be utilized for the highly efficient tetrahydropyranlation of alcohols and phenols in a short reaction time at 0–5 °C. The products were isolated simply by treatment of the final reaction mixture with dichloromethane, filtration, and removal of the solvent under reduced pressure (Table 7, entry 4).⁶⁶

Acid zeolites have also been utilized to protect alcohols and phenols. Good yields of THP derivatives of a wide range of hydroxy compounds, such as primary, secondary, tertiary, allylic, acetylenic and polyfunctional alcohols, could be obtained by using a Y zeolite with a silica/alumina ratio (SAR) of 4.86 (Table 7, entry 5).⁶⁷ However, reaction of bulky substrates was slower, and longer reaction times were required (i.e., *sec*-butanol, 90% yield in 2 h; benzyl alcohol, 70% yield in 10 h). More conveniently, the protection of phenols and alcohols could be performed under solventless conditions by using zeolites with different SARs (5.9 and 13.9, respectively) (Table 7, entry 6).⁶⁸

Frequently, zeolites present some limitations when large reactant molecules are involved, especially in liquid-phase systems, as is often the case in the synthesis of fine chemicals. To this end, Corma et al. utilized the new zeolitic material ITQ-2; in this material, the zeolite-type catalytic sites are contained within thin and readily accessible sheets.⁸ ITQ-2 was found to be an efficient catalyst to protect alcohols and phenols, including naphthols and steroids (Table 7, entry 7).⁶⁹

Mesoporous H-MCM-41 molecular sieves (SAR = 51.8) represent another zeolite-type material utilized for the reaction with bulky molecules. This material possesses a hexagonal arrangement of uniformly sized, unidimensional mesopores (diameter from ~15 to 100 Å), which give

Table 7. Protection of Hydroxylated Compounds as THP Ethers

entry ^{ref}	catalyst ^a (experimental conditions)	hydroxylated compound	THP ether	yield (%)	n. ex. (yields %)
1 ⁶⁴	Mont. K10 (CH ₂ Cl ₂ , rt, 20 min)			89	21 (63-95)
2 ⁶⁵	Sepiolite (neat, Δ, 15 min)			>99	5 (48-99)
3 ³⁰	Kaolin ^{a(5)} (CCl ₄ , rt, 2 h)			83	9 (81-91)
4 ⁶⁶	Envirocat EPZG [®] (neat, 0 °C, 1 h)			98	13 (76-99)
5 ⁶⁷	Y zeolite (hexane, Δ, 10 h)			60	13 (60-95)
6 ⁶⁸	Y zeolite ^{a(5)} (neat, rt, 1.5 h)			70	12 (66-100)
7 ⁶⁹	ITQ-2 (neat, 69 °C, 30 min)			90	6 (90-100)
8 ⁷⁰	MCM-41 ^a (hexane, 69 °C, 6.5 h)			69	6 (69-99)
9 ⁷¹	SiO ₂ /H ₂ SO ₄ (CH ₂ Cl ₂ , rt, 1 min)			80	11 (80-92)
10 ⁷²	SiO ₂ /H ₂ SO ₄ (CH ₂ Cl ₂ , rt, 3 min)			94	11 (93-100)
11 ⁷³	Silica chloride (CH ₂ Cl ₂ , rt, 10 min)			86	16 (82-93)
11b ^{73b}	SiO ₂ -SO ₃ H ^{a(4)} (CH ₂ Cl ₂ , 25 °C, 6 h)			81	9 (78-99)
12 ⁷⁴	SiO ₂ /TaCl ₅ (CH ₂ Cl ₂ , rt, 10 min)			71	6 (71-98)
13 ⁷⁵	Al ₂ O ₃ /ZnCl ₂ (neat, rt, 30 min)			80	15 (75-90)
14 ⁷⁶	Hydrated ZrO ₂ (neat, MW 2450 MHz, 7 min)			90	16 (80-98)
15 ⁷⁸	ZrO ₂ /SO ₄ ²⁻ (CH ₂ Cl ₂ , rt, 1 h)			89	11 (80-96)
16 ⁷⁹	ZrO ₂ /SO ₄ ²⁻ (neat, rt, several min)			86	8 (82-96)
17 ⁸⁰	AlPO ₄ (neat, 15 min)			85	7 (51-99)
18 ⁸¹	α-Zr(O ₃ PCH ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} (CH ₂ Cl ₂ , rt, 1.5 h)			87	12 (61-95)
19 ⁸²	Sulfated charcoal (CH ₂ Cl ₂ , rt, 5 h)			97	19 (67-98)
20 ⁸³	(P)-ATPB (CH ₂ Cl ₂ , rt, 5 h)			96	8 (95-99)
21 ⁸⁴	Nafion [®] (CH ₂ Cl ₂ , rt, 2 h)			95	7 (90-98)

^a The catalyst has been recycled (number of recycles).

molecules access to the large internal surface that enhances catalytic activity and adsorption capacity. Thus, alcohols and phenols could be protected by treatment with a small excess of DHP in hexane (Table 7, entry 8).⁷⁰ Improvement of the efficiency of the process was obtained by adding the DHP dropwise.

Furthermore, THP ethers of alcohols and phenols were efficiently prepared by carrying out the reactions in the presence of sulfuric acid adsorbed on silica gel. In most cases the reactions were complete on simple mixing reagents and catalyst in a mortar (Table 7, entry 9).⁷¹ When the reaction was carried out in the presence of dichloromethane as solvent, more complex and polyfunctional substrates could be protected in almost quantitative yield and in very short reaction times (1–10 min). The method avoided aqueous workup, reduced to merely filtration and solvent evaporation. Steroids, cinnamic and propargylic alcohols, were quantitatively converted into the corresponding THP ethers (Table 7, entry 10).⁷² The same reaction could be performed selectively by using silica chloride, a material prepared from silica and thionyl chloride (Table 7, entry 11).⁷³

Tetrahydropyranlation of alcohols at room temperature can be catalyzed by sulfonic acid-functionalized silica ($\text{SiO}_2\text{--SO}_3\text{H}$) (Table 7, entry 11b), which represents a solid catalyst that is more stable and reusable than silica simply impregnated with sulfuric acid ($\text{SiO}_2/\text{SO}_3\text{H}$).^{73b} The low acid strength of the catalyst and the mild reaction conditions allow the protection of more labile reagents such as allyl and propargyl alcohols. Protection of highly hindered alcohols can also be achieved in high yield.

$\text{SiO}_2/\text{TaCl}_5$ represents a silica-supported Lewis acid that was efficiently utilized in the production of THP ethers from alcohols. Interestingly, it was noted that this material acts as a more efficient catalyst, even at low concentrations, and requires shorter reaction times with respect to TaCl_5 alone. The reaction could be applied efficiently to benzyloxy and acid-labile sugar substrates containing acetal groups (Table 7, entry 12).⁷⁴

Ranu et al. utilized alumina-supported zinc chloride for tetrahydropyranlation of alcohols through a simple solvent-free reaction (Table 7, entry 13).⁷⁵ Also in this case, the authors mentioned that the reaction catalyzed by zinc chloride alone in the absence of alumina in tetrahydrofuran (THF) or on the alumina surface without zinc chloride was sluggish. On the other hand, when the reaction was carried out in solvents (CH_2Cl_2 or THF) under identical conditions with zinc chloride-supported alumina, the progress of THP production was practically nil. Thus, the combination of the solid surface of alumina and zinc chloride with the absence of solvent is essential for a satisfactory reaction; although this fact was not rationalized, the process showed great and interesting applicability, and some acid-sensitive functionalities, such as ketals, were safe under this procedure.

Zirconia in its pure and modified form has been employed in many synthetic and industrial processes. Microwave-accelerated tetrahydropyranlation of alcohols and phenols, catalyzed by hydrated zirconia, was reported. Allylic and acetylenic alcohols were protected without isomerization of double and triple bonds, and the corresponding THP ethers were isolated as the only products. In addition, particularly bulky substrates, such as cholesterol and naphthols, were protected in high yields within a very short time. Phenols containing a dioxolane protective group could be converted

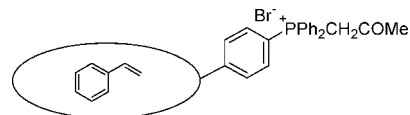


Figure 2.

into THP ethers in high yield without further transformations (Table 7, entry 14).⁷⁶

Sulfated zirconia ($\text{ZrO}_2/\text{SO}_4^{2-}$) is a popular solid superacid catalyst exhibiting the highest acid strength ($H_0 \leq -16.04$).⁷⁷ Treatment of a variety of alcohols and phenols with DHP in the presence of a catalytic amount of sulfated zirconia gave the corresponding THP ethers in high yield. The procedure could also be efficiently applied to highly acid-sensitive alcohols such as allyl and propargyl alcohols (Table 7, entry 15).⁷⁸ This solid catalyst was utilized for the tetrahydropyranlation of hydroquinone protected as the benzyl ether (Table 7, entry 16).⁷⁹

Campelo et al. utilized AlPO_4 as a solid acid catalyst for the protection of alcohols and phenols. The reaction, carried out in the presence of an excess of DHP, proceeded selectively under mild conditions in very good yields, with short reaction times (~ 15 min) and without the formation of troublesome oligomeric pyrans (Table 7, entry 17).⁸⁰ Similarly, $\alpha\text{-Zr}(\text{O}_3\text{PCH}_3)_{1.2}(\text{O}_3\text{PC}_6\text{H}_4\text{SO}_3\text{H})_{0.8}$ promoted the tetrahydropyranlation of alcohols and phenols; the reaction tolerates C–C double and triple bonds, and the yields are not affected by the steric hindrance of reagents (Table 7, entry 18).⁸¹

A large series of alcohols and phenols has been protected by using sulfated charcoal, in combination with 3-Å molecular sieve; in the absence of molecular sieves, the reaction was very slow. The process showed general applicability, and in the majority of cases, due to the very high yields, the purification of THP ethers was achieved simply by filtration (Table 7, entry 19).⁸²

Very recently, the reaction was performed using catalyst supported on organic polymers, materials that are of growing interest in organic synthesis. Thus, by using acetonyltriphenylphosphonium bromide (ATPB) supported on polystyrene (Figure 2), Hon et al. obtained good yields in the protection of a large variety of phenols and alcohols, including tertiary ones and alcohols carrying additional functional groups, such as a carbonyl group (Table 7, entry 20).⁸³













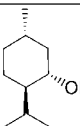
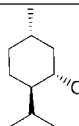


Finally, Olah et al. reported the use of Nafion for the tetrahydropyranlation of primary and secondary alcohols. To avoid the formation of a black charry material, the reaction was performed by slowly adding a solution of THP in dichloromethane to a mixture of the alcohol and Nafion in the same solvent (Table 7, entry 21).⁸⁴

2.3.2. Protection as Other Alkoxyalkyl Ethers

The methoxymethyl moiety is an important protecting group for alcohols. It is stable to a variety of commonly used reagents, such as strong bases, Grignard reagents, alkylolithiums, and lithium aluminum hydride, and it is readily removed by acid treatment.⁸⁵

Kumar et al. prepared methoxymethyl (MOM) ethers of alcohols, including tertiary ones, in satisfactory yields by reaction with chloromethyl methyl ether (MOMCl) in the presence of NaY zeolite (Table 8, entry 1).⁸⁶ Lower yields and selectivities have been obtained with the acid Y zeolite or with other zeolites such as ZSM-5, mordenite, and 4- or 5-Å molecular sieves.

Table 8. Protection of Hydroxylated Compounds as Methoxyalkyl Ethers

entry ^{ref}	catalyst ^a (experimental conditions)	hydroxylated compound	alkyl ether	yield (%)	n. ex. (yields %)
1 ⁸⁶	NaY zeolite (CH ₃ OCH ₂ Cl, CH ₂ Cl ₂ , Δ, 6 h)			70	10 (70-91)
2 ⁸⁷	Al ₂ O ₃ ^a (CH ₃ OCH ₂ Cl, neat, MW 50 Hz, 6 min)			83	10 (68-92)
3 ⁸⁸	Expansive graphite ^a (CH ₃ OCH ₂ OCH ₃ , neat, Δ, 4 h)			93	10 (60-95)
4 ⁸⁹	Envirocat EPZG ^{89a} (CH ₃ OCH ₂ OCH ₃ , CH ₂ Cl ₂ , 40 °C, 14 h)			90	11 (68-99)
5 ⁹⁰	Mont. K10 ^a (CH ₃ OCH ₂ OCH ₃ , CHCl ₃ , Δ, 6 h)			93	9 (33-93)
6 ⁹¹	3 Å Molecular sieves/FeCl ₃ (CH ₃ OCH ₂ OCH ₃ , CH ₂ Cl ₂ , rt, 1 h)			84	12 (79-99)
7 ⁹²	TiO ₂ /SO ₄ ^{2-a} (CH ₃ OCH ₂ OCH ₃ , CHCl ₃ , 41 °C, 9 h)			95	9 (77-95)
8 ⁹³	SiO ₂ /H ₂ SO ₄ ^a (MeOCH=CH ₂ , CH ₂ Cl ₂ , 5 °C, 5 min)			99	4 (84-99)

^a The catalyst has been recycled.

A very simple procedure for methoxymethylation of primary and secondary alcohols through a solvent-free reaction was based on the use of the same reagent and alumina catalyst under sonication. Thus, MOMCl was added dropwise to the alcohol adsorbed on the surface of alumina, activated by heating at 200 °C. The product was isolated by simple extraction of the solid mass with methylene chloride (Table 8, entry 2).⁸⁷ However, it must be emphasized that the use of MOMCl is restricted due to its high carcinogenicity.

To overcome the problems and limitations connected with the toxicity of MOMCl, the less problematic reagent dimethoxymethane has been efficiently utilized. Expansive graphite (Table 8, entry 3)⁸⁸ and two commercially available heterogeneous catalysts, namely Envirocat EPZG (Table 8, entry 4)⁸⁹ and montmorillonite K10 (Table 8, entry 5),⁹⁰ have been efficiently utilized to promote the conversion of different primary and secondary alcohols into the corresponding MOM ethers. Chiral centers were preserved in the reactions.

Iron trichloride, dispersed on powdered 3-Å molecular sieves, was claimed by Patney to promote the MOM protection of primary and secondary alcohols at room temperature for short reaction times (Table 8, entry 6).⁹¹ A limitation of the method is represented by the fact that it requires quenching with diluted sodium hydroxide, suggesting a possible doubt that iron trichloride could act as a real catalyst.

Sulfated titania is a catalyst which has been little utilized in organic synthesis. This material was able to convert primary and secondary (chiral) alcohols into the corresponding MOM ethers by reaction with dimethoxymethane in chloroform (Table 8, entry 7).⁹²

The 2-methoxypropyl group represents one of the most acid-sensitive protecting groups for alcohols and phenols. *p*-Methoxybenzyl alcohol reacted with 2-methoxypropene in the presence of the inexpensive SiO₂/H₂SO₄, affording the corresponding 1-methyl-1-methoxyethyl ether in 89% yield. The reaction could be applied to steroids, phenols, and cinnamic alcohols (Table 8, entry 8).⁹³ Usually the crude

products were pure enough that the purification steps were skipped due to both the high yields of the process and the soft reaction conditions.

2.3.3. Deprotection

Different solid catalysts have been utilized to remove the protective group from *O*-protected alcohols and phenols, including naturally occurring clays and acid-treated siliceous materials and polymers.

Tonsil, a commercially available Mexican bentonite earth, and montmorillonite K10 clays have been utilized to deprotect THP ethers of alcohols and phenols by methanolysis (Table 9, entries 1–3).^{94–96} An interesting application is represented by the deprotection of reagents **4** to give alcohols **5** in acceptable yields (73–77%), saving the epoxy functionality (Scheme 2).

Removal of the MOM function often requires relatively harsh acidic conditions because of its chemical stability, which has somewhat restricted its utilization in molecules containing other acid-sensitive functionalities. Behar et al. performed the deprotection of phenolic MOM ethers by using montmorillonite K10 clay. The reaction proceeded at room temperature in benzene and showed general applicability for a variety of ortho-substituted, MOM-protected phenols, though it requires the presence of a functional group bearing a heteroatom in this position. A mechanism involving chelation-assisted cleavage of the MOM ether by the Lewis acidic montmorillonite clay was also proposed (Figure 3). Moreover, the method could be successfully applied to differentiate phenolic groups in naphthoquinone- and anthraquinone-containing antitumor antibiotics with highly oxygenated frameworks (Table 9, entry 4).⁹⁷

Scheme 2

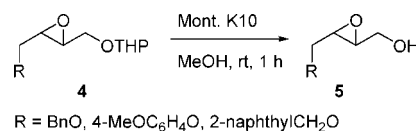


Table 9. Deprotection of Alkyl Ethers

entry ^{ref}	catalyst ^a (experimental conditions)	alkyl ether	hydroxylated compound	yield (%)	n. ex. (yields %)
1 ⁹⁴	Tonsil ^a (Me ₂ CO, rt, 30 min)			80	10 (60-95)
2 ⁹⁵	Mont. K10 (MeOH, rt, 1 h)			86	9 (80-99)
3 ⁹⁶	Mont. K10 ^a (MeOH, 50 °C, 30 min)			96	17 (91-98)
4 ⁹⁷	Mont. K10 (PhH, rt, 45 min)			95	10 (74-100)
5 ⁹⁸	Mont. K10/NH ₄ NO ₃ (clayan) (neat, MW, 2.5 min)			81	13 (70-88)
5b ^{98b}	SiO ₂ /NaHSO ₄ (CH ₂ Cl ₂ , rt, 1.5 h)			89	19 (76-100)
6 ⁹⁹	SiO ₂ /H ₂ SO ₄ (MeOH, Δ, 15 min)			90	11 (78-92)
7 ⁷⁶	Hydrated ZrO ₂ (MeOH, MW 2450 MHz, 8 min)			90	16 (75-95)
8 ¹⁰⁰	Dowex [®] 50WX2 (MeOH/H ₂ O, Δ, 3 h)			93	8 (42-97)
9 ⁸³	(P)-ATPB (MeOH, rt, 50 h)			90	21 (70-98)
10 ¹⁰¹	(P)-DCKA ^a (H ₂ O, rt, 2 h)			94	5 (67-97)

^a The catalyst has been recycled.

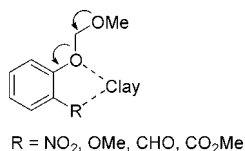


Figure 3.

Methoxyphenylmethyl (MPM) ethers have been frequently utilized in organic synthesis because of their stability toward acid, alkali, and a number of other reagents; thus, their selective deprotection into the parent hydroxy groups showed increased importance. Cleavage of MPM ethers containing a wide range of functionalities could be performed by using clayan in dry media, combined with microwave irradiation. Different functionalities survive the treatment, such as the C–C double and triple bonds (Table 9, entry 5)⁹⁸ and amino, halo, and carboxylic groups.

Silica-supported sodium hydrogen sulfate (SiO₂/NaHSO₄) was utilized as a heterogeneous catalyst for the cleavage of phenolic MOM ethers (Table 9, entry 5b).^{98b} The deprotection occurs under mild reaction conditions at room temperature in high yield. Phenolic MOM ethers can be selectively

cleaved in the presence of various functional groups such as ester and aldehyde. The method is efficiently applied for the deprotection of phenolic MOM ethers of bioactive natural products.

A further method for deprotection of THP ethers of alcohols and phenols involves the use of silica gel-supported sulfuric acid (Table 9, entry 6)⁹⁹ and hydrated zirconia (Table 9, entry 7).⁷⁶ The process with the latter catalyst was markedly accelerated by microwave irradiation.

Seto et al. reported the use of Dowex 50WX2 cationic-exchanged resin as an active catalyst for the highly efficient and selective removal of the MOM function from different protected alcohols; tertiary alcohols, which are prone to dehydration to the corresponding olefins, could be recovered in almost quantitative yield. The method was applied to a series of complex gibberellinic acid derivatives; all skeletal rearrangements of the C/D ring system were completely eliminated. This behavior was in contrast to the results from *p*-toluenesulfonic acid-catalyzed hydrolysis, which afforded a considerable amount of the rearrangement products (Table 9, entry 8).¹⁰⁰

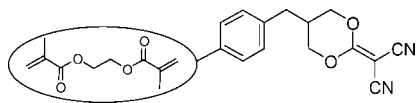
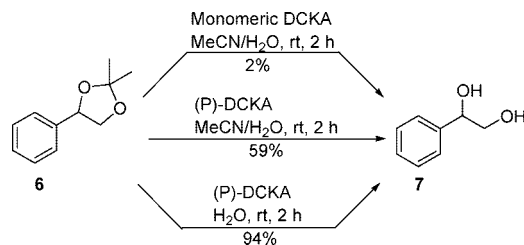


Figure 4.

Scheme 3



Some organic catalysts supported on polymeric materials have been utilized in the regeneration of alcohols from their protected derivatives. For example, poly-*p*-styryldiphenylacetonyl phosphonium bromide [(P)ATPB], a copolymer of styrene, *p*-styryldiphenylphosphine, and divinylbenzene, was utilized to perform the methanolysis of THP, 1-ethoxyethyl (EE), and tetrahydrofuran ethers of alcohols and phenols (Table 9, entry 9).⁸³ The authors observed that the catalyst could be reused, but its catalytic activity decreased slightly each time. In fact, it is well-known that phosphonium bromides react with refluxing methanol to give the corresponding debrominated ketone; however, since the present deprotection was carried out at room temperature, this side reaction might occur only in small portions.

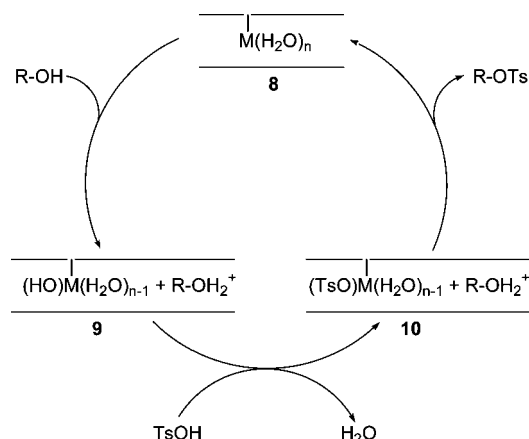
Masaki et al. utilized poly(ethylene glycol) dimethacrylate-supported dicyanoketene acetal [(P)-DCKA] (Figure 4), a material showing a quite interesting chemical behavior with respect to the deacetonidation of 1,2-diol acetonides (Table 9, entry 10).¹⁰¹ With use of the monomeric dicyanoketene acetal (DCKA) catalyst in acetonitrile/water mixture as solvent, compound **7** was obtained in no more than 2% yield with ~90% recovery of **6**, whereas 59% yield of **7** was obtained when (P)-DCKA was used as heterogeneous catalyst, probably due to the positive effect of the lipophilicity of substrate and catalyst (Scheme 3). Finally, these authors observed that, in the presence of (P)-DCKA, compound **7** was produced in 94% yield when the reaction was carried out in water as the sole solvent.

2.4. Tosylates

Tosylation of alcohols was used occasionally as a protective instrument in organic synthesis.^{14,15} The reaction was usually performed by utilizing sulfonyl chlorides or anhydrides in the presence of pyridine, triethylamine, or 1,4-diazabicyclo[2.2.2]octane (DABCO); the major problems were the moisture sensitivity and the high reactivity of the reported tosylating agents. Further, undesirable conversion of tosylates into their chlorides occurred during tosylation when TsCl/pyridine was used. Moreover, the bases which were used in molar excess for the sulfonylation of alcohols generated significant amounts of byproducts in the form of dissolved salts.

An enviro-economic route for the tosylation of alcohols and phenols mediated by metal-exchanged montmorillonite K10, employing *p*-toluenesulfonic acid (TsOH), has been recently reported by Choudary et al. The reaction required the azeotropic removal of water since water lowers the rate of the reaction by blocking the acid active sites of clay. Fe³⁺,

Scheme 4



Zn²⁺, Cu²⁺, and Al³⁺-exchanged montmorillonites K10 were tested in the tosylation of cyclohexanol: the Fe³⁺-montmorillonite showed the best activity.¹⁰² The higher activity of the Fe³⁺-montmorillonite was therefore ascribed to the induction of Lewis acidic sites through the exchange of iron in montmorillonite and also by the higher density of Brønsted acid sites. These authors suggested a plausible mechanism for the reaction (Scheme 4).

The aquo complex of metal-exchanged montmorillonite **8** protonates alcohol to form the hydroxy metal aquo complex **9**, which in turn reacts with TsOH to form the metal tosylate salt **10**. The interaction of metal tosylate and protonated alcohol gives the tosylated product and regenerates the metal aquo complex **8**.

Several alcohols were tosylated with *para*-toluene sulfonic acid in the presence of silica chloride (SiO₂/SOCl₂) in methylene chloride under reflux (Scheme 4b).^{102b} Primary and secondary alcohols (except long-chain alcohols) afforded the products in very high yields; however, with long-chain alcohols, the yields were only moderate. Phenols and tertiary alcohols did not undergo tosylation under the present experimental conditions, even after prolonged time.

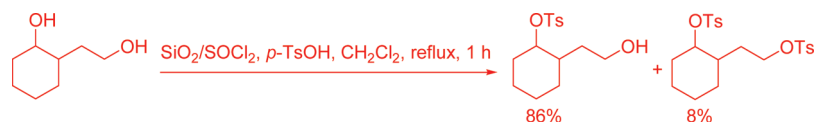
The cleavage of tosylates of phenols and alcohols usually requires drastic conditions due to their high stability. An efficient and relatively mild method was represented by the use of potassium fluoride supported on alumina as catalyst under microwave irradiation. Other functionalities in the substrate, such as benzyl, *N*-*tert*-butoxycarbonyl (*N*-Boc), and allyl groups, aliphatic acetates, acetals, and sulfides, were tolerated, whereas epoxides were not stable; the hydroxylated compounds could be recovered in high yield.¹⁰³

2.5. Selective Protection of Polyfunctional Compounds

Protection and deprotection of hydroxy groups in polyhydroxylated compounds and, in general, in multifunctional compounds represents a fundamental tool in the synthesis of elaborated target compounds such as those usually encountered in carbohydrate, amino acid, and nucleoside/nucleotide chemistry. Due to the complexity of the compounds involved, high selectivity is normally requested as well as simplicity and mildness in introducing and removing the specific function. In this section, examples of selective protection of hydroxylated polyfunctional compounds will be reported.

Highly selective protection of polyfunctional diols as acetals and amino alcohols as acetonides was performed

Scheme 4b



using DMP in the presence of montmorillonite K10 as solid catalyst (Table 10, entry 0).^{103b} In particular, cyclic, linear aliphatic and sugar diols gave satisfactory results.

Selective monotosylation of primary alcohols in the presence of secondary ones, including terminal 1,2-diols, has been performed by Choudary et al. with TsOH in combination with Fe³⁺-exchanged montmorillonite clay K10 (Table 10, entry 1).¹⁰² The reaction required azeotropic removal of the water produced, particularly when carried out in large scale. In all cases examined, tosylation of the primary hydroxy group with respect to the secondary one occurred in a ratio of more than 99/1. In the case of symmetrical diols, the reaction with 1 mol equiv of TsOH provided selective monotosylation, and with more than two molar quantities, ditosylation occurred. The observed high selectivity for primary alcohols with respect to the secondary ones was attributed to the effective steric crowding in the mesoporous system of the solid acid that renders the primary alcohols relatively uncrowded.

Y zeolite (SAR = 13.9) was utilized for the selective tetrahydropyranylation of the alcoholic group of salicylic alcohol and for the monoprotection of symmetrical diols (Table 10, entry 2).⁶⁸ More interestingly, the protection of sugars as isopropylidene derivatives was performed by condensation with acetone in the presence of ammonium-exchanged Y zeolite. Protected D-galactose, D-glucose, D-xylose, D-ribose, methyl β-D-ribofuranoside, D-glucurono-6,3-lactone, L-arabinose, and L-sorbose were obtained in moderate to satisfactory yields (Table 10, entry 3).¹⁰⁴ These authors reported that, in the protection of D-galactose, the furanose diacetal was formed in 40% yield, together with the pyranose diacetal obtained only in 20% yield. This method made it possible to synthesize in satisfactory yield the galactofuranose diacetal, which was previously produced only in low yield.

The solid, Lewis acid catalyst Al-SBA-15, was utilized to achieve protection of (*N*-Boc)amino alcohols as acetonides without damaging the Boc protection (Table 10, entry 3b).^{104b} The (*N*-Boc)amino alcohol is reacted with DMP in acetonitrile in the presence of the catalyst under reflux for 8 h. The catalyst can be reused one time with unchanged yield.

Ogawa et al. utilized silica for the selective monoacetylation of 1,*n*-diols with acetyl chloride. The high selectivity was ascribed to the formation of a monomolecular layer of the diol on the surface of the catalyst, which played a fundamental role in the monoprotection (Table 10, entry 4).¹⁰⁵ The only drawback was represented by the large amount of silica required (0.32 mmol of reagent per gram of silica).

A method for the selective monoacetylation of unsymmetrical diols such as 1,5-hexanediol **11** with ethyl acetate, promoted by SiO₂/NaHSO₄, has been reported by Breton (Scheme 5).¹⁰⁶

Selectivity for monoacetate **12** relative to **13** increased from 90/10 at 1 h to 95/5 at 9 h and finally to 97/3 at 10 h, after which it remained constant; at that time the yield of **14** began to be significant. This method eliminates the need for corrosive reagents (i.e., acetic anhydride and acetyl chloride) and does not require aqueous washing. The process was

applicable to several acyclic 1,*n*-diols (*n* = 2–16), leading to their selective monoprotection as acetates. Similar good yields of monoacetate were achieved with complex molecules; acetylation of betulin **15** afforded the primary monoacetate in 69% yield, although a 72-h reaction time was required (Figure 5). The lower reactivity of **15** relative to the acyclic diols may be attributed to the greater steric bulk encountered by this compound upon approach toward the surface of the silica gel.

The same catalyst promoted selective acetylation of aliphatic hydroxy groups in the presence of phenolic ones (Table 10, entry 5). The reaction could be successfully applied to more complex compounds: for example, the saturated secondary hydroxy group of β-estradiol **16** (Figure 5) was preferentially acylated.

Similarly, monoprotection of symmetric 1,*n*-terminal diols (*n* = 2–6, 8, 10, 12, and 16), including *cis*- and *trans*-1,4-butenediols and –1,4-butyndiol, by acylation with ethyl acetate/hexane in the presence of SiO₂/NaHSO₄ catalyst was reported by Nishiguchi et al. (Table 10, entry 6).¹⁰⁷ Kinetic studies confirm that the maximum rate of monoester formation is roughly twice that of the diester. This suggests that the reactivity of the hydroxy groups of the diol and the monoester are virtually identical. Moreover, the increased selectivity observed in the presence of the solid catalyst can be explained by postulating that (i) only the alcohols that were adsorbed on the surface of the catalyst were esterified, (ii) the diol reacted preferentially as long as it was present, and (iii) the monoester was adsorbed but reacted only after most of the adsorbed diol had been consumed. Unsupported NaHSO₄ also catalyzed monoacylation, but the selectivity was less than that in monoacylation catalyzed by the supported reagent.

Phenols too can also be selectively silylated with HDMS in the presence of silica-supported sodium hydrogen sulfate (Table 10, entry 6b).^{107b} The reaction shows great selectivity, and the system exhibits excellent selectivity for the silylation of phenols in the presence of amines and carboxylic acids. Phenols bearing strongly electron-withdrawing groups (i.e., *para*-nitrophenol) are not silylated under these conditions. The catalyst can be reused several times after activation.

The same catalyst efficiently catalyzed the formation of benzylidene acetals of partially protected glucosides in acetonitrile (13 examples, 67–99% yield).^{107c} The reaction proceeds under mild conditions at room temperature with a series of glucosides and galactosides and benzaldehyde dimethyl acetal as protecting group. In most cases, pure products were obtained by removal of the heterogeneous catalyst by simple filtration and evaporation of the solvent. A variety of functional groups such as methoxy, allyloxy, benzyloxy, azido, phenoxy, and oxazolidinone were unaffected (Scheme 5b).

The preparation of mono-THP ethers of 1,*n*-diols was carried out by reaction with DHP/hexane mixtures, catalyzed by Al₂(SO₄)₃ supported on silica gel (Table 10, entry 7).^{108,109} The catalytic activity was ascribable to the Lewis or protic acid sites of the supported sulfate, and it was demonstrated that unsupported sulfate showed no catalytic activity. An

Table 10. Selective Protection of Polyfunctional Hydroxylated Compounds

entry ^{ref}	catalyst ^a (experimental conditions)	hydroxylated compound	protected hydroxylated compound	yield (%)	n. ex. (yields %)
0 ^{103b}	Mont. K10 ^a (DMP, acetone, rt, 2 h)			90	8 (52-92)
1 ¹⁰²	Mont. K10/Fe ³⁺ (TsOH, ClCH ₂ CH ₂ Cl, Δ, 3 h)			94	8 (50-94)
2 ⁶⁸	Y zeolite ^{a(5)} (DHP, neat, rt, 1.5 h)			70	2 (70-95)
3 ¹⁰⁴	Y zeolite (Me ₂ CO, Δ, 48 h)			40	11 (20-75)
3b ^{104b}	Al-SBA-15 ^{a(1)} (DMP, MeCN, 80 °C, 8 h)			83	2 (83-86)
4 ¹⁰⁵	SiO ₂ (AcCl, hexane, Δ, 2 h)			100	6 (98-100)
5 ¹⁰⁶	SiO ₂ /NaHSO ₄ ^a (EtOAc, hexane, 50 °C, 9 h)			88	9 (59-91)
6 ¹⁰⁷	SiO ₂ /NaHSO ₄ (EtOAc, hexane, 50 °C, 4.5 h)			89	16 (58-96)
6b ^{107b}	SiO ₂ /NaHSO ₄ ^a (HDMS, neat, rt, 5 min)			94	10 (86-94)
7 ^{108, 109}	SiO ₂ /Al ₂ (SO ₄) ₃ (DHP, hexane, rt, 1.5 h)			96	12 (71-96)
8 ⁷³	Silica chloride (DHP, CH ₂ Cl ₂ , rt, 30 min)			91	7 (82-91)
8b ^{109b}	SiO ₂ /H ₂ SO ₄ ^{a(5)} [PhCH(OMe) ₂ , Ac ₂ O, MeCN, rt, 1 h]			82	10 (75-95)
9 ¹¹¹	SiO ₂ /BF ₃ (EtOAc, neat, rt, 9.5 h)			78	5 (78-84)
10 ¹¹²	SiO ₂ /LaCl ₃ (MeC(OMe) ₃ , MeOH, rt, 4 h)			98	7 (90-98)
11 ¹¹³	SiO ₂ /GeCl ₄ (MeC(OMe) ₃ , MeOH, rt, 20 min)			99	3 (99)
12 ¹¹⁴	H ₃ PW ₁₂ O ₄₀ ^a (HMDS, neat, 45 min)			100	1 (100)
13 ¹¹⁵	Dowex [®] 50WX2 (EtCO ₂ Et, octane, 100 °C, 4.5 h)			92	12 (62-92)
14 ^{116, 117}	Dowex [®] 50WX2 (DHP, PhMe, 30 °C, 10 min)			88	6 (74-95)
15 ¹¹⁸	Amberlyst 15 (Ac ₂ O, PhH, rt, 1 h)			77	4 (35-77)

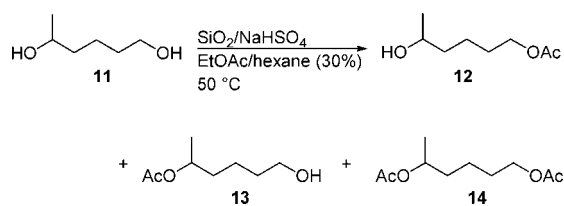
^a The catalyst has been recycled (number of recycles).

alternative but more problematic catalyst to perform the same selective reaction was represented by the silica chloride (Table 10, entry 8).⁷³

A sequential one-pot preparation of per-*O*-acetylated benzylidene acetals or isopropylidene ketals of *O*- and

S-glycosides under stoichiometric conditions has been developed using the safe and easy-to-handle silica-adsorbed sulfuric acid (SiO₂/H₂SO₄) (Table 10, entry 8b).^{109b} The dry glucoside was treated in dry acetonitrile with benzaldehyde dimethyl acetal at room temperature until conversion was

Scheme 5



complete; then acetic anhydride was added and the reaction was continued at room temperature for the selected time. Filtration and evaporation of the solvent gave the products in >95% purity.

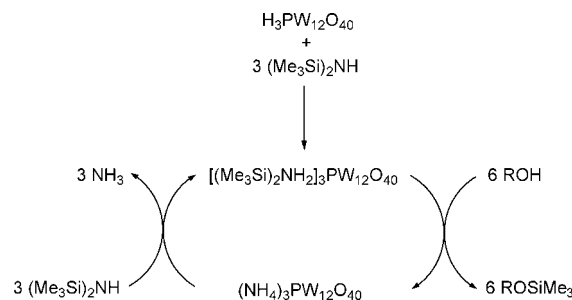
Selective acylation of aliphatic hydroxy groups with ethyl acetate utilized as solvent-reagent in the presence of phenolic groups was performed on silica gel-supported BF_3 . For example, the conversion of the natural antitumor coumarino lignoid cleomiscosin A into its analogue venkatasin¹¹⁰ has been achieved in satisfactory yield (Table 10, entry 9).¹¹¹ The unsupported BF_3 showed lower activity.

A further method for regioselective acetylation of primary hydroxy groups is based on the use of methyl orthoacetate in methanol and in the presence of a chloride of a rare earth (erbium, lanthanum, europium, or neodymium) dispersed on silica. The reaction can be successfully applied to polyhydroxylated compounds, in particular to sugars and related substances. In all cases, the regioselective protection of primary hydroxy functions in very high yields in the presence of secondary and tertiary ones could be achieved. A representative example is the case of the methyl ester of the *N*-acetylneuraminic acid, which was acetylated at the primary hydroxy group in 98% yield (Table 10, entry 10).¹¹²

Germanium chloride dispersed on silica gel ($\text{SiO}_2/\text{GeCl}_4$) afforded the selective protection of vicinal diols in polyhydroxylated compounds with methyl orthoacetate. An interesting application is represented by the quantitative protection of the hydroxy groups at the 3 and 4 positions of methyl quinate (Table 10, entry 11).¹¹³

The use of tungstophosphoric acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) was claimed by Firouzabadi et al. to selectively protect the phenol hydroxy group in the presence of the aromatic amino group by reaction with HMDS (Table 10, entry 12).¹¹⁴ Competitive experiments showed a good selectivity in the protection of different alcohols. Thus, a primary benzylic hydroxy group was protected in the presence of a secondary aliphatic alcohol with a 80/20 ratio, and a secondary aliphatic alcohol in the presence of a tertiary alcohol was protected with a 95/5 ratio. The reactions proceeded easily with the evolution of ammonia gas and the production of the corresponding silyl

Scheme 6



ethers. A catalytic reaction cycle was proposed (Scheme 6) in which the production of $[(\text{Me}_3\text{Si})_2\text{NH}_2]_3\text{PW}_{12}\text{O}_{40}$ and $(\text{NH}_4)_3\text{PW}_{12}\text{O}_{40}$ as catalysts and the production of silyl ethers and ammonia gas as the products were hypothesized.

Nishiguchi et al. reported the monoesterification of symmetrical 1,*n*-diols using a mixture of ethyl propionate and octane in the presence of Dowex 50WX2 ion-exchange resin (Table 10, entry 13).¹¹⁵ The reaction could be applied only to the production of saturated aliphatic esters. The selectivity for monoester formation was ascribed to the higher reactivity of the diol than that of the monoester. This is probably the consequence of the fact that the sulfonic acid-type ion-exchange resins usually contain 50–80% water. Thus, a strongly acidic water layer is formed on the surface of the resin, and a partition equilibrium between the aqueous layer and the aprotic ester/octane layer is set up; thus, the diols have a higher partition coefficient than the monoesters.

A similar route to the selective monotetrahydropyranylation of primary and secondary symmetrical diols has been recently reported by the same authors; the method still utilizes wet-type Dowex 50WX2 resin as a strong solid acid in DHP/toluene or DHP/hexane mixtures (Table 10, entry 14).^{116,117} The reaction was performed at room temperature, and the monoether was obtained in high yield and better selectivity with respect to the previously described methods. As in the previous case, each diol required a particular DHP/hydrocarbon ratio that gives the highest selectivity. Generally, the larger the number of carbon atoms of the diol, the smaller the DHP/hydrocarbon ratio needed to realize the highest selectivity. Kinetic studies confirm that the selectivity of the monoether formation results from the higher reactivity of the diol with respect to that of the monoether.

Selective *O*-acetylation of alcohols in the presence of amino groups was achieved by reaction with acetic anhydride in benzene and in the presence of a strong acidic Amberlyst 15 ion-exchange resin. Presumably, under these conditions, the amino function is protonated and hence prevented from undergoing acetylation (Table 10, entry 15).¹¹⁸

2.6. Selective Deprotection of Polyprotected Compounds

Montmorillonite K10 clay was utilized by Ogasawara et al. for the selective deprotection via methanolysis of a variety of THP ethers in the presence of an additional *O*-protected functional group in their molecules (Table 11, entry 1).⁹⁵ Among the compounds examined, the THP protecting group was selectively removed from substrates carrying also benzyl, allyl, MOM, acetyl, and TBDPS groups on hydroxy functions to give the corresponding alcohols in good to excellent yields (Table 12). On the other hand, TBDMS, β,β,β -trichloroethylimidyl, and ketal functionalities were unstable under these conditions.

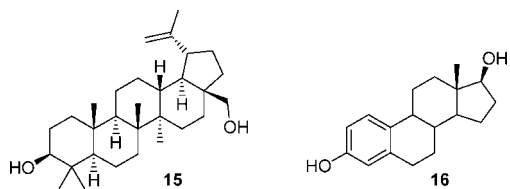


Figure 5.

Scheme 5b

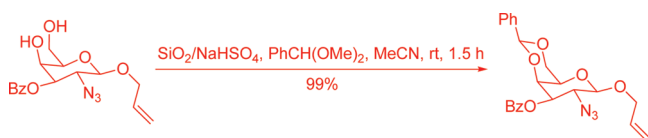


Table 11. Selective Deprotection of Polyprotected Hydroxylated Compounds

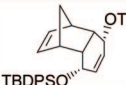
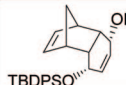
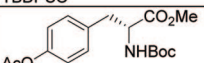
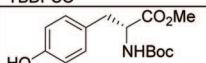
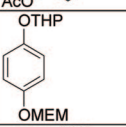
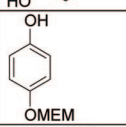
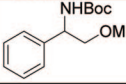
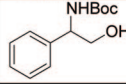
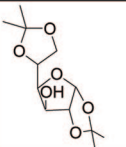
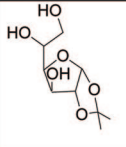
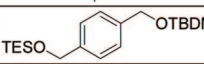
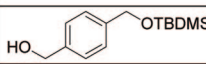



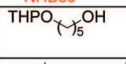
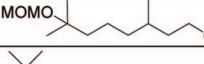
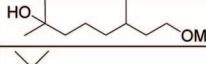
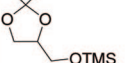
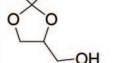
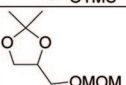
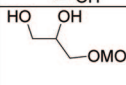
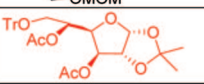
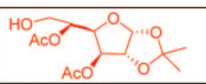
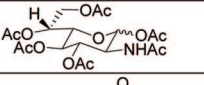
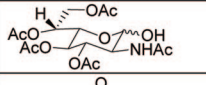
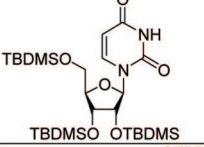
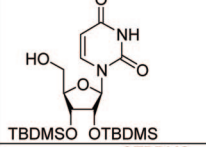
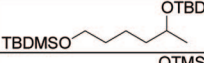
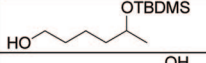
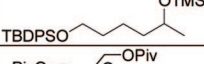
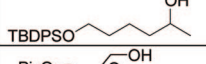
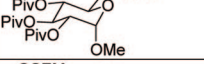
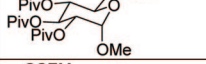
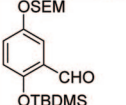
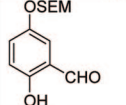
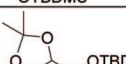
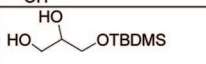
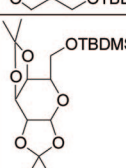
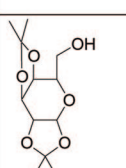
entry ^{ref}	catalyst ^a (experimental conditions)	protected hydroxylated compound	deprotected hydroxylated compound	yield (%)	n. ex. (yields %)
1 ⁹⁵	Mont. K10 (MeOH, rt, 2 h)			99	13 (25-99)
2 ¹¹⁹	Kaolin ^{u(3)} (MeOH, rt, 30 min)			93	8 (88-94)
3 ⁹⁴	Tonsil (Me2CO, rt, 30 min)			75	2 (60-75)
4 ⁹⁸	Mont. K10/NH4NO3 (clayan) (neat, MW, 2.5 min)			78	7 (70-88)
5 ¹²¹	Mont. K10/NH4NO3 (clayan) (neat, MW 650W, 3 min)			78	2 (78-84)
6 ¹²²	MCM-41 (MeOH, rt, 8 h)			97	7 (83-97)
6b ^{104b}	Al-SBA-15 ^{u(1)} (MeOH, 40 °C, 3 h)			83	2 (87-90)
7 ¹²³	SiO2/Al2O3 (MeOH, rt, 1.5 h)			97	13 (64-98)
8 ¹²³	SiO2/Al2O3 (MeOH, rt, 1.5 h)			82	13 (64-98)
9 ¹²³	SiO2/Al2O3 (MeOH, rt, 50 min)			94	13 (64-98)
10 ¹²³	SiO2/Al2O3 (MeOH, 65 °C, 5.5 h)			64	13 (64-98)
10b ^{123b}	SiO2/NaHSO4 (CH2Cl2, MeOH, rt, 2 h)			95	16 (87-100)
11 ¹²⁴	SiO2 (MeOH, 24 h)			84	11 (31-84)
12 ¹²⁶	SiO2/CAN (PrOH/CCl4 1/1, 65 °C, 8 h)			95	14 (80-95)
13 ¹²⁷	Al2O3 (hexane, rt, 17 h)			97	2 (97-98)
14 ¹²⁸	Al2O3 (hexane, rt, 16 h)			90	6 (85-97)
15 ¹³⁰	Al2O3 (neat, MW 800W, 30 min)			91	1 (91)
16 ¹³³	Al2O3/KF (MeCN, MW, 15 h)			70	4 (70-84)
17 ¹³⁴	Al2O3/Oxone [®] (neat, MW 2450 MHz, 2 min)			75	8 (73-90)
18 ¹³⁴	Al2O3/Oxone [®] (neat, MW 2450 MHz, 3.5 min)			78	8 (73-90)

Table 11. Continued

entry ^{ref}	catalyst ^a (experimental conditions)	protected hydroxylated compound	deprotected hydroxylated compound	yield (%)	n. ex. (yields %)
18b ^{134b}	Nafion [®] _{5a} (MeOH, rt, 3 h)			92	18 (80-94)
19 ¹³⁵	Dowex [®] 50WX8 (MeOH/H ₂ O 1/9, rt, 20 h)			92	4 (87-92)
20 ¹³⁵	Dowex [®] 50WX8 (MeOH/H ₂ O 1/9, rt, 22 h)			92	2 (92-96)
21 ¹³⁷	Sulfonated polystyrene (CH ₂ Cl ₂ /MeOH, rt, 36 min)			90	4 (90-95)
21b ^{62b}	LL-ALPS-SO ₃ H ^a (H ₂ O, 40 °C, 24 h)			90	15 (76-99)
21c ^{137b}	PS-barbituric acid/Pd(Ph ₃) ₄ (THF, 90 °C, 24 h)			100	45 (73-100)

^a The catalyst has been recycled (number of recycles).

Table 12. Selective Removal of THP in Diprotected 1,4-Butanediols

entry	R	yield (%)
1	Bn	92
2	allyl	82
3	MeOCH ₂	98
4	<i>t</i> -BuPh ₂ Si	82
5	MeCO	92
6	PhCO	97

Deprotection of aryl acetates in the presence of other sensitive functional groups, including aliphatic esters, represents a further example of selective deprotection of phenol hydroxy groups. The reaction was performed by using natural kaolinitic clay with a series of aryl acetates containing other protecting groups, such as oxime, THP ether, thioacetal, amide, and *tert*-butoxycarbonyl groups. An important feature of this method is that the optical purity of chiral amino acids remained unaltered (99% ee based on optical rotation) (Table 11, entry 2).¹¹⁹

A bentonitic earth (Tonsil) was utilized for selective deprotection of THP ethers from compounds containing another hydroxy group, protected as the (2-methoxyethoxy)methyl (MEM) or MOM derivative (Table 11, entry 3).⁹⁴ Indeed, when some experiments were carried out with THP–MOM and THP–MEM mixed ethers, the THP ether was cleaved and the other remained unchanged. It is remarkable that, following this procedure, it was possible to prepare farnesylhydroquinone, a natural product isolated from *Wigandia kunthii*.¹²⁰

Meshram et al. utilized clayan in the selective removal of MPM ether; the selectivity of the method is demonstrated

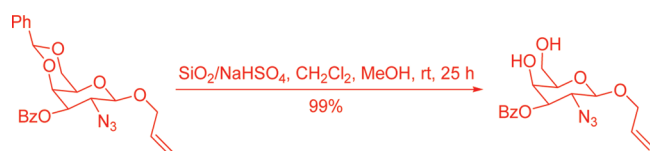
by the survival of other protected groups, such as ester, silyl ether, acetonide, Boc, acetate, and benzyl ether, by microwave treatment of a mixture of the protected substrate and clayan under solventless conditions (Table 11, entry 4).⁹⁸ Acetonide bis-protected polyols can be selectively monodeprotected in high yield with the use of the same catalyst (Table 11, entry 5).¹²¹

Selective deprotection of the TES group in the presence of the TBDMS group of mixed silyl ethers of diols was achieved with silica MCM-41 (Table 11, entry 6).¹²² Due to the very mild reaction conditions, different protected diols could be selectively deprotected in similar high yield, including propargylic- and allylic-type alcohols. It is noteworthy that the use of ZSM-5 and Y zeolites, which are too strongly acidic catalysts, resulted in unselective deprotection.

Al-SBA-15 can be employed to perform the selective deprotection of acetonides (Table 11, entry 6b).^{104b} The cleavage was performed using methanol as solvent. The reaction proceeds to completion within 3 h, giving the (*N*-Boc)amino alcohols in high yield. The catalyst can be reused one time with the same yield.

Matsumoto et al. described the deprotection of primary, secondary, and tertiary alcohols protected with THP, EE, 1-methyl-1-methoxyethyl (MME), TMS, and MOM groups, promoted by a silica–alumina gel catalyst (Table 11, entry 7).¹²³ In the presence of THP, EE, and MOM groups, selective removal of the MME group could be attained quantitatively. When the THP and TMS groups were present in the same molecule, the silyl group was cleaved selectively. The catalyst could also be utilized to selectively cleave some ether protecting groups in diol derivatives with different

Scheme 6b



classes of protected hydroxy groups. Thus, a diol containing a tertiary and a primary hydroxy group, both protected as MOM ethers, underwent selective deprotection to the tertiary alcohol (Table 11, entry 8).¹²³ The critical selective cleavage of glycerol derivatives, protected as ether and acetal, was also achieved using this catalyst. For example, the TMS group was selectively removed by carrying out the reaction at room temperature (Table 11, entry 9),¹²³ whereas the acetal group was cleaved, with the survival of MOM functionality, when the reaction was performed at 65 °C (Table 11, entry 10).¹²³

A further efficient and highly selective deprotection method applied in the sugar chemistry is the cleavage of trityl ethers catalyzed by silica-supported sodium hydrogen sulfate ($\text{SiO}_2/\text{NaHSO}_4$) (Table 11, entry 10b).^{123b} Different types of sugar with various functionalities (i.e., alkyl, benzyl, MOM, MEM, allyl, acetyl, benzoyl, and tosyl) underwent selective detritylation.

The same catalyst efficiently catalyzes the cleavage of benzylidene acetals of glucosides in acetonitrile (8 examples, 89–99% yield).^{107c} The reaction proceeds under mild conditions at room temperature with a series of protected glucosides and galactosides in a mixed-solvent methanol (or *iso*-propanol)/methylene chloride (1:4) (Scheme 6b).

Deprotection of the anomeric center of per-*O*-acetylated 2-amino sugar derivatives with different homogeneous catalysts, such as Lewis acids, nitrogen bases, or enzymes, frequently results in the production of anomeric mixtures that constitute a severe limitation of these procedures. The mild anomeric deprotection of per-*O*-acetylated 2-amino-2-deoxyglycopyranose derivatives was shown by Palacios et al. to occur with total or high stereoselectivity and with exclusive production of α -anomers by mechanically stirring a suspension of substrate and silica gel in methanol. In general, reactions with α -anomers were faster than those with β -anomers. Starting materials having either α - and β -configuration gave exclusively 1-*O*-deacetylated α -anomers, and no presence of β -anomers could be detected (by ^1H NMR analysis) (Table 11, entry 11).¹²⁴ The supposed mechanism could involve a transesterification on the silica gel surface. This feature offers a plausible explanation for the different reaction rates observed with α - and β -anomers. α -Anomers can interact easily with acidic centers of silica gel. In contrast, the approach of β -anomers to the support will be markedly impeded by axial interaction (Figure 6).

The great stereoselectivity of the process should be a consequence of a very fast mutarotation in the polar reaction medium. The deacetylation would be therefore stereospecific

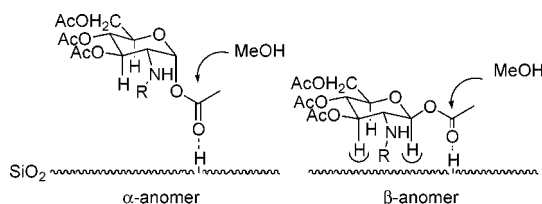


Figure 6.

Scheme 7

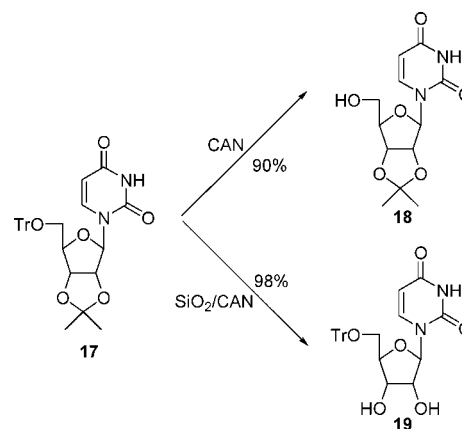


Table 13. Selective Removal of TIPS in Polyprotected Compounds

entry	R	R'	B	yield (%)
1	TIPS	TIPS	uracyl-yl	87
2	H	TIPS	uracyl-yl	91
3	TIPS	H	uracyl-yl	85
4	H	TIPS	cytosin-yl	80
5	TIPS	H	cytosin-yl	83

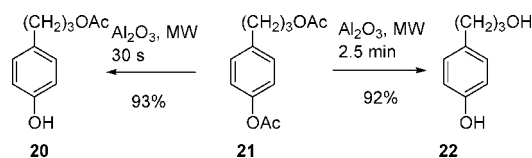
initially, but the anomeric effect had favored the exclusive formation of the thermodynamically more stable α -anomers.

Ceric ammonium nitrate (CAN) represents a one-electron-transfer catalyst utilized for removal of triphenylmethyl (Tr), monomethoxytrityl (MMTr), and Boc groups from organic compounds. Under the neutral conditions applied, several acid-sensitive groups survive, including isopropylidene, (dimethylamino)methylidene, *tert*-butyldimethylsilyl, and acyl functionalities.¹²⁵ Hwu et al. reported that CAN adsorbed on silica gel (SiO_2/CAN) efficiently removed the Tr, MMTr, DMTr, TBDMS, and triisopropylsilyl (TIPS) functionalities from a variety of polyprotected ribonucleoside substrates, rapidly converting them to the parent monodeprotected alcohols (Table 11, entry 12).¹²⁶ Comparison of the results obtained from detritylation in the presence and in the absence of silica gel as solid support suggests that the above reactions were much faster than those performed with CAN alone. On this subject, quite interesting is the comparison of activity of CAN and SiO_2/CAN with the reagent **17**. The Tr group was selectively cleaved by treatment of **17** with CAN, affording **18**, whereas the isopropylidene group was cleaved when SiO_2/CAN was utilized, affording product **19** (Scheme 7).

A further application of this powerful catalyst is represented by the selective removal of a TIPS group from di- and trisilyl ethers in very good yields (Table 13); however, the use of CAN alone resulted in the complete recovery of the starting reagents.

Activated commercial neutral alumina has been utilized by Guerrero et al. as a heterogeneous catalyst to promote selective cleavage of a primary TBDMS group in the presence of a secondary one (Table 11, entry 13).¹²⁷ Since the catalyst is inactive with some acid-sensitive groups, such as THP and MOM, the method could also be efficiently applied to the selective removal of TBDMS group in the presence of the THP function. The method could not be utilized with molecules containing silylated phenolic groups since, although complete deprotection occurs under reaction conditions similar to those requested for alcohols, the

Scheme 8



resulting phenolic compound remains highly adsorbed to the support and cannot be completely recovered.

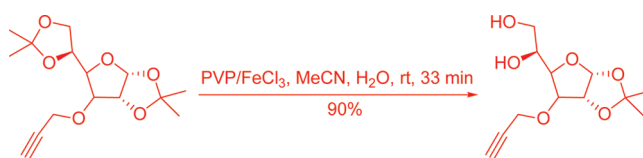
By conveniently combining the steric hindrance and the nature of the protective group, it was possible to selectively deprotect variously bis-protected diols.¹²⁸ While this process in principle should not represent any problem when the more labile silyl group (TMS) is on a primary carbon, taking into account also the order of stability of protecting groups ($\text{TMS} \ll \text{TBDMS} < \text{TBDPS}$),¹²⁹ the reverse case, with the less resistant silyl moiety occupying a secondary position, should be much more troublesome, as the higher accessibility at the more sterically hindered ether on the primary position counterbalances the higher reactivity of the less sterically hindered secondary ether. However, when the difference in steric hindrance was large enough, it was possible to remove the secondary TMS group in the presence of a primary TBDMS moiety (Table 11, entry 14). No selective desilylation could be attained when the secondary position was occupied by the TBDMS group.

By using the same catalyst, the selective deacetylation of compound **21** was accomplished under microwave irradiation by accurately selecting the reaction time; indeed, when the reaction was carried out for 30 s, the monoacetate **20** was isolated in 93% yield, whereas when the irradiation time was prolonged to 2.5 min, complete deacetylation was achieved, and product **22** was isolated in 92% yield (Scheme 8).⁴⁶

Similarly, selective deprotection at the 6 position of a fully protected pivaloyl methylglycoside was achieved by treatment with neutral alumina in combination with microwave irradiation (Table 11, entry 15).¹³⁰

Potassium fluoride supported on alumina ($\text{Al}_2\text{O}_3/\text{KF}$) appears to be unique among various supported catalysts; indeed, Weinstock et al. showed via Raman and infrared spectroscopies that, in contrast to SiO_2/KF , Celite/ KF , and molecular sieves/ KF , $\text{Al}_2\text{O}_3/\text{KF}$ exhibits a surprising degree of basicity.¹³¹ The high activity of $\text{Al}_2\text{O}_3/\text{KF}$, combined with the possibility of controlled access to fluoride ion, provided an optimum environment for desilylation. Treatment of TBDMS ethers of phenols in acetonitrile with basic $\text{Al}_2\text{O}_3/\text{KF}$ resulted in conversion to the free phenol in excellent yields. In general, higher reactivity was observed with basic $\text{Al}_2\text{O}_3/\text{KF}$ than with the acidic one. Reactions were even further facilitated by the use of ultrasound combined with $\text{Al}_2\text{O}_3/\text{KF}$. TBDMS ethers of phenols versus those of benzyl alcohols were selectively cleaved. This system is known to give both possible monosilylated products upon treatment with tetraalkylammonium fluorides, presumably due to base-catalyzed intramolecular silyl transfer.¹³² Selective removal of TBDMS in the presence of SEM-phenolic ethers was reported by Sawyer et al. to occur in the presence of KF supported on basic alumina (Table 11, entry 16).¹³³ Even in this case, lower reactivity was observed with the KF on acid alumina, as was evident through comparison of reaction times. Selectivity was observed between TBDMS ethers of phenols versus benzylic alcohols. The most likely mechanism of desilylation involves the nucleophilic addition of fluoride ion. The cooperative action of fluoride ion on the alumina

Scheme 8b



surface results in a strong “naked” nucleophilic matrix that is not possible with KF alone.

$\text{Al}_2\text{O}_3/\text{Oxone}$ represents another catalyst-reagent combination that has been efficiently utilized for the selective deprotection of acetals in substrates containing acid-labile isopropylidene, Tr, or TBDMS groups. The isopropylidene group on at least a primary hydroxy moiety underwent rapid cleavage in the presence of TBDMS or Tr groups (Table 11, entry 17).¹³⁴ When the reagent system was applied to more complex molecules, the TBDMS or Tr groups were selectively cleaved, preserving the isopropylidene function attached to secondary or tertiary hydroxy moieties (Table 11, entry 18).

A facile and chemoselective hydrolysis of terminal isopropylidene acetal has been achieved in good to excellent yields within 2–4 h using Nafion in methanol at room temperature (Table 11, entry 18b).^{134b} Similarly, trityl ethers are also deprotected to the corresponding alcohols in excellent yields under the same conditions (9 examples reported, 82–96% yield). Under these conditions, several functional groups such as benzoyl, tosyl, and TBDMS ethers remained unaffected.

The selective cleavage of isopropylidene acetals in the presence of other acid-labile protective groups such as methoxy, benzyloxy, benzoyloxy, NHBOc , TBDMS, THP, and acetoxy can be smoothly carried out in acetonitrile and in the presence of PVP/ FeCl_3 catalyst (14 examples, 87–94% yield) (Scheme 8b).^{134c}

The heterogeneous acid Dowex 50WX8 has been successfully utilized for the selective cleavage of the terminal acetonide group in variously protected polyhydroxylated compounds also containing OTs and OBn groups (Table 11, entry 19). Quite similar highly selective cleavage of terminal acetonide groups was achieved with polyhydroxylated compounds containing protected amino groups (Table 11, entry 20).¹³⁵

The utility of triphenylmethyl (Tr), MMTr, and DMTr ethers is attributed to the high selectivity for primary hydroxy groups in polyols as well as the simplicity and mildness in preparing and removing the trityl function.¹⁵ With certain compounds, such as nucleosides and pentoses, the standard deprotection methods, based on protic and Lewis acid treatment or catalytic hydrogenation, were not suitable due to the acid sensitivity of the starting material, resulting, for example, in deglycosylation. The DMTr group, which has been extensively utilized to protect the 5'-hydroxy function in nucleoside chemistry,¹³⁶ could be removed by benzene- or *p*-toluenesulfonic acid treatment, causing depurination. Salunkhe et al. reported that, by using sulfonated cross-linked gel-type and macroporous polystyrene resins, effective detritylation was selectively achieved in short reaction time with quantitative isolation of the products (Table 11, entry 21).¹³⁷ The DMTr group was cleaved with quantitative survival of the TBDMS group. This method has the advantage over the other acidic catalysts used in that the resin is filtered off immediately after the reaction and does

Table 14. Selective Removal of Isopropylidene Moiety in Polyprotected Sugar Derivatives

entry	R	R'	yield (%)
1	Bn	Bn	93
2	Ts	Bn	98
3	TBDMS	Bn	97
4	Bz	Bz	94

not remain in contact with the product, thus avoiding depurination and possible glycoside cleavage.

Alkylated polystyrene-supported sulfonic acid (LL•ALPS•SO₃H) showed high selectivity in the deprotection of TBS ethers in the presence of other protective groups such as benzyl and TBDPS (Table 11, entry 21b).^{62b} In addition, the selective deprotection of an aliphatic TBS ether in the presence of an aromatic TBS ether was attained using LL•ALPS•SO₃H catalyst in water.

The resin-supported 1-methyl-3-propyl barbituric acid in combination with Pd(PPh₃)₄ catalyzed the *N*- and *O*-deallylation as well as the *N*- and *O*-decarballyoxylation (Table 11, entry 21c).^{137b} The reactions are performed with a variety of aliphatic and aromatic substrates carrying different functional groups that survive in these specific reaction conditions.

An interesting application of the selective deprotection of complex molecules is represented by the selective cleavage

of a *myo*-inositol *trans*-isopropylidene acetal in the presence of a *cis*-isopropylidene acetal. The reaction could be performed by treatment with the acidic ion-exchanged resin Amberlite IR-120. This mild and simple procedure can be applied to variously protected compounds and, therefore, precludes the requirement of chromatographic purification procedures (Table 14).¹³⁸

2.7. Redox Deprotections

As previously shown, tetrahydropyranylation represents one of the most frequently used processes to protect hydroxy groups in the multistep organic synthesis under both homogeneous and heterogeneous catalysis. The possibility to perform direct conversion of THP ethers to the corresponding carbonyl compounds under heterogeneous catalysis represents an economically advantageous and environmentally benign process.

Heravi et al. developed a number of solid reagent-catalyst combinations to perform the process. Some examples are reported in Table 15. Bis(trimethylsilyl)chromate (BTSC) supported on montmorillonite K10 was utilized to perform the oxidative deprotection of THP ethers to aldehydes and ketones (Table 15, entry 1);¹³⁹ it must be stated that the unsupported BTSC was completely inert. It is also noteworthy that overoxidation of primary THP ethers to carboxylic

Table 15. Redox Deprotections

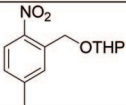
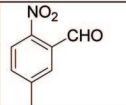
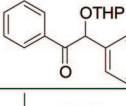
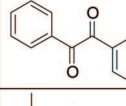
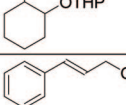
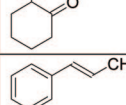
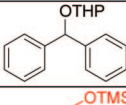
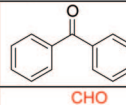
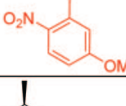
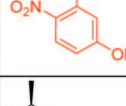
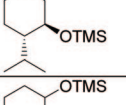
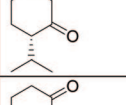
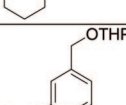
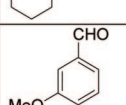
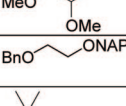
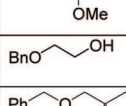
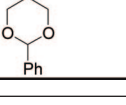
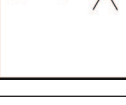


entry ^{ref}	Catalyst (experimental conditions)	protected alcohol	product	yield (%)	n. ex. (yields %)
1 ¹³⁹	Mont. K10/BTSC (CH ₂ Cl ₂ , Δ, 25 min)			88	9 (80-92)
2 ¹⁴⁰	Mont. K10/BTSC (neat, MW 900W, 2 min)			80	10 (75-92)
3 ¹⁴¹	Mont. K10/Fe(NO ₃) ₃ ·9H ₂ O (neat, MW 900W, 2 min)			90	9 (80-90)
4 ¹⁴²	ZSM-5 zeolite/Fe(NO ₃) ₃ ·9H ₂ O (CH ₂ Cl ₂ , Δ, 10 h)			78	9 (78-91)
5 ¹⁴³	SiO ₂ /K ₂ FeO ₄ (CH ₃ CN, Δ, 14 h)			92	8 (80-94)
5b ^{143b}	ZSM-5/CrO ₃ (neat, MW, 1.5 min)			99	8 (82-99)
6 ¹⁴⁴	SiO ₂ /BTSC (CH ₂ Cl ₂ , rt, 25 min)			89	10 (71-95)
7 ¹⁴⁵	Al ₂ O ₃ /CrO ₃ (neat, rt, 1 min)			90	9 (72-90)
8 ¹⁴⁶	Al ₂ O ₃ /KMnO ₄ (neat, 10 min)			90	20 (75-99)
9 ¹⁴⁸	Pd/C (H ₂ , EtOH, rt, 30 min)			96	8 (86-97)
10 ¹⁴⁹	Cu-pentasil borozelolite/Cu(NO ₃) ₂ (H ₂ , neat, 190 °C)			70	not reported

Table 16. Selective Deprotection of Diprotected Ethylene Glycols

entry	R	yield (%)
1	CF ₃	88
2	CH ₃	81
3	OCH ₃	78
4	<i>t</i> -Bu	85

acids was never observed. Mechanistic investigations showed that THP ethers were initially cleaved to the corresponding alcohols and successively oxidized to carbonyl compounds. The reaction was efficiently accelerated through microwave irradiation (Table 15, entry 2).¹⁴⁰

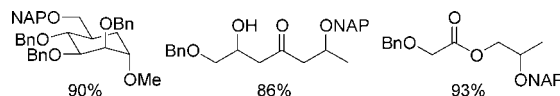
Iron(III) nitrate salt supported on montmorillonite K10 has also been utilized to perform the oxidative deprotection of THP ethers to carbonyl compounds (Table 15, entry 3).¹⁴¹ A great advantage is the easy manipulation and treatment of the reaction mixture since, in the absence of the clay, the reaction was sluggish, and more seriously sticky ferric nitrate and/or its degradation products gave an intractable solid mass, making difficult the isolation of the carbonyl compounds. Quite similar good results were achieved by using the same iron salt supported on ZSM-5 zeolite (Table 15, entry 4)¹⁴² or potassium ferrate (K₂FeO₄) supported on silica gel (Table 15, entry 5).¹⁴³

TMS-protected alcohols were directly converted into aldehydes by oxidative deprotection with a mixture of CrO₃ and ZSM-5 zeolite under microwave irradiation in the absence of solvent (Table 15, entry 5b).^{143b}

Two methods for the direct oxidation of trimethylsilyl ethers to the corresponding carbonyl compounds are based on the use of bis(trimethylsilyl) chromate on silica (SiO₂/BTSC)¹⁴⁴ and chromium oxide on wet alumina (Al₂O₃/CrO₃).¹⁴⁵ In the first case, the reaction was carried out simply by adding the SiO₂/BTSC catalyst-reagent to a solution of primary or secondary alcohol (Table 15, entry 6). In the second case, the finely ground Al₂O₃/CrO₃ reagent-catalyst was added to the neat ether in a mortar and mixed thoroughly (Table 15, entry 7). In both cases, the reaction was highly selective, and no overoxidation products were recovered when the reaction was performed with primary alcohols, the sole exception being represented by trimethylsilyl cinnamyl ether, which was oxidatively deprotected to cinnamic aldehyde, accompanied by benzaldehyde in a 7/3 molar ratio, showing that the benzylic double bond is prone to cleavage under both reaction conditions.

Alumina-supported potassium permanganate (Al₂O₃/KMnO₄) was utilized for the highly selective deprotection-oxidation of benzylic TMS and THP ethers to the corresponding carbonyl compounds (Table 15, entry 8).¹⁴⁶ The reaction shows a slower rate in the absence of alumina; moreover, allylic substrates afforded complex mixtures of overoxidation compounds.

The synthesis of polyhydroxylated compounds often requires orthogonal protecting strategies to distinguish between hydroxy groups. It would be highly desirable to develop a range of benzyl-type protecting groups with different reactivities that can be sequentially removed via catalytic hydrogenolysis over Pd/C and, in general, reductive deprotection. Spencer et al. showed that when competition experiments were conducted on model systems containing two differently substituted benzyl groups attached to ethylene glycol, the unsubstituted one was cleaved first, in competition with any of the substituted benzyl groups (Table 16). In the

**Figure 7.**

presence of this heterogeneous catalyst, the aromatic ring must lie flat on the metal surface for optimal coordination.¹⁴⁷

It is possible that substitution on the aromatic ring could have an adverse steric effect that would hamper the planar geometry required for binding and thus lower its reactivity. Thus, for a rational design of selective benzyl-type protecting group, both electronic factors and adsorption must be taken into account. To this end, the 2-naphthylmethyl (NAP) group would fulfill these criteria, since it is electron-rich and should have high affinity to the palladium surface due to its flat extended aromatic system. The hydrogenolysis of NAP/benzyl-protected dihydroxy compounds shows that the NAP group can be selectively deprotected (Table 15, entry 9).¹⁴⁸ Interestingly, the deprotection of the benzyl group is strongly inhibited, even after the NAP group has been completely removed. It is possible that the 2-methylnaphthalene released during the reaction can compete with the benzyl groups for the active sites on the palladium. The synthetic utility of this finding is shown in the highly selective removal of the NAP group in different substrates containing benzyl protecting groups, some of which are reported in Figure 7.

Finally, the reductive ring-opening of 1,3-dioxanes via hydrogenation was catalyzed by 4% copper(II) nitrate impregnated in the pentasil-type borosilicate (Table 15, entry 10).¹⁴⁹ Compounds obtained were 3-oxoalkylpropanols used as intermediates containing a monoprotected diol as benzyl ether. The reaction could be applied to a great number of symmetrical 1,3-dioxanes in high yield and selectivity. No information is available about the regiochemistry of the ring-opening of unsymmetrical 1,3-dioxanes.

In conclusion, it must be emphasized that, even if the majority of examples reported in Table 15 and discussed in this paragraph deal with supported reagents, the authors showed that the inorganic support notably enhances the reaction rate, renders more easy the isolation and purification of product, and minimizes or completely avoids production of byproducts and/or tar materials.

3. Thiol Protecting Groups

Under heterogeneous catalysis, thiols are usually protected as acetates; the few articles on this topic deal with methodologies previously studied and applied for alcohols. A versatile method is represented by the use of acetic anhydride with montmorillonite KSF; no selectivity was observed when the reaction was carried out with 2-mercaptoethanol (Table 17, entry 1).^{22,23} Another solvent-free method is represented by the use of FER zeolite; the thiol acetates were recovered in high purity (Table 17, entry 2).²⁶ The reaction rate of this process can be increased by applying microwave irradiation; thus, by employing basic alumina in the presence of pyridine, the acetylation of thiophenols was accomplished with acetic anhydride in a few minutes (Table 17, entry 3).³⁶ Quite interestingly, under these conditions, selective protection at the SH group in some aminothiophenols was achieved.

Another solid acid catalyst that is efficient in thiophenol acetylation is represented by the commercially available Nafion (Table 17, entry 4).⁴⁵ Thiols can also be protected with DHP as tetrahydropyranyl thioethers. The reaction

Table 17. Protection of Thiols

entry ^{ref}	catalyst ^a (experimental conditions)	thiol	protected thiol	yield (%)	n. ex. (yields %)
1 ^{22, 23}	Mont. KSF (Ac ₂ O, neat, rt, 1.5 h)			92	2 (92)
2 ²⁶	FER zeolite ^a (Ac ₂ O, neat, 75 °C, 5 h)			94	2 (91-94)
3 ³⁶	Al ₂ O ₃ ^a (Ac ₂ O, pyridine, neat, MW 300W, 1 min)			96	5 (72-96)
4 ⁴⁵	Nafion [®] (4) (Ac ₂ O, CH ₂ Cl ₂ , rt, 2 h)			99	1 (99)
5 ⁷⁶	ZrO ₂ (hydrated) (DHP, MW 2450 MHz, 10 min)			89	4 (88-90)
5b ^{32b}	SiO ₂ /HClO ₄ ^{a(5)} (Ac ₂ O, neat, rt, 15 min)			95	4 (90-99)

^a The catalyst has been recycled (number of recycles).

catalyzed by hydrated zirconia and accelerated by microwave irradiation was very selective, as no thiol dimerization occurred (Table 17, entry 5).⁷⁶ Interestingly, by using the same catalyst, the detetrahydropyranylation could be accomplished simply by adding methanol to the mixture of acetate/hydrated zirconia.⁶⁵ Finally, acetylation of aromatic thiols can be efficiently performed with acetic anhydride catalyzed by perchloric acid adsorbed on silica (Table 17, entry 5b).^{32b}

4. Carboxy Protecting Groups

Although many useful and reliable methods for esterification of carboxylic acids are usually employed, there is still a need to find versatile processes to replace the classical methodologies with more benign alternatives, characterized by general applicability.

4.1. Protection

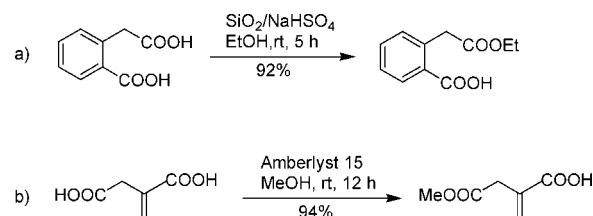
Selective esterification of carboxylic acids represents an important reaction for the manipulation of functional groups in multistep organic synthesis. Here we present a selection of procedures aimed at obtaining esters as protective groups under heterogeneous catalysis, although esters often represent target molecules as fine chemicals.

The protection of carboxylic acids as esters is usually performed by reacting the acid with a suitable alcohol in the presence of different heterogeneous acid catalysts.

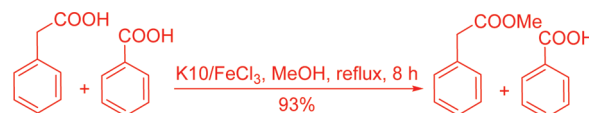
Most of the reported methods suffer from some drawbacks, which include the use of hazardous and expensive reagents, drastic reaction conditions, long reaction times, and incompatibility with other functional groups in the molecule. In this respect, two papers reported the selective esterification of aliphatic carboxylic acids in the presence of aromatic ones under mild and heterogeneous conditions.^{150,151}

Silica gel-supported NaHSO₄ promoted the selective formation of esters in good yield, reacting with a wide range of aliphatic carboxylic acids and alcohols (Table 18, entry 1).¹⁵⁰ The methyl ester of cinnamic acid was obtained in lower yield (42%). The selectivity was demonstrated by using molecules possessing both aromatic and aliphatic carboxylic

Scheme 9



Scheme 9b



groups as well as by competitive experiments; thus, in the reaction with homophthalic acid, the aliphatic acid was selectively esterified (Scheme 9-a).

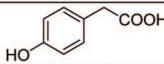
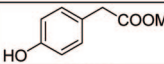
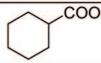
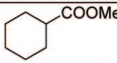
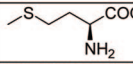
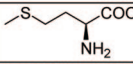
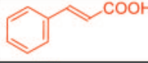
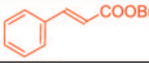
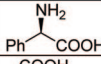
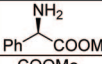
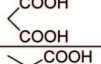
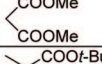
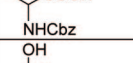
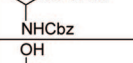
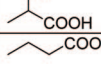
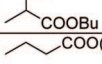
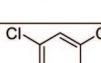
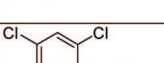
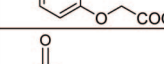
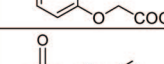
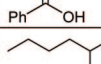
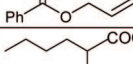
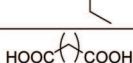
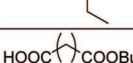
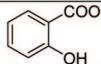
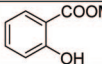
In the second paper, nonconjugated carboxylic acids were selectively esterified in the presence of conjugated ones over Amberlyst 15 as condensing agent in methanol or ethanol (Table 18, entry 2).¹⁵¹ Thus, itaconic acid was selectively protected at the allylic carboxylic group (Scheme 9-b).

The same catalyst was employed to obtain amino acid esters, which are key raw materials in the manufacture of important compounds such as pharmaceuticals and flavors. The common problem in the esterification process is the vulnerability of the amino group to alkylation and the possible racemization. Chiral amino acids were esterified in high yield and optical purity by stirring with Amberlyst 15 in methanol or ethanol (Table 18, entry 3).¹⁵²

Efficient esterification of both aliphatic and aromatic carboxylic acids with methanol in equimolecular ratios was performed with montmorillonite enwrapped titanium (Mont./Ti⁴⁺) (Table 18, entry 3b).^{152b} The same selective monoesterification of homophthalic and itaconic acids depicted in Scheme 9 can be achieved in high yield with Mont./Ti⁴⁺ catalyst.

Aromatic and aliphatic carboxylic acids underwent facile and high-yielding esterification with alcohols in the presence of K10/FeCl₃ (26 examples, 72–96%).^{152c} When aliphatic

Table 18. Protection of Carboxylic Acids

entry ^{ref}	Catalyst ^a (experimental conditions)	acid	ester	yield (%)	n. ex. (yields %)
1 ¹⁵⁰	SiO ₂ /NaHSO ₄ (MeOH, rt, 5 h)			95	15 (42-96)
2 ¹⁵¹	Amberlyst 15 (MeOH, rt, 14 h)			81	11 (75-94)
3 ¹⁵²	Amberlyst 15 (MeOH, rt, 16 h)			82	8 (70-82)
3b ^{152b}	Mont./Ti ³⁺ (3) (MeOH, 70 °C, 6 h)	CH ₃ (CH ₂) ₄ COOH	CH ₃ (CH ₂) ₄ COOMe	98	14 (82-99)
3c ^{152d}	SiO ₂ /SOCl ₂ (Bu ^t OH, reflux, 9 h)			83	23 (79-97)
4 ¹⁵³	USY zeolite ^a (MeOH, 130 °C, 0.5 h)			86	4 (14-86)
5 ¹⁵⁴	MoO ₃ /ZrO ₂ ^a (MeOH, 85 °C, 6 h)			95	7 (57-95)
6 ¹⁵⁵	MgSO ₄ /H ₂ SO ₄ (<i>t</i> -BuOH, CH ₂ Cl ₂ , rt, 18 h)			87	13 (60-93)
7 ¹⁵⁶	D001/AlCl ₃ (BuOH, PhH, Δ, 2.5 h)			99	11 90-99
8 ¹⁵⁷	Salicylic resin/FeCl ₃ (C ₃ H ₁₁ OH, PhH, Δ, 123 min)			97	10 94-97
9 ¹⁵⁸	SiO ₂ (<i>i</i> -OctOH, neat, MW 175 W, 5 min)			97	4 (95-99)
10 ¹⁵⁹	Celite/CsF (CH ₂ =CHCH ₂ Br, MeCN, Δ, 1.5 h)			99	27 (79-98)
11 ¹⁶⁰	SiO ₂ /PBGSiCl ^a (ClCOOPh, neat, 120 °C, 9 h)			98	9 (92-98)
12 ^{161, 162}	Dowex [®] 50WX2 (butyl formate-octane, 100 °C, 100 min)	HOOC(CH ₂) ₆ COOH	HOOC(CH ₂) ₆ COOBu	92	18 (72-95)
13 ¹⁶⁵	Beta zeolite (DMC, 150 °C, 4 h)			92	1 (92)

^a The catalyst has been recycled (number of recycles).

and aromatic acids were reacted in competition, the selective production of the aliphatic acid ester was observed (Scheme 9b).

Silica chloride, an easily preparable and cheap solid catalyst, can be efficiently utilized in the esterification of a great variety of aliphatic and aromatic acids with different alcohols including tertiary ones, which are reported to give the esters with difficulty (Table 18, entry 3c).^{152d} In this case, conjugated acids gave esters in high yield including these with tertiary alcohols.

A salt-free esterification of α-amino acids catalyzed by ultrastable Y zeolite (USY), originally prepared for large-scale industrial processes, has been recently reported by Sheldon et al. The authors showed that esterification over a solid acid catalyst could, in principle, yield the ester as the free base in a salt-free, noncorrosive process. Indeed, in conventional homogeneous processes, the generation of the free amino acid esters implies the concomitant generation of at least 1 equiv of inorganic salt. Various α-amino acids, i.e., D-phenylglycine, L-phenylalanine, D,L-homophenylalanine, and D-*p*-hydroxyphenylglycine, reacted with alcohols over H-USY (SAR = 5), giving the corresponding esters (Table 18, entry 4).¹⁵³ To explain the partial racemization observed, the authors showed that the amino acid ester undergoes thermal racemization, even in refluxing methanol.

A general method to convert aromatic and aliphatic mono- and dicarboxylic acids into the corresponding esters was

reported employing primary alcohols over the binary oxide MoO₃/ZrO₂ (Table 18, entry 5).¹⁵⁴ Secondary alcohols were recovered unchanged.

The protection of carboxylic acid as *tert*-butyl esters is a useful synthetic procedure due to the relative resistance to nucleophilic attack and ready removal by acidolysis. A specific and convenient preparation of *tert*-butyl esters, promoted by sulfuric acid-impregnated anhydrous magnesium sulfate, was reported by Wright et al. Indeed, aliphatic, olefinic, heteroaromatic, and *N*-protected amino acids reacted with an excess of *tert*-butyl alcohol as in situ source of isobutylene, affording *tert*-butyl esters in good yields (Table 18, entry 6).¹⁵⁵ The sulfuric acid is adsorbed onto the magnesium sulfate, and the pH of the reaction solvent remains neutral. The use of magnesium sulfate or sulfuric acid alone failed to afford the product ester. This method is quite specific for *tert*-butyl alcohol, since other tertiary alcohols, e.g., *tert*-amyl alcohol, afforded a lower yield of the corresponding ester and primary and secondary alcohols were converted into their *tert*-butyl ethers.

The use of Lewis acids supported on sulfonated cross-linked polystyrene or salicylic acid resin was reported to promote the synthesis of aliphatic acid esters (Table 18, entries 7 and 8).^{156,157} Both methods present the drawback that an excess of alcohol must be employed.

An interesting study on the synthesis of 2,4-dichlorophenoxy acetic acid esters has been published by Ruiz-Hitzky

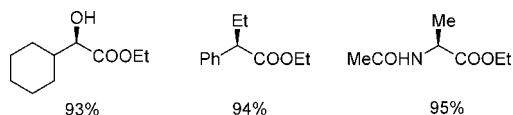


Figure 8.

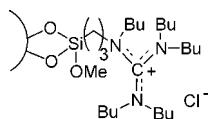
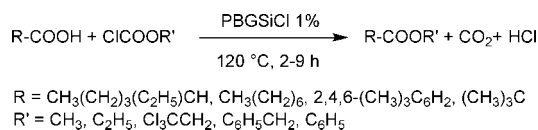


Figure 9.

Scheme 10



et al.; they reported the synthesis of these esters using microparticulate inorganic solids such as silica, clay, and zeolite as reaction media, without organic solvents, either by conventional heating or by using microwaves. Under microwave irradiation, the esters were obtained in high yield in shorter reaction time (3–10 min vs 2–6 h) (Table 18, entry 9).¹⁵⁸

A different approach to esterification involved the use of alkyl halides or chloroformates as reagents instead of alcohols. Aromatic, aliphatic, and heteroaromatic carboxylic acids were converted into the corresponding esters by reaction with allyl and benzyl bromides or alkyl iodides over Celite/CsF as a solid base in refluxing acetonitrile (Table 18, entry 10).¹⁵⁹ Esterification of chiral α -substituted carboxylic acids proceeded in excellent yields with retention of configuration (Figure 8). Chemoselective esterification was obtained for phenolic carboxylic acids, accompanied by a slight amount of dialkylated products.

An efficient and selective esterification of carboxylic acids with chloroformates was reported using silica-supported hexaalkyl guanidinium salt ($\text{SiO}_2/\text{PBGSiCl}$) (Table 18, entry 11)¹⁶⁰ (Figure 9). Aliphatic and aromatic carboxylic acids, also sterically hindered, reacted with phenyl, benzyl, and 2,2,2-trichloroethyl chloroformate without solvent at 120 $^{\circ}\text{C}$, giving the corresponding esters in high yields (Scheme 10). Methyl chloroformate was unsuccessful, as it was unstable under the reaction conditions.

This supported catalyst promoted the selective formation of esters, avoiding anhydride and carbonate production. The authors suggested the formation of carboxylic acid-guanidinium complexes which easily reacted with chloroformates, affording the acyl chlorides and alcohols, which finally recombined into the corresponding esters. It is noteworthy that the process required a small amount of catalyst (1%).

Particularly interesting is the selectivity obtained by Nishiguchi et al. in the monoesterification of symmetrical dicarboxylic acids catalyzed by ion-exchanged resins. Dicarboxylic acids with 4–14 carbon atoms were converted into monoesters by heating with a butyl formate-octane mixture over wet Dowex 50WX2 resin (Table 18, entry 12).^{161,162} The use of propyl formate or ethyl propionate instead of butyl formate afforded the propyl or ethyl monoesters of hexanedioic acid. The reaction selectivity was high, the diesters being obtained in only 3–8% yield. The amount of catalyst was crucial: to realize high selectivities, 1 g/mmol with respect to the dicarboxylic acid was employed, which is about 10 times as much as that used in the

selective acylation¹⁶³ and tetrahydropyranylation¹⁶⁴ of diols. The authors showed that a certain amount of water in the resin is essential for the high selectivity. Taking into account that the diacid reacts much more rapidly than the monoester, they presumed that the selectivity arises from a partition equilibrium between the aqueous layer and the aprotic ester-hydrocarbon layer which is different for the diacid and monoester.

Recently, the esterification of salicylic acid over zeolites has been reported using dimethyl carbonate (DMC) (Table 18, entry 13).¹⁶⁵ This reagent overcomes the main drawback of esterification reactions involving alcohols, i.e., the necessity to remove the water formed which would deactivate the catalyst. DMC is an environmentally friendly methylating agent that affords methanol as an esterification byproduct, which can be recycled for the production of DMC. BEA (SAR = 16) and ZSM-5 zeolites (SAR = 50) were effective catalysts, giving the methyl salicylate, an important industrial intermediate, in high yield and selectivity (>95%). Kinetic studies revealed that catalyst acidity, especially in the strong acid sites, is the main characteristic that explains the activity order, i.e., BEA > ZSM-5 \gg Y (SAR = 60).

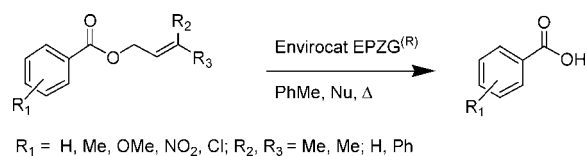
4.2. Deprotection

Selective deprotection of esters in the presence of sensitive functional groups is an important goal in synthetic organic chemistry, in particular when different ester functionalities are present in the same compound.

Allyl and cinnamyl esters could be chemoselectively deprotected by kaolinitic clay (Table 19, entry 1)¹⁶⁶ and Envirocat EPZG (Scheme 11). Upon heating the esters at reflux in toluene in the presence of anisole as nucleophile, both catalysts promoted the conversion to the parent acids with identical results. The catalyst activity was attributed to Brønsted and Lewis acid centers present on their surface. The authors showed that alkyl esters remain unchanged under the reaction conditions. An interesting substituent effect, not rationalized, was observed for cinnamyl esters of aromatic acids: meta-substituted esters were hydrolyzed quantitatively to the corresponding acids, and ortho-substituted esters were hydrolyzed in moderate yields (46–60%), whereas *para*-substituted esters remained almost unaltered.

An improvement in deprotection of allyl esters was then shown by carrying out a solvent-free, microwave-assisted reaction catalyzed by montmorillonite K10 (Table 19, entries 2 and 3).¹⁶⁷ The time required for completion of the reaction was appreciably shorter (10–20 min) than that required when using thermal condition (5–20 h). Toluene was used as the nucleophile when allylic esters were hydrolyzed, whereas more nucleophilic aromatic species, such as anisole, were employed for cinnamyl esters. Aryl and alkyl esters remained unaffected under these reaction conditions.

Scheme 11



Scheme 12

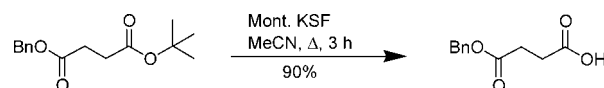
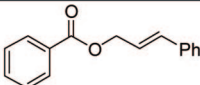
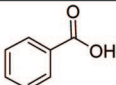
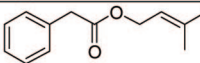
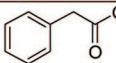
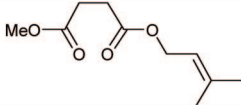
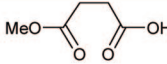
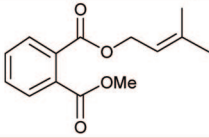
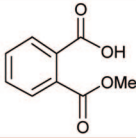
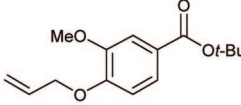
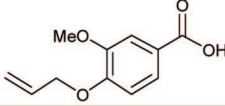
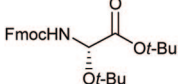
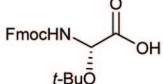
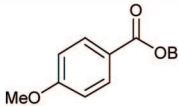
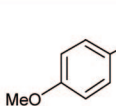
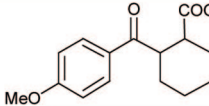
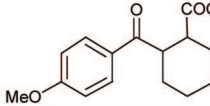
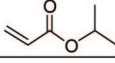

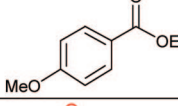
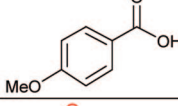
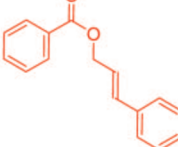
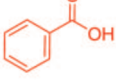


Table 19. Deprotection of Esters

entry ^{ref}	catalyst ^a (experimental conditions)	ester	acid	yield (%)	n. ex. (yields %)
1 ¹⁶⁶	Kaolin (PhOMe, PhMe, Δ, 5 h)			95	15 (53-100)
2 ¹⁶⁷	Mont. K10 (MW, 20 min)			97	18 (60-98)
3 ¹⁶⁷	Mont. K10 (MW, 20 min)			72	18 (60-98)
4 ¹⁶⁸	Sulfated SnO ₂ (PhMe, Δ, 2 h)			72	13 (50-92)
5 ¹⁶⁹	Mont. KSF ^{a(3)} (MeCN, Δ, 4 h)			90	13 (80-95)
6 ¹⁷⁰	SiO ₂ (PhMe, Δ, 1.25 h)			76	9 (68-94)
7 ¹⁷¹	Al ₂ O ₃ (MW, 7 min)			89	7 (89-95)
8 ¹⁷²	SiO ₂ /InI ₃ (MW, 45 min)			83	13 (70-93)
9 ¹⁷³	Al ₂ O ₃ /KF (MW, neat)			96	20 (90-98)
10 ¹⁷³	Al ₂ O ₃ /KF (MW, neat)			98	20 (90-98)
10b ^{173b}	Beta zeolite (PhOMe, PhMe, reflux, 3 h)			96	15 (70-96)

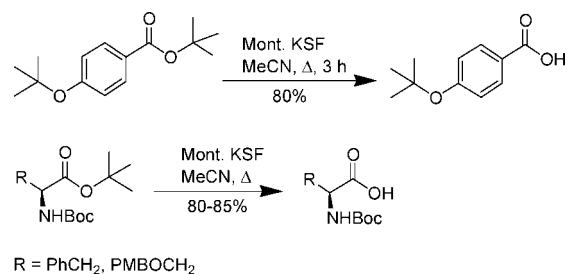
^a The catalyst has been recycled (number of recycles).

Allyl esters were easily deprotected also by sulfated SnO₂ in refluxing toluene (Table 19, entry 4).¹⁶⁸ Anisole was used as the nucleophilic aromatic reagent when cinnamyl and crotyl esters were reacted. The authors showed that this reaction constitutes “hydrolysis” under anhydrous conditions and that methyl esters remain unaffected.

Recently, a highly chemoselective hydrolysis of *tert*-butyl esters promoted by montmorillonite KSF was reported by Yadav et al. (Table 19, entry 5).¹⁶⁹ The authors attributed the wide range of functional groups tolerated to the mild conditions and to the short reaction time. Indeed, this method selectively cleaves *tert*-butyl esters, leaving benzyl, methyl, and allyl esters intact (Scheme 12).

Moreover, *tert*-butyl esters can be selectively removed in the presence of other acid-sensitive protecting groups, such as carbamates, ethers, and olefins (Scheme 13). Interestingly,

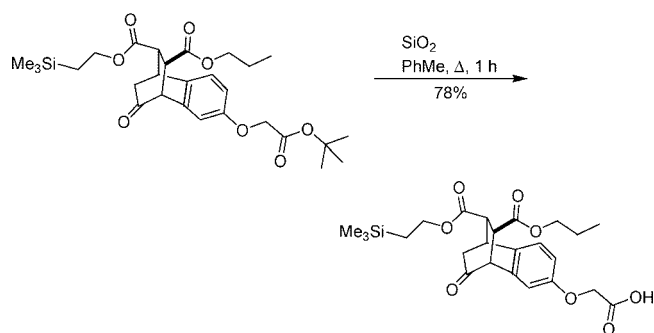
Scheme 13



it was reported that when a stereogenic center is present in the α-position, the parent acids can be isolated with complete retention of configuration.

The cleavage of *tert*-butyl esters was previously reported using silica gel in refluxing toluene (Table 19, entry 6).¹⁷⁰

Scheme 14



The selectivity obtained for *tert*-butyl esters over *tert*-butyl ethers was substrate-dependent (product ratio from 9/1 to 2.1/1), whereas it was complete over trimethylsilyl esters (Scheme 14). The reaction required a large amount of silica (5 g/mmol of ester). Interestingly, the hydrophobic substrates needed longer reaction times than the more polar amino acid derivatives, due to the relative affinity of the starting material for the silica gel.

Aromatic and aliphatic benzyl esters were easily deprotected under mild conditions on neutral or acidic alumina when subjected to microwave irradiation for short times (Table 19, entry 7).¹⁷¹ Microwave irradiation was more efficient than conventional heating. The amount of catalyst required for optimum yield was high, i.e., 12–14 g/mmol ester.

Two general procedures for esters hydrolysis were reported using impregnated catalysts. Aliphatic, alicyclic, and aromatic carboxylic acids were obtained in high yields on moist silica gel impregnated with indium triiodide under microwave irradiation (Table 19, entry 8).¹⁷² The reaction conditions were tolerant to ketone, hydroxy, methoxy, and C=C moieties.

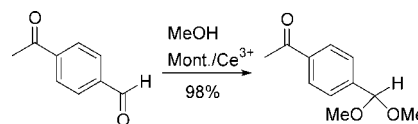
Finally, potassium fluoride-doped alumina promoted the hydrolysis of a variety of esters derived from aromatic, vinyl, and aliphatic acids and primary, secondary, and tertiary alcohols under microwave irradiation. The corresponding acids were obtained in excellent yields (Table 19, entries 9 and 10).¹⁷³

Aromatic allyl esters can be deprotected in the presence of beta zeolite in refluxing toluene (Table 19, entry 10b).^{173b} The reaction allows the selective deprotection of allyl esters in the presence of methyl ones; in addition, aliphatic esters do not undergo deprotection under the conditions suitable for the deprotection of aromatic esters.

5. Carbonyl Protecting Groups

The electrophilic nature of the carbonyl group is a dominant feature of its extensive chemistry. One of the major challenging problems during many multiuse syntheses is how to protect a carbonyl from nucleophilic attack until its electrophilic properties can be exploited. The protection of aldehydes and ketones has been served by a relatively small repertoire of protecting groups and, of these, acetals, thiacetals, oxathiolanes, 1,1-diacetates, and nitrogenous derivatives have proven to be the most serviceable.

Scheme 15



5.1. Acetals

5.1.1. Protection

Due to the great importance of these protecting groups, many methods for their formation under heterogeneous catalysis have been reported in recent years (Table 20).

Montmorillonite KSF has been reported for the protection of carbonyl compounds as 1,5-dihydro-3*H*-2,4-benzodioxepines (Table 20, entry 1).¹⁷⁴ Under these conditions, aldehydes and aliphatic ketones were easily protected, but aromatic ketones were highly resistant, and benzophenone was unreactive. The same catalyst has been employed, without any solvent, under microwave irradiation, to protect aldehydes and ketones with orthoformates or by dioxolane exchange with 2,2-dimethyl-1,3-dioxolane (DMD) (Table 20, entry 2).¹⁷⁵

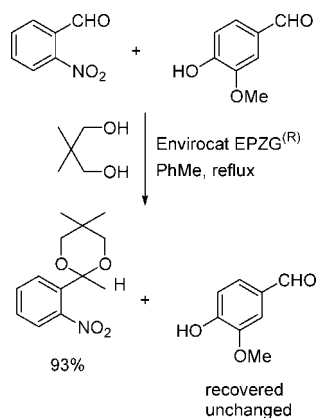
The acetalization of carbonyl compounds with methanol was investigated by Uemura et al. in the presence of a cation-exchanged montmorillonite (M^{n+} -Mont; $M^{n+} = Ce^{3+}, Zr^{4+}, Fe^{3+}, Al^{3+}, Zn^{2+}, H^+, \text{ and } Na^+$) (Table 20, entry 3).¹⁷⁶ The order of catalytic efficiency of the montmorillonite/ M^{n+} is montmorillonite/ $Ce^{3+} > Fe^{3+}, Al^{3+}, Zr^{4+} \gg Zn^{2+}, Na^+, H^+$. However, linear ketones and aldehydes were converted incompletely under these conditions. It must be pointed out that the acetalization of 4-acetylbenzaldehyde occurred only at the formyl group (Scheme 15).

Natural kaolinitic clay was found to be a convenient catalyst for the chemoselective protection, with ethylene glycol, of a variety of aliphatic, aromatic, heteroaromatic, and α,β -unsaturated aldehydes (Table 20, entry 4), while ketones failed to undergo protection.¹⁷⁷

Isatin ketals can be efficiently prepared by carrying out the reaction with montmorillonite K10 using microwave irradiation (73 W); the ethylene glycol (or 1,3-propanediol) was added in two steps (Table 20, entry 4b).^{177b} The 1,3-dioxolane ketals were formed faster than the equivalent 1,3-dioxane ones. Experiments on clay reutilization showed a yield decrease of 5–11% in the first run and of 8–15% in the second recycle.

Envirocat EPZG has been reported to give acetals with 1,2-benzenedimethanol (Table 20, entry 5),¹⁷⁸ and, because the protection of the ketones needs longer reaction times, the chemoselective protection of an aldehyde in the presence of a ketone could be achieved by the appropriate choice of the reaction time. The same catalyst was efficiently applied for the acetalization of the carbonyl compounds with ethylene glycol (Table 20, entry 6).¹⁷⁹ When 2,2-dimethyl-1,3-propanediol was employed under Envirocat EPZG catalysis, both ketones and aldehydes (Table 20, entry 7) were easily protected.¹⁸⁰ Moreover, some more reactive compounds were acetalized in the presence of less reactive or sterically hindered ones; for example, when a mixture of *o*-nitrobenzaldehyde and 3-methyl-4-hydroxybenzaldehyde was allowed to react with 1 equiv of 2,2-dimethyl-1,3-propanediol and a catalytic amount of Envirocat EPZG, a 93% yield of the former protected aldehyde was obtained, whereas the latter one was recovered unchanged (Scheme 16).

Scheme 16



A series of 2-substituted and 2,2-disubstituted 1,3-benzodioxolanes has been synthesized by reaction of catechol and pirogallol with aldehydes and ketones, catalyzed by montmorillonite KSF or K10 (Table 20, entry 8). Ketones gave better yields than aldehydes, although highly sterically hindered ones such as steroidal ketones or diaryl ketones failed to react at all. Dicarbonyl compounds can selectively provide monobenzodioxolanes with the use of an excess of ketone (Scheme 17).¹⁸¹

Kaneda et al. reported the use of titanium-exchanged montmorillonite for the selective acetalization of carbonyl compounds with ethylene glycol (Table 20, entry 9); the catalyst smoothly transforms various kinds of cyclic, aliphatic, and aromatic ketones into acetals. Remarkably, bulky ketones gave quantitative yields of the corresponding acetals. The catalyst was efficiently employed for the chemoselective acetalization of polyfunctionalized compounds (Scheme 18).¹⁸² For example, 4-oxo-4*H*-1-benzopyran-3-carboxyaldehyde was exclusively protected at the formyl group (Scheme 18a), whereas ethyl 2-oxocyclopentanecarboxylate afforded an acetal, leaving the ester function intact (Scheme 18b). More interestingly, the unconjugated keto function of the Wieland-Miescher ketone was selectively protected with respect to the conjugated one (Scheme 18c).

Y zeolite HSZ-360 has been demonstrated to be effective in the formation of 1,3-dioxolanes with several aldehydes or ketones without the need for water removal. The method (Table 20, entry 10) shows good selectivity since other functionalities such as phenolic and alcoholic hydroxy groups, (Z)-carbon-carbon double bond, cyano, ether, bromide, and sulfone were preserved. When 1,4- and 1,3-diketones were employed as starting materials, double 1,3-dioxolanes were obtained, while with high enolizable starting compounds the mono-1,3-dioxolane was produced, in moderate yield. Chiral 1,3-dioxolanes were also prepared in excellent yield from (*R,R*)-dimethyltartrate, with complete retention of optical activity (Scheme 19).¹⁸³

The use of other Y zeolites was reported by Corma et al. for the preparation of dimethyl and cyclic ethylene acetals by treatment of the corresponding carbonyl compounds with trimethyl orthoformate (Table 20, entry 11)¹⁸⁴ or with ethylene glycol. Better yields were obtained with the first procedure; in this case, the level of acidity of the zeolite on the initial reaction rate revealed that only strong acid sites ($pK_a < 0$) were active.

A mild catalytic method for acetalization of carbonyl compounds, such as 1,5-dihydro-2,4-benzodioxepines (Table

20, entry 12), with benzene 1,2-dimethanol using acidic ZSM-5 zeolites has been reported. Removal of water with this catalyst was not necessary; however, a drawback of this procedure was the need to activate the catalyst by heating at 400 °C for 6 h before use.¹⁸⁵

The catalytic activity of delaminated zeolites (ITQ-2) in the acetalization of aldehydes with trimethyl orthoformate (Table 20, entry 13) has been compared with mesoporous MCM-22 aluminosilicate, beta zeolites, and amorphous aluminosilicate, all of them with similar SAR. The results obtained indicate that when the reactions involve bulky reactants, ITQ-2 shows the highest activity as a consequence of the combination of its delaminated structure, which allows easy access to the active sites, and the presence of strong acid sites.⁶⁹

Sulfuric acid adsorbed on silica gel has been found to be a good catalyst for the ketalization of ketosteroids with ethylene glycol (Table 20, entry 14),⁹³ while silica gel-supported metallic sulfates were found to efficiently promote the protection of both aromatic and aliphatic aldehydes as 1,3-dioxolanes under microwaves, in solvent-free conditions (Table 20, entry 15). Several aliphatic, aromatic, α,β -unsaturated, and heterocyclic aldehydes were selectively protected in high yields. Among various metallic sulfates supported on silica gel [$\text{Ce}(\text{SO}_4)_2$, MgSO_4 , and NaHSO_4], the last was found to be the most effective.¹⁸⁶

The sulfonic acid-functionalized amorphous silica has been utilized as reusable catalyst for acetalization of aldehydes and ketones with methanol at room temperature in air. Different aromatic aldehydes, conjugated aldehydes, aliphatic aldehydes, including linear aldehydes, and cyclic ketones underwent smooth transformation to the corresponding acetal in good yield (Table 20, entry 15b);^{73b} linear ketones did not react at all. An important advantage of this method is represented by the high turnover numbers: for example, by using a very small amount of the catalyst (0.01% mol), the acetal yield for 1-butanal was 90% after 60 h, which corresponds to a turnover number of 9000.

The highly acidic sulfated zirconia ($\text{ZrO}_2/\text{SO}_4^{2-}$), with $H_0 \leq -16.04$, has been proposed for the synthesis of acetals from aldehydes and ketones with 2,2-dimethyl-1,3-propanediol (Table 20, entry 16) and with removal of water.⁷⁸ The same reaction has been successfully tested with yttria-zirconia in chloroform at room temperature (Table 20, entry 17).¹⁸⁷

2,2-Disubstituted and 2-monosubstituted 1,3-benzodioxoles were prepared by $\text{ZrO}_2/\text{SO}_4^{2-}$ catalysis (Table 20, entry 18). When catechol was heated with several aldehydes or ketones and in the presence of $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid, the 1,3-benzodioxoles were obtained in good yields. Ketones allowed better yields than aldehydes, and the authors found that the reaction rate of cyclic ketones was influenced by the ring size (five- and six-membered ring ketones gave higher yields).¹⁸⁸

Zirconium sulfophenyl phosphonate [$\text{Zr}(\text{CH}_3\text{PO}_3)_{1.2}(\text{O}_3\text{-PC}_6\text{H}_4\text{SO}_3\text{H})_{0.8}$] has been investigated for the preparation of 1,3-dioxolanes, 1,3-dioxanes, and 1,3-dioxepane from several carbonyl compounds (Table 20, entry 19). The reaction in general occurs in satisfactory to good yields, whereas it failed when α,β -unsaturated and aromatic ketones were reacted with propane-1,3- and butane-1,4-diols.¹⁸⁹

A method for the protection of carbonyl compounds has been carried out under $\text{Pt}/\text{MoO}_3/\text{ZrO}_2$, a catalyst that is not easily available (Table 20, entry 20). Various aldehydes and

Table 20. Protection of Carbonyl Groups as Acetals

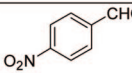
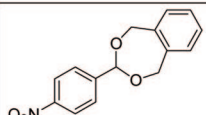
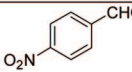
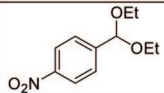
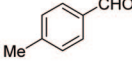
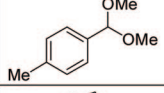
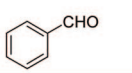
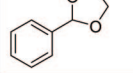
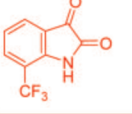
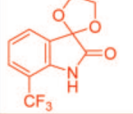
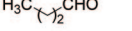
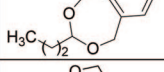
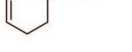
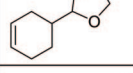
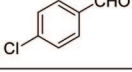
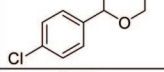

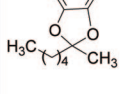
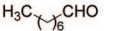
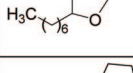
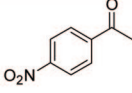
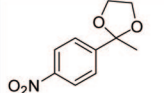
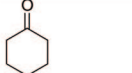
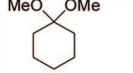
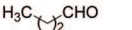
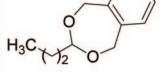
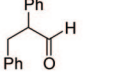
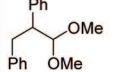
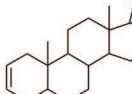
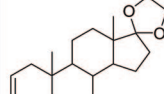
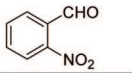
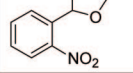


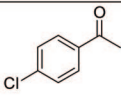
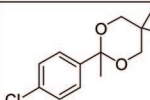

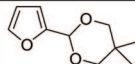
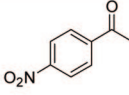
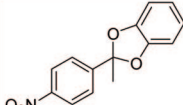

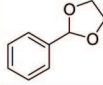

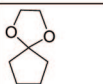
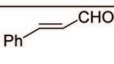
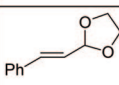

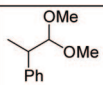

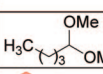

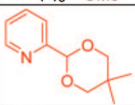

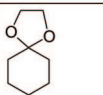
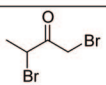
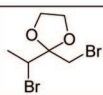
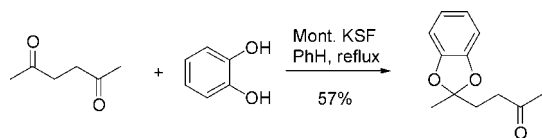
entry ^{ref}	Catalyst ^a (experimental conditions)	carbonyl compound	acetal	yield (%)	n. ex. (yields %)
1 ¹⁷⁴	Mont. KSF (1,2-benzenedimethanol, PhH, Δ, 1 h)			99	16 (45-99)
2 ¹⁷⁵	Mont. KSF [CH(OEt) ₃ , neat, MW 150W, 2 min]			97	17 (0-97)
3 ¹⁷⁶	Mont./Ce ³⁺ a(3) (MeOH, rt, 30 min)			99	21 (24-99)
4 ¹⁷⁷	Kaolin ^{a(3)} [(CH ₂ OH) ₂ , PhH, Δ, 2 h]			95	17 (0-95)
4b ^{177b}	Mont. K10 [(CH ₂ OH) ₂ , MW 73W, 15 min]			83	16 (77-94)
5 ¹⁷⁸	Envirocat EPZG [®] (1,2-benzenedimethanol, PhMe, Δ, 45 min)			99	9 (92-99)
6 ¹⁷⁹	Envirocat EPZG ^{®a(2)} [(CH ₂ OH) ₂ , neat, MW 800W, 2 min]			96	12 (23-96)
7 ¹⁸⁰	Envirocat EPZG ^{®a(3)} (neopentyl glycol, PhMe, Δ, 3 h)			98	11 (80-98)
8 ¹⁸¹	Mont. KSF ^a (catechol, PhMe, Δ, 12 h)			97	23 (0-99)
9 ¹⁸²	Mont./Ti ⁴⁺ a(1) [(CH ₂ OH) ₂ , PhMe, Δ, 1 h]			99	14 (90-99)
10 ¹⁸³	Y zeolite HSZ-360 ^{a(5)} [(CH ₂ OH) ₂ , PhMe, Δ, 5 h]			100	27 (60-100)
11 ¹⁸⁴	Y zeolite [CH(OMe) ₃ , CH ₂ Cl ₂ , rt, 2 h]			96	10 (38-96)
12 ¹⁸⁵	ZSM-5 zeolite ^{a(5)} (1,2-benzenedimethanol, CH ₂ Cl ₂ , Δ, 3 h)			95	12 (75-95)
13 ⁶⁹	Delaminated zeolite ITQ-2 ^{a(1)} [CH(OMe) ₃ , CCl ₄ , Δ, 1 h]			75	3 (75-95)
14 ⁹³	SiO ₂ /H ₂ SO ₄ [(CH ₂ OH) ₂ , PhMe, Δ, 1 h]			98	3 (77-98)
15 ¹⁸⁶	SiO ₂ /NaHSO ₄ [(CH ₂ OH) ₂ , neat, MW 650W, 3 min]			98	21 (71-98)
15b ^{73b}	SiO ₂ -SO ₃ H ^{a(3)} (MeOH, rt, 3 h)			91	9 (82-97)

Table 20. Continued

entry ^{ref}	Catalyst ^a (experimental conditions)	carbonyl compound	acetal	yield (%)	n. ex. (yields %)
16 ⁷⁸	ZrO ₂ /SO ₄ ²⁻ (neopentyl glycol, PhH, Δ, 6 h)			99	14 (65-99)
17 ¹⁸⁷	Y ₂ O ₃ /ZrO ₂ (neopentyl glycol, CHCl ₃ , rt, 8 h)			96	11 (80-96)
18 ¹⁸⁸	ZrO ₂ /SO ₄ ²⁻ (catechol, PhMe, Δ, 11 h)			98	20 (21-98)
19 ¹⁸⁹	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} ^{a(3)} [(CH ₂ OH) ₂ , CH ₂ Cl ₂ , Δ, 2 h]			90	30 (33-98)
20 ¹⁹⁰	Pt/MoO ₃ /ZrO ₂ [(CH ₂ OH) ₂ , PhMe, Δ, 6 h]			98	9 (80-100)
21 ¹⁹¹	AlPO ₄ /Al ₂ O ₃ [(CH ₂ OH) ₂ , MeCN, 78 °C, 1.7 h]			100	9 (80-100)
22 ¹⁹²	Mesoporous Aluminosilicate MCM-41 [CH(OMe) ₃ , CCl ₄ , Δ, 5 h]			93	3 (70-93)
23 ¹⁹³	Siliceous Mesoporous MCM-41 (MeOH, Δ, 5 h)			100	9 (18-100)
23b ^{104c}	Al-SBA-15 ^{a(5)} [HOCH ₂ C(Me) ₂ CH ₂ OH, ClCH ₂ CH ₂ Cl, reflux, 5 h]			93	23 (57-100)
24 ¹⁵⁷	Salicylic Acid Resin supported FeCl ₃ ^{a(5)} [(CH ₂ OH) ₂ , PhH, 90 °C, 2 h]			99	10 (41-99)
25 ¹⁹⁴	Nafion [®] /TMS [(CH ₂ OSiMe ₃) ₂ , neat, 95 °C, 89 h]			90	14 (10-100)

^a The catalyst has been recycled (number of recycles).

Scheme 17

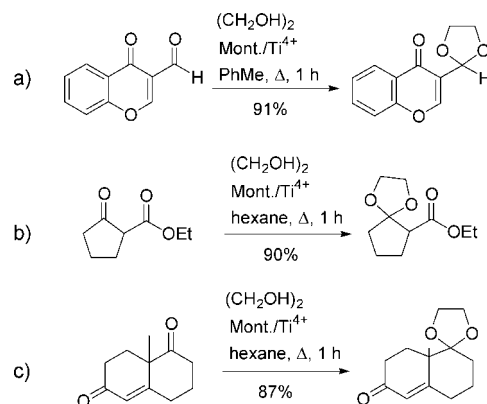


ketones, including α,β -unsaturated ones, can be protected with ethylene glycol.¹⁹⁰

Carbonyl compounds were acetalized, with ethylene glycol, on AlPO₄ (Table 20, entry 21) or Al₂O₃/AlPO₄ catalysis. Both catalysts are able to efficiently promote the acetalization reaction, although AlPO₄ seems to be more adequate for ketones while Al₂O₃/AlPO₄ was more effective with aldehydes.¹⁹¹

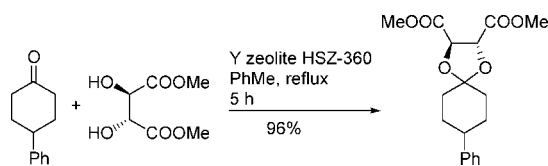
An interesting study of different catalysts for the preparation of dimethylacetals of aldehydes by reaction with trimethyl orthoformate has been made by Corma et al.¹⁹² Large-pore Y and beta zeolites as well as mesoporous and amorphous silica–aluminas have been used as catalysts.

Scheme 18



It was found that, with small size aldehydes, zeolites were intrinsically more active than the mesoporous materials. However, when using reactants with molecular size larger than 7 Å (as it is commonly done in the field of fine chemicals), geometric constraints do not allow their diffusion

Scheme 19



inside the pores, and only the external surface area of these materials becomes available to the reactants. In these circumstances, the large pores of MCM-41 make this material more adequate for carrying out the acetalization reactions (Table 20, entry 22). A similar mesoporous catalyst was also employed by Iwamoto et al. for the acetalization of aldehydes and ketones with methanol (Table 20, entry 23).¹⁹³

Al-SBA-15 catalyst was employed by Srivastava et al. in the protection of carbonyl compounds with neopentyl glycol in refluxing ethylene dichloride for 5 h (Table 20, entry 23b).^{104b} The catalyst is efficient for protection of aliphatic and aromatic aldehydes, including cinnamaldehyde, a well-known acid-labile substrate. Other protecting reagents such as ethylene glycol, 1,2-propanediol, and 2,3-butanediol also can be employed.

Some examples of application of resins showing Lewis as well as protic acidity have been reported. For example, the salicylic acid resin-supported FeCl₃ was utilized for the acetalization of different aldehydes and ketones (Table 20, entry 24), showing a good efficiency combined with a noncorrosive effect.¹⁵⁷ Similarly, α -haloketones were acetalized in the presence of Nafion/TMS (Table 20, entry 25)¹⁹⁴ with 1,2-bis(trimethylsilyloxy)ethane (BTSE). The reaction was usually performed in refluxing chloroform, but for sterically crowded haloketones and dihaloketones, heating at 90–100 °C in the absence of solvent was needed. This is an important advantage since α -haloketones are prone to rearrange under acidic conditions.

5.1.2. Deprotection

The regeneration of carbonyl compounds from their acetals is generally performed under acidic conditions and, for this purpose, different heterogeneous catalysts have been proposed.

Cyclic acetals of ketosteroids were cleaved by using sulfuric acid⁹³ or copper(II) sulfate¹⁹⁵ supported on silica (Table 21, entries 1 and 2). Concerning the second procedure, from the results reported it is evident that the method was useful for removal of cyclic acetals in solvents of low polarity, such as dichloromethane, chloroform, or benzene, while more polar solvents, like tetrahydrofuran, ethyl acetate, or acetone, completely inhibited the reaction. It should be noted that, under appropriate conditions, the method allowed chemoselective removal of cyclic acetals in the presence of cyclic thioacetals (Scheme 20) and did not affect cyanohydrin and ester functions.

Silica-supported perchloric acid is reported to be an inexpensive, efficient, and reusable catalyst for the deprotection of acetals and ketals (Table 21, entry 2b).^{195b} Various aldehydes and ketones can be restored from their corresponding dimethyl or diethyl acetals and ketals simply by stirring, at room temperature, their solution (MeOH/EtOH–H₂O) in the presence of a small amount (0.5% mol) of the catalyst.

Commercially available montmorillonite K10 has been utilized for the easy cleavage of acetals (Table 21, entries 3

and 4);^{196,197} it should be noted that a larger amount of catalyst was needed for cyclic acetals.

NaY zeolites promoted the cleavage of acetals in the presence of nitrobenzene at room temperature (Table 21, entry 5).¹⁸⁴ It has been demonstrated that water molecules that remained adsorbed on the zeolite after thermal activation were active during the hydrolytic cleavage. When no external water was added to the system, the progress of the reaction depended on the water absorbed on the zeolite. Mordenite zeolite (SAR = 19.2) has also been utilized for the cleavage of acetals (Table 21, entry 6). The results showed that a wide range of acetals, including saturated, α,β -unsaturated, aliphatic, aromatic, and heteroaromatic compounds, can be cleaved under these conditions.¹⁹⁸

(P)-DCKA was found to be an effective water-tolerant catalyst in the selective deprotection of dimethyl and ethylene acetals (Table 21, entries 7 and 8). Chemoselective hydrolysis of the ethylene acetals in the presence of acid-labile OH-protecting groups such as MOM, THP, TBDMS, and TBDPS could be performed under these conditions.^{101,199}

A mild and easy regeneration of the carbonyl compounds from their benzylic dioxolanes has been carried out by Habibi et al. under potassium dodecatungstocobaltate trihydrate (Table 21, entry 9). The method seems to be unaffected by the bulkiness of the starting acetals.⁶⁰

Oxidative deprotection of linear and cyclic acetals to their corresponding carbonyl derivatives could be performed by a convenient combination of oxidant and heterogeneous supports. For example, potassium ferrate supported on montmorillonite K10 allowed the cleavage of acetals under microwave irradiation in dry media (Table 21, entry 10). It is noteworthy that the use of the unsupported catalyst resulted in incomplete deprotection, even for prolonged reaction time under microwaves.²⁰⁰

A further efficient procedure for the selective cleavage of acetals has been carried out by using Oxone with alumina under microwaves and solvent-free conditions (Table 21, entry 11). It is worthy of note that the reaction allows the easy regeneration of a variety of aldehydes without over-oxidation.²⁰¹

Finally, a manipulatively simple and rapid method for the oxidative deprotection of ethylene acetals was obtained with Al₂O₃/KMnO₄ under solvent-free conditions without over-oxidation reactions (Table 21, entry 12).¹⁴⁶ The yield and rate of the transformation of ethylene acetals into the corresponding carbonyl compounds with potassium permanganate alone were lower.

5.2. Dithioacetals

5.2.1. Protection

Dithioacetals are obtained by protic or Lewis acid-catalyzed condensation of carbonyl compounds with thiols or by transdithioacetalization of acetals, and recently several heterogeneous catalysts have been proposed for this goal.

Different Lewis acids supported on silica gel were reported to efficiently promote the thioacetalization of carbonyl compounds. The main advantages derived from the use of these supported catalysts are (i) the higher activity of the supported catalyst with respect to the unsupported counterpart and (ii) the easier removal of the catalyst from the reaction medium.

A rapid, mild, and efficient method for thioacetalization has been proposed by Patney based on the use of anhydrous

Table 21. Deprotection of Acetals

entry ^{ref}	catalyst ^a (experimental conditions)	Acetal	carbonyl compound	yield (%)	n. ex. (yields %)
1 ⁹³	SiO ₂ /H ₂ SO ₄ (wet PhMe, 0.2 h)			99	3 (92-99)
2 ¹⁹⁵	SiO ₂ /CuSO ₄ (CHCl ₃ , 60 °C, 5 h)			93	9 (61-95)
2b ^{195b}	SiO ₂ /HClO ₄ ^a (MeOH/H ₂ O, rt, 30 min)			82	29 (80-95)
3 ¹⁹⁶	Mont. K10 (wet Me ₂ CO, Δ, 5 h)			95	15 (87-98)
4 ¹⁹⁷	Mont. K10 (CH ₂ Cl ₂ , rt, 2 h)			76	8 (71-100)
5 ¹⁸⁴	NaY zeolite (PhNO ₂ , CCl ₄ , rt, 2 h)			95	10 (71-97)
6 ¹⁹⁸	Mordenite zeolite ^{a(1)} (PhMe-H ₂ O, Δ, 3 h)			90	13 (89-99)
7 ²⁰⁰	(P)-DCKA ^a (MeCN-H ₂ O = 9:1, rt, 6 h)			71	19 (17-100)
8 ¹⁰¹	(P)-DCKA ^a (H ₂ O, rt, 20 h)			88	3 (34-93)
9 ⁶⁰	K ₅ CoW ₁₂ O ₄₀ ·3H ₂ O ^a (Me ₂ CO, Δ, 10 min)			95	14 (60-100)
10 ²⁰⁰	Mont. K10/K ₂ FeO ₄ (neat, MW 900W, 8 min)			95	8 (80-95)
11 ²⁰¹	Al ₂ O ₃ /Oxone [®] (neat, MW 2450MHz, 1.8 min)			93	8 (84-94)
12 ¹⁴⁶	Al ₂ O ₃ /KMnO ₄ (neat, mortar, rt, 15 min)			92	6 (75-98)

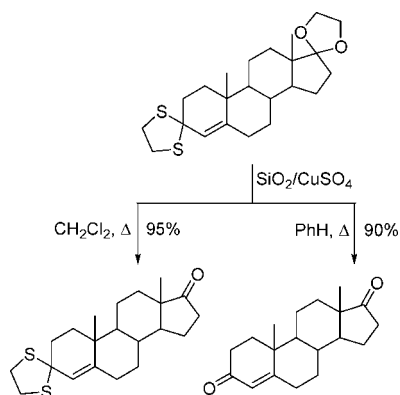
^a The catalyst has been recycled (number of recycles).

iron(III) chloride dispersed on silica gel. Different ethylene thioacetals have been obtained (Table 22, entry 1) from aldehydes as well as from ketones, in nearly quantitative yields and in very short reaction time.²⁰² Moreover, the protection of carbonyl compounds as 1,5-dihydro-2,4-benzodithiepinones (Table 22, entry 2) could be possible with aromatic, aliphatic, and α,β -unsaturated aldehydes.²⁰³ The drawback of this methodology is represented by the consumption of the catalyst, since the reaction results in production of water.

The same author claimed the use of bis(trimethylsilyl)sulfate on silica gel to promote thioacetalization of carbonyl compounds (Table 22, entry 3). It should be noted that in the absence of silica, the reaction required forcing conditions such as boiling benzene with azeotropic removal of water.²⁰⁴

Sodium hydrogen sulfate supported on silica gel was reported by Das et al. to efficiently convert a series of aromatic, heterocyclic, aliphatic, and conjugated aldehydes into the corresponding thioacetals by treatment with thioethanol in methylene chloride at room temperature. Various ketones also underwent thioacetalization. Several functional groups such as hydroxyl, halogen, nitro, ether, and allyl remained intact (Table 22, entry 3b).^{204b} It is interesting to note that a different selectivity was achieved when the reaction was carried out using different thiols: with long-chain thiols, aromatic aldehydes were protected with the same efficiency, whereas aliphatic aldehydes or ketones afforded no protection products under similar reaction conditions. This behavior was exploited to perform selective thioacetalization of carbonyl compounds as reported in Scheme 20b.

Scheme 20



Perchloric acid adsorbed on silica gel showed a high efficiency in the 1,3-dithiane and 1,3-dithiolane formation. Aromatic, heteroaromatic, and alicyclic aldehydes and ketones can be protected under solventless conditions at room temperature (Table 22, entry 3c).^{204c} An excellent chemoselectivity was observed for α,β -unsaturated substrates: any competitive conjugate addition was detected.

Moreover, anhydrous $\text{SiO}_2/\text{CoBr}_2$ ²⁰⁵ and $\text{SiO}_2/\text{ZrCl}_4$ ²⁰⁶ were found to be good catalysts for the thioacetalization of the carbonyl compounds in dichloromethane (Table 22, entry 4 and 5). With both catalysts, less reactive aromatic ketones also reacted at room temperature, affording the corresponding dithioacetals in high yields.

Finally, solvent-free thioacetalization was performed using $\text{SiO}_2/\text{Cu}(\text{OTf})_2$ catalysis (Table 22, entry 6). The procedure needed shorter reaction times for the protection of aldehydes with respect to ketones; consequently, a moderate chemoselective thioacetalization of an aldehyde in the presence of a ketone functionality could be achieved. The keto group of a β -ketoester could also be thioacetalized in satisfactory yield. Hindered ketones, such as benzophenone and camphor, did not react in the solvent-free conditions at room temperature; however, the reaction could be efficiently performed in toluene at 80 °C.²⁰⁷

Production of dithianes and dithiolanes could be achieved in the presence of montmorillonite KSF clay without solvent (Table 22, entry 7). Qualitative kinetic studies suggested the possibility of performing the reaction with chemoselective control; in fact, in a competitive experiment carried out with an equimolar mixture of benzaldehyde, acetophenone, and ethane-1,2-dithiol, only the dithiolane of benzaldehyde was quantitatively formed. On the basis of these results, 4-acetylbenzaldehyde was subjected to reaction with ethane-1,2-dithiol exclusively, affording the thioacetalization of the formyl group.²⁰⁸ The same catalyst was utilized for the protection of carbonyl compounds with 1,2-benzene-dimethanethiol (Table 22, entry 8).²⁰⁹ Similar good results with regard to both yield and chemoselectivity were achieved by utilizing natural kaolinitic clay (Table 22, entry 9).¹⁷⁷

A commercial Mexican bentonitic clay was reported to be an excellent catalyst for the preparation of dithioacetals in high yields via condensation of 1,3-propanedithiol (Table 22, entry 10) and benzyl and butyl mercaptans with several carbonylic compounds.²¹⁰ Comparison experiments showed that this clay was more active than the montmorillonite KSF; this is probably due to the great difference of the surface area (200 vs 10 m²/g). From the mechanistic point of view, the interaction with the acid sites of the bentonitic clay should

enhance the electrophilic character of the carbonyl substrate, facilitating the nucleophilic action of the thiol.

Two Lewis acid-supported clays, namely, montmorillonite K10/ POCl_3 (Table 22, entry 11)²¹¹ and Envirocat EPZG (Table 22, entry 12),²¹² have been utilized for a rapid and selective thioacetalization with 1,2-ethanedithiol. It must be stated that by using montmorillonite K10/ POCl_3 as catalyst, a good degree of chemoselectivity was observed; in fact, benzaldehyde and cinnamaldehyde both were nearly quantitatively thioacetalized in the presence of acetophenone.

Kumar et al. reported the use of Y zeolite (SAR = 4.8) to prepare thioacetals of aldehydes (Table 22, entry 13)²¹³ and ketones, including the more hindered ones such as benzophenone. It should be mentioned that the use of zeolites such as ZSM-5 (SAR = 90) and mordenite (SAR = 20.2) was not very encouraging. The observed best performance of Y zeolite compared to ZSM-5 (pore size 0.54 × 0.56 and 0.51 × 0.55 nm) and mordenite (pore size 0.67 × 0.79 nm) could be attributed to its larger openings (0.74 nm), the presence of a three-dimensional channel system, and the higher concentration of acid sites. Further studies on the use of mordenites or Y zeolites were later developed by the same (Table 22, entry 14)²¹⁴ and other authors (Table 22, entry 15).²¹⁵

Y zeolite HSZ-360 can be conveniently used for the thioacetalization under mild conditions (Table 22, entry 16). Satisfactory to high yields were obtained, even with steroidal ketones and aromatic aldehydes possessing electron-withdrawing or electron-releasing groups. The method is mild enough to preserve other functionalities such as (Z)-double bond, nitro, cyano, tetrahydropyranyl, and ester groups.²¹⁶

Zirconium sulfophenyl phosphonate has been proposed for the preparation of 1,3-dithiolanes (Table 22, entry 17) and 1,3-dithianes in refluxing dichloromethane from several carbonyl derivatives, including aromatic, aliphatic, and α,β -unsaturated aldehydes and ketones. No differences in the reactivity depending on the structure of the carbonyl compound or dithiol have been observed.¹⁸⁹

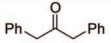
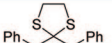
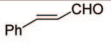
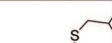

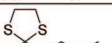




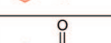

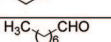
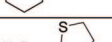

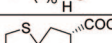
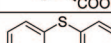
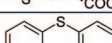
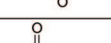


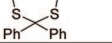
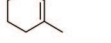
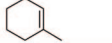
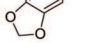
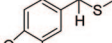
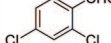
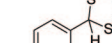
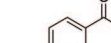
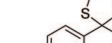
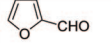
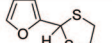
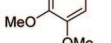
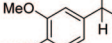
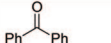
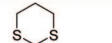


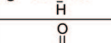
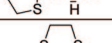
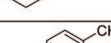
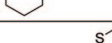
Firouzabadi et al. reported an interesting application of tungstophosphoric acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) as heterogeneous catalyst for the chemoselective thioacetalization of aldehydes and ketones (Table 22, entry 18).²¹⁷ The method can even be successfully applied for the protection of hindered ketones such as (+)-camphor and benzophenone. In addition, the chemoselective conversion of α - or β -diketones into the corresponding monodithioacetal was also achieved (Scheme 21).

Dowex 50W-X8 was reported to catalyze the formation of thioacetals with ethane-1,2-dithiol (Table 22, entry 19) in the absence of any solvent and in the minimum reaction time.²¹⁸ This catalyst, pretreated with HCl, presumably increases the electrophilicity of the carbonyl group, favoring the addition of the dithiol, and can be utilized for the protection of acid-sensitive species (indole and methylenedioxide derivatives).

5.2.2. Deprotection

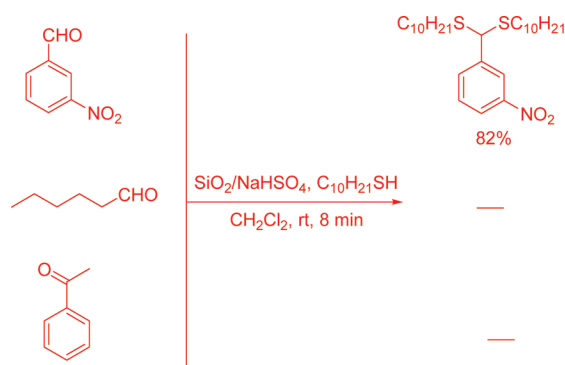
The large number of methods which address the problem of dethioacetalization may be taken as evidence that the reaction often proves refractory, especially in sensitive substrates, and, in this context, a wide range of reagents and catalysts is available for the cleavage of thioacetals to the parent carbonyl derivatives, and heterogeneous catalysis plays an important role.

Table 22. Protection of Carbonyl Groups as Dithioacetals

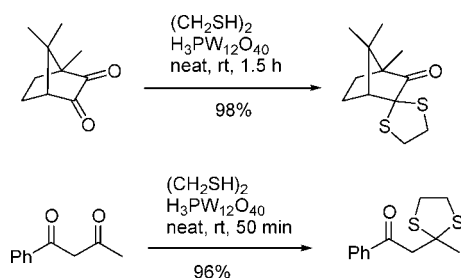
entry ^{ref}	catalyst ^a (experimental conditions)	carbonyl compound	mono- or dithiol	yield (%)	n. ex. (yields %)
1 ²⁰²	SiO ₂ /FeCl ₃ [(CH ₂ SH) ₂ , CH ₂ Cl ₂ , rt, 1 min]			98	15 (91-99)
2 ²⁰³	SiO ₂ /FeCl ₃ (1,2-benzenedimethanethiol, CH ₂ Cl ₂ , rt, 1 min)			95	16 (84-99)
3 ²⁰⁴	SiO ₂ /BTS [(CH ₂ SH) ₂ , dry CH ₂ Cl ₂ , rt, 1 h]			98	17 (75-99)
3b ^{204b}	SiO ₂ /NaHSO ₄ (EtSH, CH ₂ Cl ₂ , rt, 5 min)			96	26 (75-98)
3c ^{204c}	SiO ₂ /HClO ₄ ^{a(2)} [(CH ₂ SH) ₂ , rt, 30 min]			95	38 (75-100)
4 ²⁰⁵	SiO ₂ /CoBr ₂ [(CH ₂ SH) ₂ , dry CH ₂ Cl ₂ , rt, 3 min]			99	18 (89-99)
5 ²⁰⁶	SiO ₂ /ZrCl ₄ [(CH ₂ SH) ₂ , dry CH ₂ Cl ₂ , rt, 1 min]			99	17 (96-99)
6 ²⁰⁷	SiO ₂ /Cu(OTf) ₂ [(CH ₂ SH) ₂ , neat, rt]			93	20 (75-99)
7 ²⁰⁸	Mont. KSF [(CH ₂ SH) ₂ , CH ₂ Cl ₂ , rt]			100	14 (48-100)
8 ²⁰⁹	Mont. KSF (1,2-benzenedimethanethiol, PhH, Δ, 40 h)			99	15 (87-99)
9 ¹⁷⁷	Kaolin ^a [(CH ₂ SH) ₂ , PhH, Δ, 2 h]			90	9 (85-98)
10 ²¹⁰	Bentonite (HS(CH ₂) ₃ SH, dry PhMe, Δ, 3 h)			90	15 (60-95)
11 ²¹¹	Mont./POCl ₃ [(CH ₂ SH) ₂ , CH ₂ Cl ₂ , rt, 2 min]			98	16 (80-98)
12 ²¹²	Envirocat EPZG [®] [(CH ₂ SH) ₂ , PhH, Δ, 110 min]			93	12 (90-96)
13 ²¹³	Y zeolite [(CH ₂ SH) ₂ , dry hexane, Δ, 1 h]			94	12 (90-96)
14 ²¹⁴	Y zeolite (HS(CH ₂) ₃ SH, hexane, Δ, 1.5 h)			96	19 (60-96)
15 ²¹⁵	Y zeolite ^{a(1)} (HS(CH ₂) ₃ SH, hexane, Δ, 1 h)			95	4 (80-96)
16 ²¹⁶	Y zeolite HSZ-360 [(CH ₂ SH) ₂ , CH ₂ Cl ₂ , rt, 15 h]			100	14 (60-100)
17 ¹⁸⁹	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} ^a [(CH ₂ SH) ₂ , CH ₂ Cl ₂ , Δ, 1 h]			95	8 (69-95)
18 ²¹⁷	H ₃ PW ₁₂ O ₄₀ (HS(CH ₂) ₃ SH, petroleum ether 60-80 °C, Δ, 1 min)			98	20 (89-98)
19 ²¹⁸	Dowex [®] 50WX8 ^{a(1)} [(CH ₂ SH) ₂ , neat, rt, 3 h]			60	7 (60-90)

^a The catalyst has been recycled (number of recycles).

Scheme 20b



Scheme 21



Natural kaolinitic clay has been utilized by Bandgar et al. for the selective cleavage of thioacetals, under solventless conditions (Table 23, entry 1). Due to its specific activity in the regeneration of aldehydes, the methodology is useful for the chemoselective removal of a thioacetal in the presence of a thioketal (Scheme 22). It is also pertinent to note that phenolic, methylenedioxy, and methoxy groups tolerate the reaction conditions.²¹⁹

Different clay-supported nitrates have been successfully utilized to cleave cyclic and acyclic thioacetals derived from aldehydes and ketones. Clayfen was employed by Varma et al. to deprotect thioacetal derivatives under solvent-free conditions and with the help of microwaves (Table 23, entry 2). No side products were formed, the only exception being substrates bearing free phenolic moieties, where some ring nitration occurred. However, the protocol avoids the use of excess of solvent and toxic oxidants, and no further oxidation of the carbonyl compound was observed.²²⁰ The same catalyst has been reported to give good yields in the cleavage of 1,3-dithiolanes and 1,3-dithianes, but without the need for microwave irradiation (Table 23, entry 3).²²¹ Clayan was also reported by Meshram et al. to be a good catalyst/reagent for this deprotection reaction, carried out in dichloromethane (Table 23, entry 4),²²² or under solventless conditions using microwave irradiation (Table 23, entry 5).²²³ Although both methods tolerate common groups such as esters and ethers, they failed in the selective cleavage of thioacetals in the presence of acetanides.

Silica gel has been utilized as a support for metal nitrates, affording reagent-catalyst combinations that are useful for the thioacetals deprotection. An efficient regeneration of carbonyl compounds from 1,3-dithiolanes and 1,3-dithianes can be carried out under $\text{SiO}_2/\text{Cu}(\text{NO}_3)_2$ catalysis (Table 23, entry 6)²²⁴ by recovering the corresponding ketones and the aldehydes in quantitative yield. Similarly, a combination of $\text{Fe}(\text{NO}_3)_3$ and silica gel regenerated aldehydes and ketones from 1,3-dithianes and 1,3-dithiolanes under an inert atmosphere (Table 23, entry 7, 8).^{225,226} In the case of aromatic substrates, the electronic property of the substituents and their

position on the benzene ring did not affect the rate nor the product selectivity. It is important to point out that in the absence of silica gel, the reaction was sluggish. It must be noted that in all cases, the catalyst was prepared in situ simply by mixing the oxidant with silica gel. Quite similarly, Curini et al. reported the cleavage of cyclic thioacetals using Oxone on alumina (Table 23, entry 9).²²⁷

Dimethyl sulfoxide in combination with silica gel chloride has been efficiently used for the deprotection of thioacetals into aldehydes.²²⁸ The authors suggest a mechanism in which dimethyl sulfoxide, silica chloride, and dimethylsulfonium chloride play a cooperative role in the entire process. Thioacetals derived from ketones show a quite different behavior; in fact, in the case of thioacetals derived from ketones without enolizable hydrogens, deprotection proceeded very well to give the corresponding ketones in high yields (Table 23, entry 10). In contrast, thioketals with enolizable methyl and methylene groups undergo ring-expansion reactions, affording 1,4-dithiepins and 1,4 dithiins.

Deprotection of thioacetals was also carried out using silica-supported sodium hydrogen sulfate. Various thioacetals were easily converted into the parent carbonyl compounds by carrying out the reaction in methylene chloride/water at room temperature (Table 23, entry 10b);^{204b} the yields were excellent in 10–20 min. The deprotection reaction also can be performed using methanol, a more eco-compatible solvent, but the time required was longer (2–3 h).

Commercially available acidic resins such as Amberlyst 15 (Table 23, entry 11)²²⁹ and Dowex 50W (Table 23, entry 12)²³⁰ have been employed for the dethioacetalization via equilibrium exchange with aqueous acetone/paraformaldehyde. Using this method, acid-sensitive groups, such as esters or ethers, were not affected; in addition, *cis*-methyl pinonoate was regenerated without epimerization at C-3 (Scheme 23). The method is applicable to more complex intermediates involved in the alkaloids synthesis.

Layered zirconium sulfophenyl phosphonate has also been utilized with similar good results for the mild hydrolysis of 1,2-dithiolanes and 1,3-dithianes to their parent carbonyl compounds (Table 23, entry 13). In this case, the glyoxylic acid monohydrate was employed as exchange reagent.²³¹

5.3. 1,3-Oxathiolanes

1,3-Oxathiolanes constitute an important class of compounds that are more stable than the corresponding *O,O*-acetals under acidic conditions and, compared with *S,S*-acetals, are more easily deprotected. Moreover, they can also be utilized as acyl anion equivalents in C–C bond formation; consequently, different procedures for their preparation from carbonyl compounds have been reported under both homogeneous and heterogeneous catalysis.

Natural clays promoted the efficient chemoselective production of a variety of oxathiolanes by a dithiolane exchange reaction from aldehydes or ketones with 2,2-dimethyl-1,3-oxathiolane (Scheme 24)²³² under microwave irradiation or by reaction of aldehydes and ketones with 2-mercaptoethanol (Scheme 25).²³³ When β -keto esters were treated under these conditions, both transesterification and ketone protection could be possible. The authors suggest that the catalytic activity of the acid-activated clay could be attributed to the significant amount of both Lewis acidity derived from Al remaining in the edges of the platelets and Brønsted acidity of coordinated hydroxy groups of Al^{3+} , Fe^{3+} , and Ti^{4+} ions relocated in the interlamellar space of the clay.

Table 23. Deprotection of Dithioacetals

entry ^{ref}	catalyst ^a (experimental conditions)	Dithioacetal	carbonyl compound	yield (%)	n. ex. (yields %)
1 ²¹⁹	Kaolin ^{a(4)} (few drops of H ₂ O, MW, 2 min)			78	18 (78-96)
2 ²²⁰	Clayfen (neat, MW 900W, 20 sec)			90	9 (87-98)
3 ²²¹	Clayfen (hexane, 50 °C, 10 min)			97	42 (74-100)
4 ²²²	Clayan (dry CH ₂ Cl ₂ , N ₂ , rt, 19h)			81	13 (75-90)
5 ²²³	Clayan (neat, MW, 2 min)			88	13 (81-89)
6 ²²⁴	SiO ₂ /Cu(NO ₃) ₂ (CCl ₄ , rt, 15 min)			98	30 (93-99)
7 ²²⁵	SiO ₂ /Fe(NO ₃) ₃ (hexane, 50 °C, N ₂ , 10 min)			100	11 (86-100)
8 ²²⁶	SiO ₂ /Fe(NO ₃) ₃ (hexane, Ar, 50 °C, 10 min)			85	19 (85-100)
9 ²²⁷	Al ₂ O ₃ /Oxone [®] (CHCl ₃ , Δ, 20 min)			84	11 (70-99)
10 ²²⁸	Silica chloride (dry DMSO, dry CH ₂ Cl ₂ , rt, 60 min)			90	18 (88-96)
10b ^{204b}	SiO ₂ /NaHSO ₄ (CH ₂ Cl ₂ /H ₂ O, rt, 20 min]			83	8 (76-96)
11 ²²⁹	Amberlyst 15 (CH ₂ O, Me ₂ CO/H ₂ O, 80 °C, 24 h)			70	8 (53-76)
12 ²³⁰	Dowex 50W (CH ₂ O, Me ₂ CO/H ₂ O, Δ, 4 h)			90	6 (50-90)
13 ²³¹	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} (CHOCOOH·H ₂ O, 60 °C, 0.5 h)			92	14 (75-95)

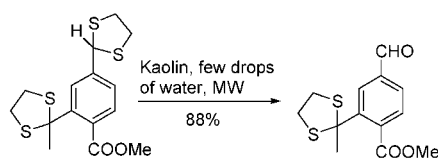
^a The catalyst has been recycled (number of recycles).

Montmorillonite K10 was found to be an efficient catalyst for the preparation of 1,3-oxathiolanes from aldehydes and aliphatic ketones in the presence of 2-mercaptoethanol. The process was carried out in methylene chloride at room temperature; aromatic ketones did not afford the corresponding oxathiolanes under the same reaction conditions.^{233b} The catalyst can be successfully utilized for the selective protec-

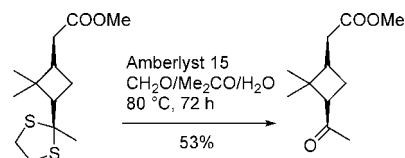
tion of the aldehyde functionality in β -ketoaldehydes toward the ketone one, as shown in Scheme 25b.

The formation of oxathiolanes from α,β -unsaturated carbonyl derivatives was also achieved by Duñach et al. in good yields using aminopropylated silica gel hydrochloride (APSG·HCl) with 2-mercaptoethanol.²³⁴ The presence of 1 equiv of trimethyl orthoformate as desiccant was needed,

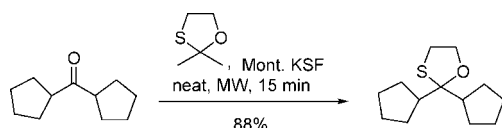
Scheme 22



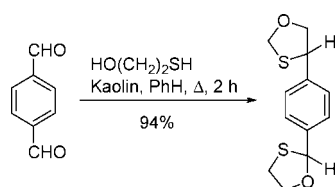
Scheme 23



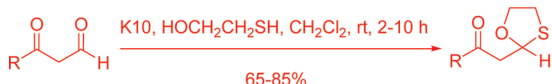
Scheme 24



Scheme 25

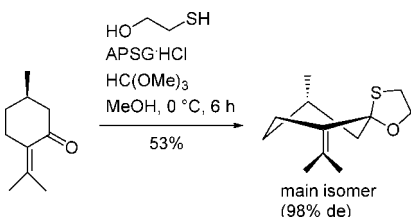


Scheme 25b



R = Bn, Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄, 2-thiophene, 2-furan

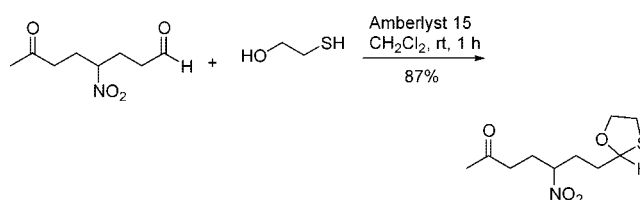
Scheme 26



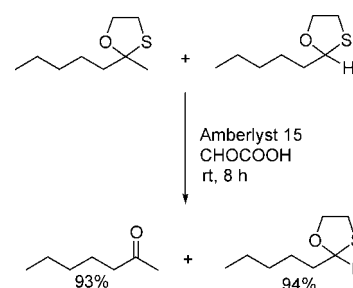
since dehydrating agents such as magnesium sulfate or 4-Å molecular sieves led to a lower conversion. It is well-known that the direct production of oxathiolanes from α,β -unsaturated carbonyl compounds is accompanied by some drawbacks that lower the selectivity. For this reason, it is important to prepare the above-mentioned derivatives via transoxathiolanation from acetals. The authors showed that, with APSG·HCl, the direct oxathiolanation of α,β -unsaturated aldehydes and ketones has been performed selectively and in good isolated yields. A further interesting result is the protection of pulegone with the same catalyst with a good diastereoselective control (98% de) (Scheme 26).

The conversion of carbonyl compounds into oxathioacetals by reaction with mercaptoethanol can be accomplished by using silica-supported polyphosphoric acid. In this process, the SiO₂/PPA serves both as a water scavenger and as an acid catalyst. It is noteworthy that, when silica alone was used, the reaction did not proceed under similar conditions. Although the reaction with homogeneous PPA in the model

Scheme 27



Scheme 28



reaction with benzaldehyde gave quite similar yields (86 vs 99%), it is impossible to recover it from the reaction mixture for a possible reuse; on the contrary, SiO₂/PPA can be easily recovered by simple filtration and reused for six cycles with almost the same activity.^{234b}

Amberlyst 15 can be utilized for the conversion of carbonyl compounds to 1,3-oxathiolanes.²³⁵ Following the above procedure, a wide range of carbonyl compounds can be efficiently transformed into their corresponding 1,3-oxathiolanes, and the protection of an aldehyde in the presence of a ketone group can be performed in high yield and chemoselectivity (97%), the reaction of the aldehydes being faster than that of ketones (Scheme 27).

1,3-Oxathiolanes can be deprotected by using montmorillonite K10 in benzene at reflux. The procedure is useful for aliphatic and aromatic ketones and aldehydes. As expected, the presence of electron-withdrawing substituents on the aromatic ring of the oxo-compound retarded the reaction and lower yields were obtained. The catalyst can be recovered and reused after regeneration without loss of activity.^{235b}

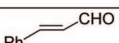
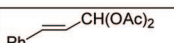
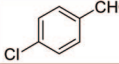
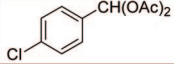
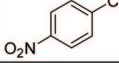
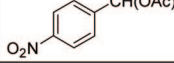
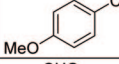
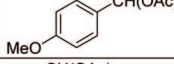
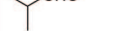
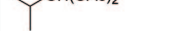
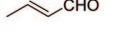
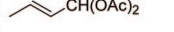
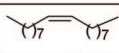
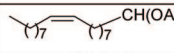
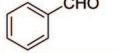
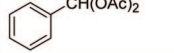
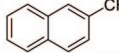
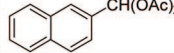
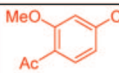
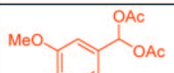
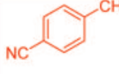
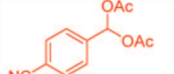
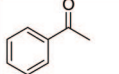
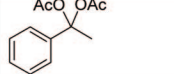
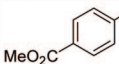
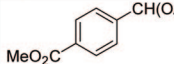
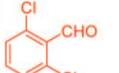
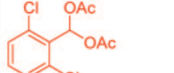
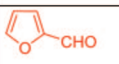
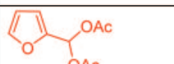
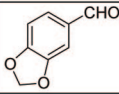
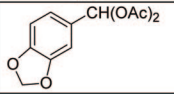
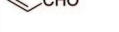
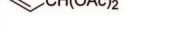
Carbonyl compounds were also regenerated from the parent 1,3-oxathiolanes via an equilibrium exchange with glyoxylic acid and Amberlyst 15, under solvent-free conditions at room temperature or under microwave irradiation.²³⁶ A wide variety of oxathiolanes derived from ketones and aldehydes was shown to undergo facile cleavage under these conditions. However, because the ketones are regenerated faster than aldehydes, this process was utilized in effecting selective deprotection, as shown in Scheme 28.

5.4. 1,1-Diacetates (Acylals)

5.4.1. Protection

Montmorillonites K10 and KSF were utilized by Zhang et al. as catalysts to convert both aromatic and aliphatic aldehydes into their 1,1-diacetates (Table 24, entry 1).²³⁷ It is worth noting that hydroxy groups in 2-hydroxy- and 3-methoxy-4-hydroxybenzaldehyde were also acetylated; quite surprisingly, the authors reported that with 4-hydroxybenzaldehyde and 4-(dimethylamino)benzaldehyde, no reaction occurred at all. As an explanation, they proposed the selective adsorption of the phenolic and amino groups on

Table 24. Protection of Carbonyl Group as 1,1-Diacetates

entry ^{ref}	catalyst ^a (experimental conditions)	carbonyl compound	1,1-diacetate	yield (%)	n. ex. (yields %)
1 ²³⁷	Mont. KSF (Ac ₂ O, neat, rt, 0.5 h)			97	17 (0-98)
2 ²³⁸	Mont. K10 (Ac ₂ O, neat, MW 2450 Hz, 6 min)			98	12 (75-98)
3 ²³⁹	Envirocat EPZ10 [®] (Ac ₂ O, neat, MW, 40 s)			89	13 (83-92)
4 ²⁴⁰	Envirocat EPZG [®] (Ac ₂ O, neat, 60 °C, 3 h)			99	11 (69-99)
5 ²⁴¹	Beta zeolite (Ac ₂ O, neat, 60 °C, 2.5 h)			90	10 (51-93)
6 ²⁴²	Y zeolite (Ac ₂ O, neat, rt, N ₂ , 3 min)			85	9 (72-98)
7 ²⁴³	Y zeolite HSZ-360 ^{a(6)} (Ac ₂ O, neat, rt, 7 h)			90	16 (80-98)
8 ²⁴⁴	ZSM-5 zeolite (Ac ₂ O, neat, rt, 0.25 h)			98	15 (4-98)
9 ²⁴⁵	SiO ₂ /FeCl ₃ (Ac ₂ O, neat, MW 300W, 4 min)			90	12 (78-95)
9b ^{245b}	SiO ₂ /HClO ₄ ^{a(4)} (Ac ₂ O, rt, 2 min)	CH ₃ (CH ₂) ₇ -CHO	CH ₃ (CH ₂) ₇ -CH(OAc) ₂	98	24 (90-99)
9c ^{245c}	SiO ₂ -OSO ₃ H (Ac ₂ O, rt, 35 min)			85	20 (65-96)
9d ^{245d}	Al ₂ O ₃ /P ₂ O ₅ (Ac ₂ O, rt, 45 min)			86	22 (70-90)
10 ²⁴⁶	Sulfated zirconia (Ac ₂ O, neat, 110 °C, 2.5 h)			96	12 (84-96)
11 ²⁴⁷	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} ^a (Ac ₂ O, neat, rt, 0.4 h)			74	14 (55-91)
11b ^{247b}	AlPW ₁₂ O ₄₀ (Ac ₂ O, rt, 15 min)			95	12 (88-96)
11c ^{247c}	SiPW ^{a(3)} (Ac ₂ O, rt, 30 min)	CH ₃ (CH ₂) ₂ -CHO	CH ₃ (CH ₂) ₂ -CH(OAc) ₂	94	11 (89-98)
11d ^{247d}	Amberlyst 15 ^{a(3)} (Ac ₂ O, CH ₂ Cl ₂ , rt, 45 min)			90	16 (80-98)
12 ²⁴⁸	Expansive graphite (Ac ₂ O, CCl ₄ , rt, 3 h)			98	14 (65-98)
13 ²⁴⁹	Poly(vinyl chloride)/FeCl ₃ ^a (Ac ₂ O, neat, rt, 10 min)			75	12 (75-95)

^a The catalyst has been recycled (number of recycles).

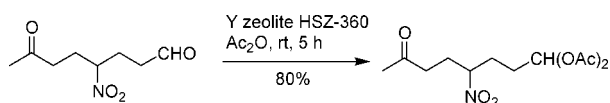
the catalyst that keeps the aldehyde functional group away from the active site of the clay, thus blocking the reactive sites and inhibiting the reaction. Under microwave irradiation, the preparation of acylals was performed in remarkably lower reaction times (Table 24, entry 2).²³⁸

Envirocats, exhibiting both Lewis and Brønsted acidity, have been utilized by Bandgar et al. for the acetylation of a variety of aldehydes (Table 24, entries 3 and 4). A faster reaction rate was observed with the use of EPZ10 (ZnCl₂-exchanged clay)²³⁹ under microwave irradiation with respect to the use of EPZG (FeCl₃-exchanged clay)²⁴⁰ alone. The efficiency of the catalyst was clearly visualized in the case of aromatic aldehydes having an electron-withdrawing group (Table 24, entry 3), where the corresponding acylals have

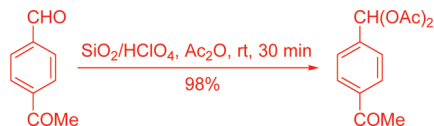
been obtained in excellent yields and in very short time. A drawback of the use of these catalysts was represented by the inhibition of their activity under heating or cooling in air.

Different kinds of commercially available zeolites have been employed for the acetylation of carbonyl compounds with acetic anhydride. For example, Kumar et al. reported that high conversions and high yields can be achieved using beta zeolite (SAR = 60) with small-sized aldehydes (Table 24, entry 5);²⁴¹ however, the reaction with bulky substrates, such as 2-methyl-3,5-dimethoxybenzaldehyde, was sluggish and the yield was lower. Two Y zeolites with different SAR were also utilized in protecting aromatic and aliphatic aldehydes. With an Y zeolite showing SAR = 8, very fast

Scheme 29



Scheme 29b



reaction times were observed (Table 24, entry 6),²⁴² except for *p*-nitrobenzaldehyde, which required prolonged times, possibly due to the strong electron-withdrawing nitro substituent that lowers the interaction of the formyl group with the surface acid sites of the catalyst. Y zeolite HSZ-360 (SAR = 14), utilized without previous thermal or chemical treatment, has been claimed to be a reusable catalyst for the solvent-free synthesis of diacetates of aldehydes (Table 24, entry 7).²⁴³ Other functionalities, such as nitro, ether, cyano, furyl, and (*Z*)-double bond, were preserved, and, more importantly, since ketones were not reactive with this reagent, the method offers the advantage to perform the protection of an aldehyde functionality in the presence of a ketone (Scheme 29).

HZSM-5 catalyst (SAR = 180) was employed to promote the protection of different aldehydes (Table 24, entry 8),²⁴⁴ showing a remarkable shape selectivity; in fact, a substantial difference in the reaction rate for the *ortho*- and *para*-substituted aromatic aldehydes was observed.

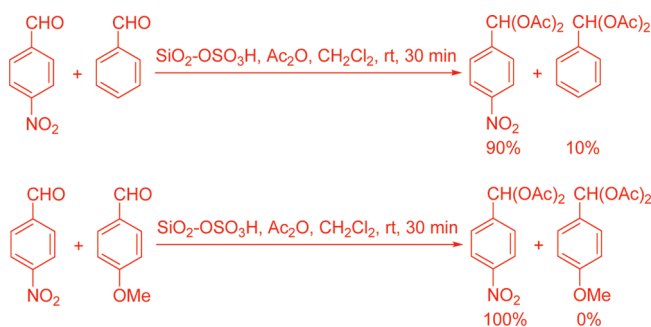
Acylals were synthesized in a few minutes and in high yield by acylation of aldehydes with acetic anhydride in the presence of $\text{SiO}_2/\text{FeCl}_3$ under microwave irradiation (Table 24, entry 9).²⁴⁵

Kamble et al. reported the use of $\text{SiO}_2/\text{HClO}_4$ for the synthesis of acylals from aldehydes and acetic anhydride under solvent-free conditions (Table 24, entry 9b).^{245b} Various functional groups on the aromatic aldehydes, such as methoxy, nitro, halogens, allyloxy, methylenedioxy, and phenoxy were tolerated under the present conditions. Acid-sensitive substrates such as furfural, thiophene aldehyde, and conjugated aldehydes gave the corresponding 1,1-diacetates in excellent yields without any side reactions, which are normally encountered under acidic conditions. Since ketones undergo acylation more slower than aldehydes, the chemoselective protection of aldehydes in the presence of ketones was performed (Scheme 29b).

The catalytic efficiency of $\text{HClO}_4/\text{SiO}_2$ was also exploited for other acid anhydrides, namely, propionic, butyric, and isobutyric anhydrides. In the model reaction with benzaldehyde, the corresponding geminal dicarboxylates were isolated in 88–93% yield. Finally, the recovered catalyst, after activation (heating under vacuum at 80 °C for 2 h), was reused for four more acylations of benzaldehyde, affording 93%, 90%, 88%, and 85% yields, respectively.

The preparation of acylals from aldehydes and acetic anhydride can be carried out using silica sulfuric acid ($\text{SiO}_2\text{--OSO}_3\text{H}$) at room temperature under solvent-free conditions (Table 24, entry 9c).^{245c} Aromatic, aliphatic, and α,β -unsaturated aldehydes produced acylals in good yields; furfural was converted into the corresponding 1,1-diacetate in moderate yields, whereas 4-(*N,N*-dimethylamino)benzaldehyde was completely inactive, probably due to the electron donation of the dimethylamino group. When 2-hydroxyben-

Scheme 29c



zaldehyde and vanillin were utilized, both carbonyl and phenolic hydroxyl groups were acylated. The selective conversion of *para*-nitrobenzaldehyde versus benzaldehyde and of *para*-nitrobenzaldehyde versus *para*-methoxybenzaldehyde was tested (Scheme 29c).

These reactions proceed with high selectivity, showing the importance of the electronic effects in the presence of $\text{SiO}_2\text{--OSO}_3\text{H}$ catalyst. The same activity and chemoselectivity can be achieved by carrying out the reactions in the presence of $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ (Table 24, entry 9d).^{245d}

The use of sulfated zirconia, reported by Raju, represents the sole example of efficient conversion of both aldehydes and ketones into their 1,1-diacetates (Table 24, entry 10).²⁴⁶ The reaction was quite general, probably due to the great efficiency of the sulfated zirconia, which exhibits both Lewis and Brønsted superacid sites ($H_a = -26$). Layered zirconium sulfophenyl phosphonate was found to catalyze the synthesis of acylals from aldehydes (Table 24, entry 11).²⁴⁷ The acid strength of the catalyst lies between $\text{p}K_a$ values of -5.6 and -8.2 , similar to that of montmorillonite and higher than that of Amberlyst 15; however, this catalyst promotes the same reaction in shorter times.

$\text{AIPW}_{12}\text{O}_{40}$ is reported to be an efficient and chemoselective catalyst for the preparation of acylals from structurally different aldehydes in the presence of acetic anhydride at room temperature under solvent-free conditions (Table 24, entry 11b).^{247b} Activated and deactivated aromatic aldehydes and aliphatic as well as α,β -unsaturated aldehydes were converted to their corresponding diacetates in excellent yields; in addition, the catalyst can be employed for the selective protection of aldehydes in the presence of ketones.

Wang described an efficient process for the preparation of 1,1-diacetates from aliphatic and aromatic aldehydes using heteropolyacids encapsulated into mesoporous silica frameworks (SiPW) (Table 24, entry 11c).^{247c} As some aliphatic and aromatic ketones were not reactive under the described experimental conditions, the highly selective conversion of aldehydes was observed. The catalyst can be easily separated and recycled without a significant loss of activity and selectivity for the preparation of 1,1-diacetates.

Amberlyst 15 can be utilized as catalyst for the protection of aldehydes as acylals (Table 24, entry 11d);^{247d} the reaction is carried out in methylene chloride at room temperature, and the catalyst can be reused for at least three times.

Finally, other two heterogeneous catalysts, namely, expansive graphite (Table 24, entry 12)²⁴⁸ and poly(vinyl chloride)-supported ferric chloride (Table 24, entry 13),²⁴⁹ were also found to convert, in high yields, aldehydes into 1,1-diacetates. It is important to emphasize that both catalysts must be prepared in the laboratory and that the expansive graphite preparation is quite tedious, difficult, and harmful

Table 25. Deprotection of 1,1-Diacetates

entry ^{ref}	catalyst ^a (experimental conditions)	1,1-diacetate	carbonyl compound	yield (%)	n. ex. (yields %)
1 ²⁵⁰	Mont. KSF (CH ₂ Cl ₂ , Δ, 30 min)			95	12 (93-99)
2 ²⁵²	Envirocat EPZG [®] (neat, MW, 2.5 min)			93	14 (87-94)
3 ²⁴³	Y zeolite HSZ-360 ^a (neat, MW 500W, 20 min)			99	7 (86-99)
4 ²⁵³	Al ₂ O ₃ (neat, MW 800W, 40 s)			95	7 (88-98)
5 ²⁵⁴	SiO ₂ /CAN (CH ₂ Cl ₂ , rt, 15 min)			98	5 (90-98)
5b ^{254b}	SiO ₂ /H ₂ SO ₄ (CH ₂ Cl ₂ , rt, 7 min)			90	19 (80-100)
6 ²⁵⁵	TiO ₂ /SO ₄ ²⁻ (CH ₂ Cl ₂ , Δ, 10 min)			98	10 (96-99)
7 ²⁴⁷	Zr(CH ₃ PO ₃) _{1.2} (O ₃ PC ₆ H ₄ SO ₃ H) _{0.8} (Dioxane, 50 °C, 1 h)			95	14 (32-95)

^a The catalyst has been recycled.

since it requires the use of concentrated sulfuric acid, nitric acid, and potassium permanganate.²⁴⁸

5.4.2. Deprotection

The conventional deprotection of acylals is achieved under basic conditions by using either sodium hydroxide or potassium carbonate in aqueous tetrahydrofuran.

The use of montmorillonite K10 or KSF has been developed by Li et al. as a general method for the regeneration of aldehydes from their acylals (Table 25, entry 1).²⁵⁰ Both catalysts afforded similar good results in terms of yield and selectivity. The reactions were usually carried out in dichloromethane at 40 °C, apart from those with aromatic aldehydes bearing electron-withdrawing groups, which required refluxing in benzene. Different functionalities, such as ethers, acetals, and furan rings,²⁵¹ could be preserved. The mechanism of the present reaction is obviously different from that of the classical hydrolysis in aqueous hydrochloric acid, since the process is carried out in the absence of water; furthermore, since neither additional water nor anhydrous conditions affect the reaction rate, the authors conclude that the reaction undergoes a unimolecular decomposition of 1,1-diacetate to give the corresponding aldehyde and acetic anhydride, in which the clay plays a Lewis acid role. A similar mechanism has been proposed for the reaction carried out with Envirocat EPZG under microwave irradiation (Table 25, entry 2).²⁵²

The combination of commercially available solid catalysts such as Y zeolite (Table 25, entry 3)²⁴³ and neutral alumina (Table 25, entry 4)²⁵³ with microwave irradiation has been demonstrated to be efficient for the cleavage of different acylals; it must be mentioned that in both procedures, a large

amount of solid catalyst was needed, probably due to the fact that the reactants must be completely adsorbed on the surface of the catalyst in order to achieve good results.

Deprotection of aromatic aldehyde diacetates was selectively carried out by Cotellet et al. using CAN coated on silica gel (Table 25, entry 5);²⁵⁴ the reaction occurred selectively only with aromatic aldehydes, and some side reactions, such as the partial nitration and oxidation of the electron-rich aromatic rings, have been observed due to the nature of CAN. Of particular interest was the survival of the aryl acetate function usually cleaved under acidic or alkaline conditions.

Acylals can be reconverted into the corresponding aldehydes and ketones by using Caro's acid supported on silica gel (Table 25, entry 5b).^{254b} The process is carried out in methylene chloride at room temperature for a few minutes.

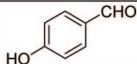
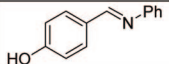

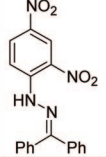
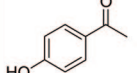
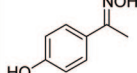
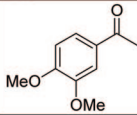
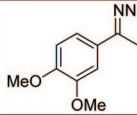
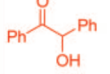
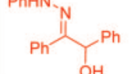
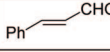
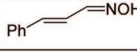
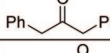
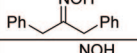
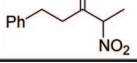
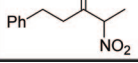
Strongly acidic materials have been also applied for the selective cleavage of aromatic or cinnamic diacetates; TiO₂/SO₄²⁻ (Table 25, entry 6)²⁵⁵ promoted the reaction in very short times (5–10 min), whereas zirconium sulfophenyl phosphonate (Table 25, entry 7)²⁴⁸ needed longer times (1–24 h). In both cases, nitro derivatives provided lower conversion rates in refluxing dichloromethane, whereas good yields were achieved in refluxing benzene.

5.5. Nitrogenous Derivatives

5.5.1. Protection

The easy protection of aldehydes and ketones as imines or enamines has been reported to occur by simply mixing the carbonyl compounds with primary and secondary amines and submitting the mixture to microwave irradiation in the presence of a catalytic amount of Envirocat EPZG (Table

Table 26. Protection of Carbonyl Groups as Nitrogenous Derivatives

entry ^{ref}	Catalyst ^a (experimental conditions)	carbonyl compound	amino derivative	yield (%)	n. ex. (yields %)
1 ²⁵⁶	Envirocat EPZG [®] (PhNH ₂ , neat, MW 900W, 3 min)			91	6 (90-97)
2 ²¹⁵	Y zeolite ^{a(1)} (2,4-dinitrophenylhydrazine, MeOH, Δ, 10 min)			95	4 (83-95)
3 ²⁵⁷	3 Å molecular sieves (NH ₂ OH·HCl, neat, rt, 15 min)			94	17 (30-98)
4 ^{258,259}	SiO ₂ (NH ₂ NMe ₂ , neat, NaOH, 10 min)			100	20 (80-100)
4b ^{259b}	SiO ₂ /H ₂ SO ₄ (PhNHNH ₂ , rt, 8 min)			91	16 (65-91)
5 ²⁶⁰	Al ₂ O ₃ (NH ₂ OH·HCl, neat, MW, 5 min)			99	18 (30-99)
6 ²⁶¹	TiO ₂ /SO ₄ ²⁻ (NH ₂ OH·HCl, neat, 130 °C, 10 min)			90	20 (75-96)
7 ²⁶²	Amberlyst A-21 (NH ₂ OH·HCl, EtOH, rt, 1h)			88	18 (70-100)

^a The catalyst has been recycled (number of recycles).

26, entry 1).²⁵⁶ This approach avoided the need for a large excess of mineral support, long reaction times, and large quantities of aromatic solvents needed in the conventional solution phase, which also requires azeotropic removal of water.

Srinivasan et al. have reported the use of Y and divalent cation-exchanged acidic zeolites in protecting the carbonyl group of ketones and aldehydes as phenylhydrazones (Table 26, entry 2).²¹⁵ The authors stressed that when the nonacidic NaY zeolite was employed as catalyst, no hydrazones were isolated; this ruled out any significant role of the basic zeolite framework in the derivatization and indicated the need for the presence of acidic sites in the framework. Thus, when acidic zeolites such as Y, CaY, and MgY were used, the formation of protected carbonyl compounds was clean and smooth. The acidity in CaY and MgY zeolites can be explained by the dissociation of coordinatively bound water molecules under the action of the electrostatic field associated with the divalent cations. Quite similar high yields were obtained in the protection of aldehydes and ketones as oximes by using 3-Å molecular sieves as water scavenger under solventless conditions (Table 26, entry 3).²⁵⁷

Hajipour reported the synthesis of oximes, hydrazones, and semicarbazones of aldehydes and ketones in nearly quantitative yield under solventless dry conditions using silica gel in the presence of sodium hydroxide (Table 26, entry 4).^{258,259} The reaction was very fast with both aldehydes and ketones, but competitive experiments carried out with an equimolecular mixture of an aldehyde and a ketone in the presence of hydroxylamine showed that only the aldehydic function was protected, whereas the ketone one was recovered unchanged. In the absence of silica gel, nitrogen derivatives were obtained in lower yield (~20%).

Silica sulfuric acid (SiO₂/H₂SO₄) can be utilized for the preparation of hydrazones (Table 26, entry 4b).^{259b} The reaction is simply carried out by grinding in a mortar the mixture of ketone, phenylhydrazine, and catalyst.

Basic Al₂O₃ has been tested, in two different ways, for the preparation of keto- and aldioximes. The first method employed irradiation of the reactants in a domestic microwave oven (Table 26, entry 5). The second method made use of local heat produced by grinding the reactants in the presence of molecular sieves for driving the chemical reaction. Although the two techniques allowed the formation of oximes, microwave treatment produced better yields in a shorter reaction time.²⁶⁰ The method showed general applicability with respect to both aromatic and aliphatic aldehydes and ketones, including α,β-unsaturated ones and hydroxybenzaldehydes.

Sulfated titania was utilized by Jin et al. in a green synthetic procedure for the generation of aromatic oximes (Table 26, entry 6).²⁶¹ Aromatic ketones were not as active as aromatic aldehydes owing to their steric hindrance and lower electrophilicity, whereas anthrone did not react at all. The authors found that the acidity of Lewis acid centers on the surface of the catalyst was enhanced owing to the strong inductive effect of the S=O group; in addition, when the catalyst absorbed some water, Brønsted acid centers were produced. These two kinds of acid centers could readily interconvert, thus synergistically enhancing the acidity of the sulfated titania (Figure 10).

Finally, Amberlyst A-21 was reported to catalyze the synthesis of oximes of aldehydes and ketones (Table 26, entry 7).²⁶² The catalyst did not affect labile functional groups (ether, cyano, sulfone, nitro, hydroxy, tetrahydropyranyl, (Z)-C=C double bond), and its mildness was demonstrated

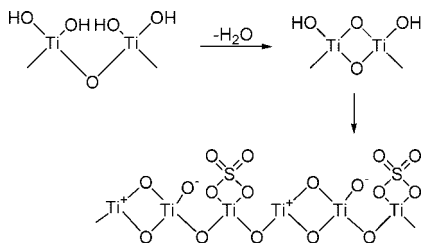
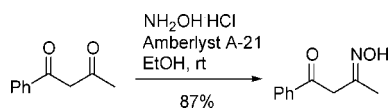


Figure 10.

Scheme 30

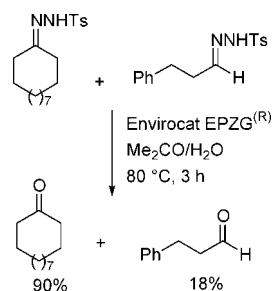


by the survival of α -nitrocyclohexanone during the oximation process that did not undergo the ring cleavage. The method allowed the selective monooximation of the carbonyl group at position 3 of 1-phenyl-1,3-butanedione (Scheme 30); this behavior can be explained with the high enolization of the β -dicarbonyl compounds.

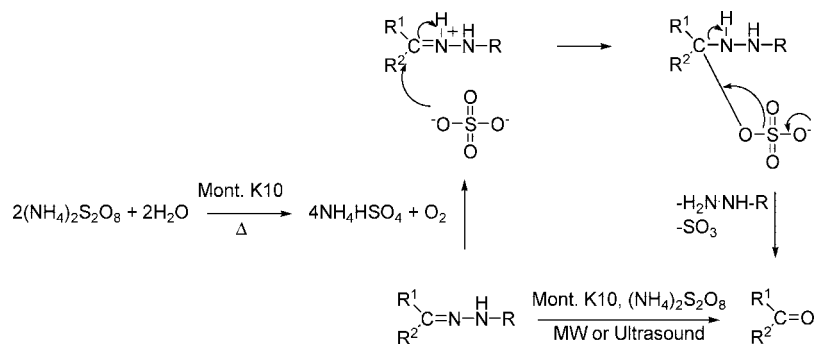
5.5.2. Deprotection

Deprotection of nitrogenous derivatives of carbonyl compounds such as oximes, hydrazones, and semicarbazones was performed under heterogeneous conditions by oxidation, reduction, or hydrolysis in the presence of another carbonyl compound according to the methods previously reported under homogeneous conditions. In fact, usually the reactions are performed by mixing the nitrogenous derivative with the oxidizing or reducing reagent (frequently utilized in a large excess) in the presence of a heterogeneous material. However, it is quite difficult to imagine that under the above conditions, a real heterogeneous catalysis occurs, even if it cannot be excluded a synergic activation effect. More realistically, we could think that the role of the heterogeneous material is simply that of making the workup easier by absorbing tar materials. For these reasons, in the first part

Scheme 31



Scheme 32



of this section we will briefly summarize these methods on the basis of the nature of the support/catalyst, and then we will discuss some deprotection reactions occurring under *real* heterogeneous catalysis.

Various ammonium and metal nitrates and potassium permanganate mixed with clays were reported to regenerate carbonyl compounds from oximes and semicarbazones.^{263–269,269b} In some cases, the reaction occurs simply by grinding all the reagents in a mortar. The same reactions can be performed in shorter times by microwave irradiation.^{270–273}

Y²⁷⁴ and ZSM-5,^{275,275b} zeolites, combined with potassium permanganate or iron and thallium nitrate, respectively, have been efficiently utilized in deoximation reactions of ketones; lower yields were observed with aldehydes, probably due to the overoxidation processes.

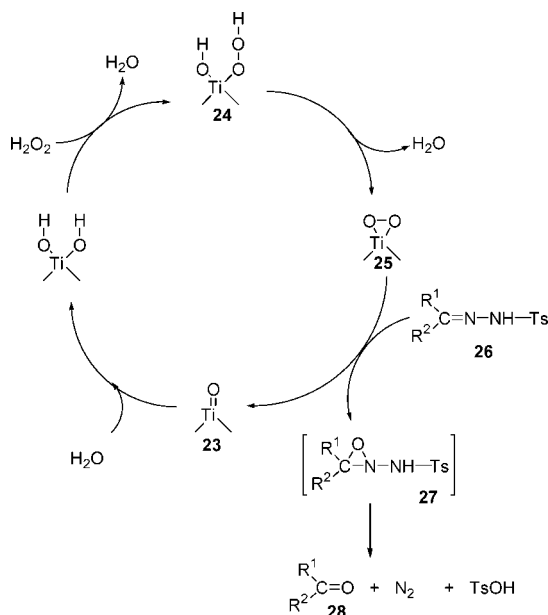
Silica gel has been more extensively employed than clays and zeolites as heterogeneous support in performing oxidative deprotection of nitrogenous derivatives. A wide number of oxidizing reagents, namely, nitrates,^{276,224,276b,c} chromates,^{277–279,279b,c} persulfates,^{280,281,281b} iodates,²⁸² chlorides/ O_2 ,²⁸³ permanganates,^{283b} and perchlorates,²⁸⁴ were reported to be effective in performing the cleavage. In many cases, by using microwave irradiation, the deprotection reactions occurred faster and cleaner;^{285–294} in fact, it has been reported that silica gel, in contrast to other cheap solid materials, is a good microwave conductor.²⁸⁵

Chlorochromates,^{295–299,299b} fluorochromates,³⁰⁰ and permanganates,^{301,301b} in combination with alumina, have been utilized for the regeneration of carbonyl compounds from semicarbazones, hydrazones, and oximes. The reactions showed general applicability for both aldehyde and ketone derivatives, including camphor and benzophenone.

Concerning a more realistic heterogeneous catalysis in the deprotection reaction of nitrogenous derivatives, Ballini et al. reported the use of the familiar solid acid Envirocac EPZG for the selective regeneration of ketones from their tosylhydrazones carried out in acetone/water. The reaction seems to involve a hydrolytic transfer of the protective group to acetone. Aldehyde tosylhydrazones were less reactive, even after long reaction times, and these results suggested that the procedure could be employed for the satisfactory regeneration of ketone in the presence of both ketone and aldehyde tosylhydrazones, as reported in Scheme 31.³⁰² A quite similar strategy has been applied with the use of layered zirconium sulfophenyl phosphonate.³⁰³

The same deprotection reaction was reported by Varma et al. to occur in the presence of ammonium persulfate adsorbed on montmorillonite K10 under the influence of microwaves.³⁰⁴ The authors suggested the mechanism reported in Scheme 32.

Scheme 33



Ammonium persulfate, in the presence of the water adsorbed on the clay, generates O_2 and NH_4HSO_4 ; the HSO_4^- species is responsible for the oxidative cleavage of the hydrazone. It is remarkable that in the absence of mineral supports, the attempted cleavage of semicarbazones failed with ammonium persulfate under both microwave and ultrasonic irradiation conditions, even after prolonged reaction periods. The crucial role of the acidic clay is also probably ascribable to the activation of the carbon–nitrogen double bond through protonation.

A solid catalyst largely utilized in oxidative reactions, titanium silicate molecular sieves (TS-1), has been claimed to catalyze the oxidative cleavage of various tosylhydrazones to the parent aldehydes and ketones in moderate to good yields. The method is particularly convenient since diluted hydrogen peroxide is utilized as an oxidizing reagent.³⁰⁵ The authors described the catalytic cycle reported in Scheme 33, where the cleavage of the carbon–nitrogen double bond was attributed to the presence of randomly distributed Ti^{4+} ions in the lattice.

The species **23** present on the surface of the catalyst first reacts with $H_2O-H_2O_2$, leading to the peroxo species **25** via an intermediate hydroxy-peroxy titanium complex **24**. This species is responsible for the formation of the unstable oxaziridine **27** from tosylhydrazone **26**, which decomposes, affording the ketone **28** and restoring the catalyst.

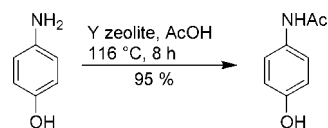
6. Amino Protecting Groups

Nitrogen protection continues to attract a great deal of attention in a wide range of chemical fields, such as peptide, nucleoside, polymer, and catalyst ligand synthesis. Moreover, in recent years, a number of nitrogen-protected groups have been used as chiral auxiliaries. Thus, the design of new, milder, and more effective methods for nitrogen protection still is an active topic in synthetic chemistry.

6.1. Protection

Among the different means for protection of the amino groups, acylation has received the greatest attention, and it is a very important transformation also from an industrial

Scheme 34



point of view. The use of acetic acid rather than acetic anhydride or acetyl chloride is both economically and environmentally advantageous, producing only water as a byproduct instead of acetic acid or hydrochloric acid.

A few such procedures have been developed over the past decade (Table 27, entries 1–3). Kulkarni et al. (Table 27, entry 1)³⁰⁶ reported that alkyl, aryl, and heterocyclic amines were converted to the corresponding acetamides with acetic acid over Y zeolite (SAR = 5.2). No leaching of aluminum or silicon was observed. Arylamines reacted faster than alkylamines. The authors also observed a selective acylation of an amino group in the presence of a hydroxy group (Scheme 34).

Y zeolite can also be used for the same transformation using microwave activation (Table 27, entry 2).³⁰⁷ The reaction is simple, producing no toxic byproducts. It is applicable to a variety of saturated and unsaturated amines. Yields are much lower without microwave irradiation.

Acylation of an amino group has also been performed at room temperature using Nafion in the presence of a methylene chloride solution of the amine and acetic acid (Table 27, entry 3).⁴⁵

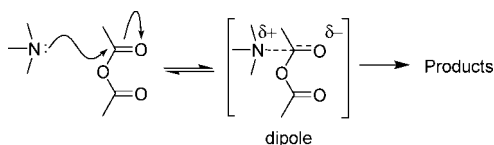
Amino groups could also be acylated with acetic anhydride in solventless conditions using FER zeolite (Table 27, entry 4).²⁶ The mildness of the method is evident by the retention of configuration of the chiral center. The system tolerates other acid-sensitive functionalities.

Modified alumina has been used by Yadav et al. as a solid-phase catalyst to prepare acetamides. It was reported that KF over neutral Al_2O_3 could promote the acylation of aliphatic and aromatic amines (Table 27, entry 5).³⁸ In this case, acetic anhydride was superior to acetyl chloride. Under these conditions, aliphatic amines such as *tert*-butylamine reacted very quickly, affording the corresponding amide. As expected, aromatic amines carrying electron-withdrawing groups (e.g., 4-nitroaniline, 4 h) reacted more slowly than other aromatic amines (e.g., 4-chloroaniline, 6 min). A rate enhancement was observed when the reaction was run without any solvent. Under these conditions, 4-nitroaniline afforded the corresponding acetanilide in only 15 min.

Acetic anhydride and pyridine over basic alumina have been used as solid catalysts to carry out acetylation of aliphatic, aromatic, and heterocyclic amines under solvent-free conditions and microwave irradiation (Table 27, entry 6).³⁶ Significantly lower yields were obtained using oil-bath heating rather than microwave irradiation. The acetic acid byproduct remained adsorbed on the alumina, and it was not released into the atmosphere. The authors suggested that this rate enhancement could be explained by the microwave stabilization of the dipole formed in the transition state (Scheme 35).

Fe-exchanged montmorillonite K10 can be utilized as reusable catalyst for the selective and efficient protection of sulfonamides using anhydrides. The reactions are carried out in acetonitrile, chosen as solvent for its ability to stabilize the acylium intermediate. Various primary as well as secondary sulfonamides were reacted with three anhydrides,

Scheme 35



namely, acetic, benzoic, and trifluoroacetic anhydride: the acetic one was found to be more reactive (Table 27, entry 6b).^{307b}

Interestingly, sterically hindered and electron-deficient anilines can be efficiently protected. The acetylation process is carried out under solvent-free conditions by using perchloric acid adsorbed on silica gel (Table 27, entry 6c).^{32b}

Polymer-supported 1-hydroxybenzotriazole [(P)-HOBT] (Figure 11) from macroporous SM-2 polystyrene beads was used by Kalivretenos et al. for the preparation of various amides from carboxylic acids and primary and secondary amines. The method efficiently gave amides in high yields and purity. In contrast to Merrifield resins, SM-2 beads do not swell or contract and can thus be used in a variety of solvents, including water (Table 27, entry 7).³⁰⁸

Alumina was utilized as catalyst for the Boc-protection of amines in excellent yield (Table 27, entry 7b).^{308b} Because of the fact that the reactions of amines with Boc-anhydride are so fast in comparison to those of the aliphatic alcohols, the selective protection of an amine in the presence of an aliphatic alcohol was attempted. The reaction of 2-(*N*-methyl)amino ethanol with Boc-anhydride was complete in 10 min, affording the 2-Boc-2-(*N*-methyl)amino ethanol in 97% yield.

The *tert*-butoxycarbonylation of primary and secondary amines was also performed in the presence of the commercially available heteropoly acid H₃PW₁₂O₄₀ (Table 27, entry 7c).^{308c} Sterically hindered amines (i.e., *tert*-butylamine) or poorly reactive ones (i.e., 4-nitroaniline) are also protected; 1,2-phenylenediamine exclusively affords the mono *N*-*tert*-butoxycarbonyl protected product in 86% yield. In this case, too, the reaction is chemoselective, as with 2-phenylglycinol, *N*-benzylethanolamine, and ephedrine; the corresponding *N*-Boc protected products were uniquely obtained. In addition, the catalyst was reused showing the same high activity; for example, the reaction of (*S*)- α -methylbenzylamine and Boc-anhydride afforded the corresponding derivative in 88%, 88%, and 87% yields over three cycles.

Imides were prepared from the corresponding acid anhydrides and amines using a base-free and solvent-free procedure (Table 27, entry 8).³⁰⁹ This methodology made use of tantalum pentachloride supported on silica as catalyst, which was admixed thoroughly to the reagents adsorbed on activated silica gel. The mixture was then irradiated in a microwave oven for 5 min. This procedure has proven to be superior in the preparation of maleimide derivatives, and less reactive succinic and glutaric anhydride could be converted to the corresponding imides. The mildness of the method was proven by the retention of optical purity observed in the preparation of (+)-(*R*)- α -methylbenzylamine maleimide (Scheme 36).

N-Alkylation was used as a protective method for nitrogen, especially when benzyl groups are introduced. In this regard, cesium fluoride supported on Celite could be used as the solid base to accomplish the reaction. In this way, Bayer et al. benzylated anilines, carboxamides, and heterocyclic compounds at the nitrogen in acetonitrile (Table 27, entry

9).³¹⁰ When primary amines were reacted, satisfactory selectivities of the monobenzylated product could be obtained. The authors reported that Celite/CsF was less reactive than potassium and tetralkylammonium fluorides and required longer reaction times. On the other hand, it is easier to handle and cheaper.

The same benzylation could be obtained, in certain instances, in the gas phase at ca. 300 °C, using benzyl alcohol as the alkylating agent and γ -alumina as the catalyst (Table 27, entry 10).³¹¹ The alcohol served also as the diluent (alcohol/amine ratio of 20/1 was used), and the only byproduct was water. Benzylation of benzylamine with benzyl alcohol afforded the bis-alkylated product in 78% yield.

The solvent-free preparation of aldimines and enamines was achieved using montmorillonite K10 clay. Equimolar amounts of carbonyl compound and primary or secondary amine were added with the clay in an open glass container and irradiated in a microwave oven for a few minutes (Table 27, entry 11).³¹² This method afforded the products quickly (oil-bath heating, reaction times of a few hours) and avoided the use of solvents for azeotropic removal of water. Other functional groups, such as phenols, phenolethers, and tertiary amines, were unaffected.

A solvent-free preparation of *N'*-derivatives of *N*-arylpiperazine using silica as the solid support and microwave irradiation was reported by Williams (Table 27, entry 12).³¹³ The method could be used to prepare *N'*-sulfonyl, *N'*-acyl, and *N'*-benzyl derivatives of piperazines. It was simple, high-yielding, and afforded products with high purity. The silica gel support also removed all the hydrochloric acid formed in the reaction, and no acid scavenger was needed. The reaction parameters were initially optimized by irradiation of reagents supported on glass-backed TLC silica plates, this technique being applicable to a combinatorial preparation of such derivatives.

6.2. Deprotection

The *tert*-butoxycarbonyl group still is one of the most popular amino protecting groups. The most common method for its removal is the use of trifluoroacetic acid either neat or in dichloromethane solution. Other mineral acids or Lewis acids have also been used, although less frequently. Methods based on solid catalysts have been developed only recently.

In the course of a preparation of indole-3-acetic acids, any attempted *N*-Boc deprotection under the usual conditions was unsuccessful, affording mainly large amounts of resinous materials. Adsorbing the reagent onto silica gel and keeping it at 50 °C under reduced pressure cleanly afforded the free indole (Table 28, entry 1).³¹⁴ When the reaction was performed at atmospheric pressure, only trace amounts of the product could be detected after 24 h. The method was later applied to the deprotection of *N*-Boc-protected anilines and indoles (Table 28, entry 2).³¹⁵ An interesting selectivity was noted for the deprotection of Boc groups attached to aniline, indole, or imidazole nitrogens over Boc groups attached to aliphatic amines (Scheme 37).

The same activity can be achieved by using beta zeolite in 1,2-dichloroethane at reflux (Table 28, entry 2b).^{315b} Interestingly, the method is selective for the deprotection of *N*-Boc-protected anilines in the presence of acetals or *tert*-butyl ester groups; Boc-substituents at aliphatic amines also remain unaffected.

Table 27. Protection of Nitrogen-Containing Functional Groups

entry ^{ref}	catalyst ^a (experimental conditions)	amino compound	protected amino compound	yield (%)	n. ex. (yields %)
1 ³⁰⁶	Y zeolite ^{a(3)} (AcOH, Δ, 5 h)			98	15 (78-99)
2 ³⁰⁷	Y zeolite (AcOH, MW, 40 min)			93	12 (80-97)
3 ⁴⁵	Nafion [®] (AcOH, CH ₂ Cl ₂ , rt, 20 h)			96	2 (96-97)
4 ²⁶	FER zeolite (Ac ₂ O, neat, rt, 2 h)			99	2 (99)
5 ³⁸	Al ₂ O ₃ /KF (Ac ₂ O, PhMe, 4 h)			97	5 (92-97)
6 ³⁶	Al ₂ O ₃ (Ac ₂ O, pyridine, MW 300 W, 2 min)			100	32 (65-100)
6b ^{307b}	Mont. K10/FeCl ₃ ^{a(4)} (Ac ₂ O, MeCN, 60 °C, 15 min)			91	13 (62-98)
6c ^{32b}	SiO ₂ /HClO ₄ ^{a(4)} (Ac ₂ O, rt, 30 min)			91	2 (83-91)
7 ³⁰⁸	(P)-HOBT (BzOH, DCC, CH ₂ Cl ₂ , rt, 3.5 h)			96	22 (64-99)
7b ^{308b}	Al ₂ O ₃ (Boc ₂ O, 25 °C, 5 min)			97	3 (95-97)
7c ^{308c}	H ₃ PW ₁₂ O ₄₀ ^{a(2)} (Boc ₂ O, CH ₂ Cl ₂ , rt, 10 min)			85	17 (80-98)
8 ³⁰⁹	SiO ₂ /TaCl ₅ (phthalic anhydride, neat, MW 448 W, 5 min)			92	10 (74-92)
9 ³¹⁰	Celite/CsF (BnCl, MeCN, Δ, 48 h)			98	23 (29-100)
10 ³¹¹	Al ₂ O ₃ (BnOH, gas phase, 290 °C)			78	1 (78)
11 ³¹²	Mont. K10 (PhCHO, neat, MW 800 W, 3 min)			98	5 (95-98)
12 ³¹³	SiO ₂ (2-nitrophenylsulfonyl chloride, neat, MW 585 W, 5 min)			91	9 (75-99)

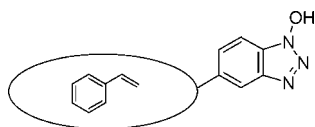
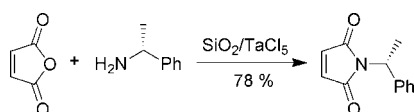
^a The catalyst has been recycled (number of recycles).

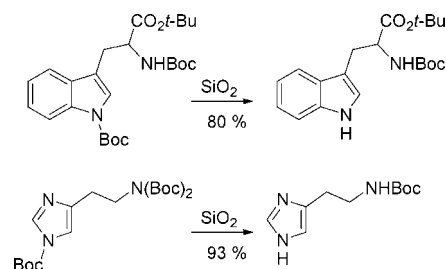
Figure 11.

Scheme 36



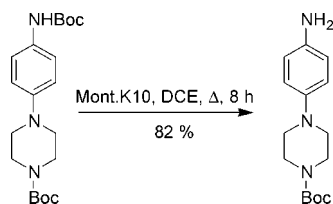
Montmorillonite K10 and kaolinitic clays were found by Bedekar et al. to be effective catalysts in the removal of aromatic *N*-Boc groups (Table 28, entry 3).³¹⁶ The method

Scheme 37



worked on chloro-, nitro-, methoxy-, and hydroxy-substituted aromatic amines and was compatible with a series of other

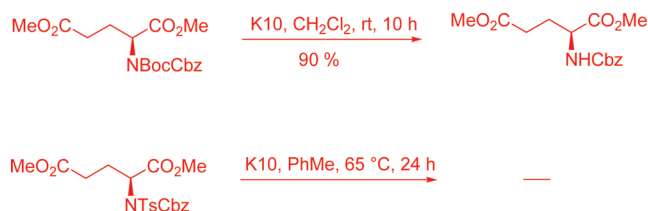
Scheme 38



functionalities, such as acetals. A clean selectivity for aromatic amines over aliphatic ones was observed (Scheme 38).

The selective monodeprotection of a series of *N,N*-Boc-diprotected amino derivatives containing several protecting groups and functionalities can be obtained by employing montmorillonite K10 as catalyst in toluene at 65 °C (Table 28, entry 3b);^{316b} this methodology also can be applied to protected α -amino acids without any detectable racemization. Interestingly, the cleavage of the *N*-Boc group can be achieved in the presence of *O*-Boc protective groups; in addition, the *tert*-butyl ester function remains unaffected under these conditions. The methodology has also been

Scheme 38b



extended to other situations in which the nitrogen is doubly protected with different protecting groups together with the *N*-Boc protection. When another carbamoyl-based protecting group, such as Cbz, was used, the cleavage of the Boc group was accomplished cleanly and selectively, yielding the corresponding *N*-Cbz amino derivative, whereas when the nitrogen was protected as the *N*-Cbz-*N*-acyl derivative, the substrate remained unaltered in the presence of montmorillonite K10 even after 24 h at 65 °C, demonstrating the high selectivity in favor of *N*-Boc cleavage (Scheme 38b).

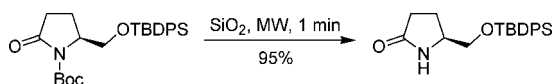
A solvent-free deprotection of *N*-Boc-protected amides and amines was achieved by irradiating with microwaves the silica gel-adsorbed substrates. This methodology turned out

Table 28. Deprotection of Nitrogen-Containing Functional Groups

entry ^{ref}	catalyst ^a (experimental conditions)	Protected amino compound	amino compound	yield (%)	n. ex. (yields %)
1 ³¹⁴	SiO ₂ (neat, 50 °C, 24 h, 1 mmHg, dark)			92	11 (58-92)
2 ³¹⁵	SiO ₂ (neat, 50 °C, 8 h, 0.2 mmHg)			93	6 (83-93)
2b ^{315b}	Beta zeolite ^{a(5)} (ClCH ₂ CH ₂ Cl, reflux, 5 h)			99	13 (77-100)
3 ³¹⁶	Mont. K10 (ClCH ₂ CH ₂ Cl, Δ, 1.5 h)			98	8 (64-99)
3b ^{316b}	Mont. K10 ^{a(4)} (PhMe, 65 °C, 12 h)			91	21 (55-95)
4 ³¹⁷	SiO ₂ (neat, MW 650 W, 1 min)			96	10 (56; 86-98)
5 ³¹⁸	SiO ₂ /Yb(OTf) ₃ (neat, 40 °C, 1 h)			97	10 (96-100)
5b ^{318b}	HAP/Pd ^{a(1)} (H ₂ , MeOH, 40 °C, 1 h)			99	9 (84-99)
6 ³¹⁹	Amberlite IR-120 (MeOH, rt, 12 h)			100	6 (84-100)
6b ^{323b}	SiO ₂ /K ₂ Na (THF, rt, 8 h)			96	11 (61-96)
7 ³²⁴	SiO ₂ (CH ₂ Cl ₂ /MeOH = 98/2, rt, 48 h)			88	6 (55-88)
7b ^{123b}	SiO ₂ /NaHSO ₄ (CH ₂ Cl ₂ /MeOH, rt, 3.5 h)			95	2 (90-95)

^a The catalyst has been recycled (number of recycles).

Scheme 39



to be noticeably cleaner and faster than deprotection without microwave irradiation (Table 28, entry 4).³¹⁷ This method was extremely mild and, avoiding acidic conditions, it was compatible with a series of acid-sensitive groups, such as silyl ethers (Scheme 39).

Modified silica gel was also used for the same deprotection. Thus, $\text{SiO}_2/\text{Yb}(\text{OTf})_3$ promoted the thermal deprotection of *N*-Boc carboxamides under solvent-free conditions (Table 28, entry 5).³¹⁸ *N*-Benzyloxycarbonyl (*N*-Cbz) or *N*-Boc amino groups did not react under these conditions. The reaction in the presence of an organic solvent under heterogeneous conditions took a longer time than the solvent-free methodology. This procedure left esters, ketones, and cyclic acetals unaffected.

The deprotection of *Z*-protected amino acids catalyzed by HAP/Pd in the presence of molecular hydrogen in methanol at 40 °C was reported by Kaneda et al. Excellent yields of the corresponding amino acids, including those sterically hindered, were obtained. The hydrogenolysis of *Z* groups in the presence of *tert*-butyl ones, potentially decomposed at elevated temperature, was achieved under mild conditions in high yields (96–99%) (Table 28, entry 5b).^{318b}

Li et al. reported an efficient deprotection of the *N*-*p*-toluenesulfinyl group of β -branched Baylis-Hillman adducts with the use of Amberlite IR-120 (plus) ion-exchange resin (Table 28, entry 6).³¹⁹ The deprotection of these substrates is particularly interesting since it affords free α -alkylidene β -amino acid esters, which are employed in the preparation of β -lactam antibiotics, peptidomimetics, and other biologically important molecules.^{320–323} Another interesting feature of this procedure is that at the end of the reaction, the product remains adsorbed on the resin. This allows for a very easy purification of the amino ester: the resin is thoroughly washed with methanol and then the product is released with 15% NH_4OH in methanol overnight. No racemization was observed during the deblocking, and *N*-Boc groups remained unaffected. The authors suggest that the true deprotecting agent was the methoxonium ion (MeOH_2^+) generated in situ. The hypothesis was supported by the fact that this deprotection did not work in other protic solvents.

A novel method to cleave toluenesulfonamides was performed by carrying out the deprotection reaction in THF at room temperature by using K_2Na absorbed onto silica gel (Table 28, entry 6b).^{323b} Detosylation tolerates phenyl and ether moieties and is successful for both primary and secondary amines. The mesyl moiety is also cleanly cleaved.

Imidazopyridine trifluoroacetamides could be mildly deprotected by using silica gel (Table 28, entry 7).³²⁴ All attempts to perform this deblocking using basic conditions such as NaOH or Hünig's base failed, leading instead to imidazopyridine ring-opening.

Finally, the deprotection of trityl-protected amines can be accomplished in the presence of silica-supported hydrogen sulfate; the yields of the generated amines are excellent by performing the reaction at room temperature for 3.5 h (Table 28, entry 7b).^{123b}

7. Concluding Remarks

The preparation of complex organic molecules demands the availability of different protective groups to allow the survival of reactive functional groups during the various synthetic operations, finally resulting in the selective production of the target molecule.

As shown in this review, a large number and extreme diversity of heterogeneous catalysts have been utilized in the field of protective groups chemistry during the past decade. This is the consequence of both the attention to environmentally friendly methods of making organic compounds and the continuous need for improving the selectivity in protective groups chemistry applied to multifunctional molecules.

Some of the catalysts described in this review are commercially available, such as most of the clays, zeolites, and metal oxides; some others must be expressly prepared, such as the supported acids, bases, and transition metal complexes. Obviously, the application of heterogeneous catalysis in organic synthesis makes the reaction handling easier with special attention to product purification. A further advantage is represented by the possibility of performing reactions under solventless conditions and in very short times under microwave irradiation. Many examples of highly selective protection of multifunctional molecules have been reported within the review, and in some cases they are assumed to be promoted by a synergic contribution of the catalytic site and some specific surface peculiarities, such as the polarity, hydrophobicity, hydrophilicity, and pore dimension, in a way resembling the enzymatic catalysis.

However, still more questions remain, especially concerning the nature of the catalytic sites and their interaction with reactant and solvent molecules in order to rationalize the catalytic activity and to achieve the optimum performance. Moreover, although theoretically all the heterogeneous catalysts could be recovered from the reaction mixtures simply by filtration and reused, this aspect has been scantily taken into consideration. In fact, the catalyst reusability was verified in only about 20% of the cited papers.

This presentation and discussion highlights a growing field where the interdisciplinary cooperation between synthetic organic chemistry, physical chemistry, and analytical chemistry has made it possible to obtain interesting and promising results in protective group chemistry.

8. Abbreviations

ATPB	acetyltriphenylphosphonium bromide
BTSC	bis(trimethylsilyl)chromate
BTSE	1,2-bis(trimethylsilyloxy)ethane
Bz	benzoyl
DCKA	dicyanoketene acetal
DHP	3,4-dihydro-2 <i>H</i> -pyran
DMC	dimethyl carbonate
DMD	2,2-dimethyl-1,3-dioxolane
DMTr	dimethoxytrityl
DMP	2,2-dimethoxypropane
EE	1-ethoxyethyl
Fmoc	9-fluorenylmethoxycarbonyl
HMDS	1,1,1,3,3,3-hexamethyldisilazane
MME	1-methyl-1-methoxyethyl
MMTr	monomethoxytrityl
MPM	methoxyphenylmethyl
MW	microwave
NAP	2-naphthylmethyl
SAR	silica/alumina ratio

SEM	2-(trimethylsilyl)ethoxy methyl
TES	triethylsilyl
THP	tetrahydropyran

9. Acknowledgments

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