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Solid-Supported Acids as Mild and Versatile Reagents for the Deprotection of Aromatic Ethers

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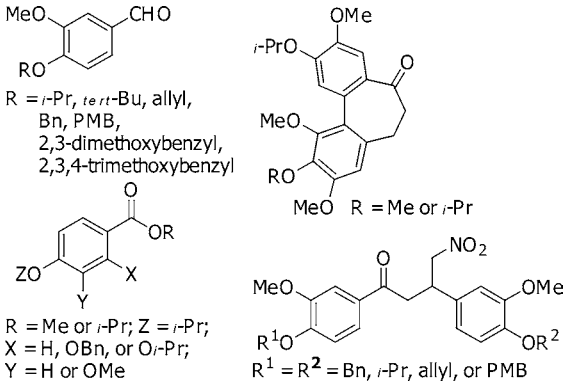
ABSTRACT



***p*-Toluene sulfonic acid (*p*-TsOH) immobilized either on polystyrene (PS) or silica (Si) was found to be effective in cleaving aromatic ethers containing isopropyl, *tert*-butyl, allyl, and benzyl groups, as well as mono-, di-, and trimethoxylated benzyl groups, in moderate to excellent yields (54–95%). These protecting groups could be selectively deprotected when they were simultaneously present on the same or different aromatic rings in a substrate.**

Protecting groups are important tools in organic synthesis as they have found extensive use in many different areas of complex syntheses of natural products, biomolecules, and materials.[1] Crucial features of protecting groups are their ease of preparation and removal as well as their relative stability toward different reaction conditions. A number of moieties such as benzyl, isopropyl, *tert*-butyl, and mono- or polymethoxylated benzyl, among others, have been developed as protecting groups for both aliphatic and aromatic hydroxy functionalities.[2] Reaction conditions for preparing and removing these protecting groups have been investigated.[3] New reagents and reaction conditions have been continually developed for protecting and/or deprotecting purposes.[4]

Current awareness and interest in green chemistry has prompted many research groups, including ours, to investi-

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(1) (a) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477−5480. (b) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757−3760. (c) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960−15961. (d) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989−16999.

(2) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, Germany, 2003.

(3) (a) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593−2598. (b) Cruz-Almanza, R.; Pérez-Flores, F. J.; Avila, M. *Synth. Commun.* **1990**, *20*, 1125−1131. (c) Ma, S.; Venanzi, L. M. *Tetrahedron Lett.* **1993**, *34*, 8071−8074. (d) Molnár, A.; Beregszászi, T. *Tetrahedron Lett.* **1996**, *37*, 8597−8600.

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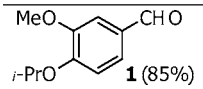
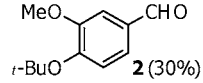
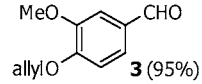
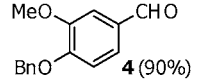
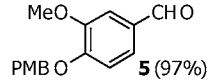
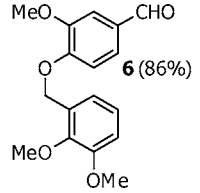
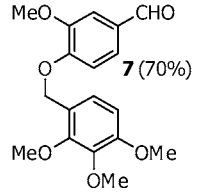
gate other alternatives in performing reactions.[5] The use of solid supports, as either reagents or anchors, contributes significantly to the progress of practicing green chemistry because they render the reaction more efficient and environmentally friendly. Employing solid-supported reagents, in particular, generates less organic and aqueous waste as a result of simplified experimental procedures. Herein, we wish to report the results of our investigation of the generality and selectivity in the use of *p*-TsOH immobilized on either silica (PTS-Si) or polystyrene (PS)−divinyl benzene (DVB) polymer (Amberlyst-15) for the deprotection of aromatic ethers.

Vanillin was chosen as a model and was converted into the corresponding ethers by using either conventional or newly reported procedures.[6] A total of seven ethers (**1**−**7**) were prepared in 30−97% yields. Table 1 summarizes the result of our investigation. All ethers of vanillin were found to be effectively cleaved in 54−95% yields under mild reaction conditions, employing either Amberlyst-15 or PTS-Si in toluene at elevated temperatures (≤110 °C) with or without methanol as additive in relatively short reaction times (≤4 h).

In most cases, only substoichiometric amounts of the acids (0.3−0.6 equiv) were required. Different protecting groups require slightly different reaction conditions for their removal. Throughout the reactions, the pH of the reactions as measured from toluene remained neutral. Decreasing the amount of acids employed in the reactions resulted in longer reaction time. In addition, the deprotection reactions employing PTS-Si were generally faster than those employing Amberlyst-15 under identical conditions due to the greater surface area of silica.[7]

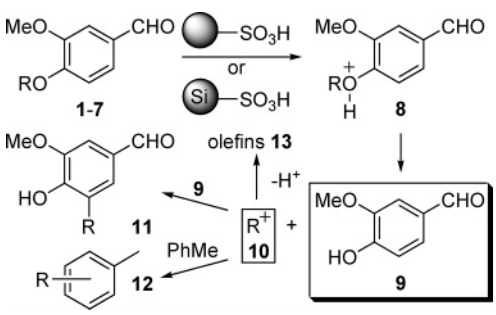
Table 1. Deprotection of Vanillin Ethers (**1**−**7**) to Vanillin with Amberlyst-15 and PTS−Si[a]

vanillin ether[b]	acid[c]	equi[d]	temp (°C)[e]	time (h)	yield (%)[f]
 **1** (85%)	A[g]	0.6	110	4	81
	B[g]	0.3	110	2	81
 **2** (30%)	A	0.6	80	1	83
	B	0.6	rt	7	87
 **3** (95%)	A	0.6	110	3	57
	B	0.6	110	2	54
 **4** (90%)	A[h]	0.6	110	2	81
	B	0.6	65	1	80
 **5** (97%)	A	0.6	110	1	95
	B[i]	0.6	80	0.5	91
 **6** (86%)	A[j]	2.2	110	1	95
	B[k]	0.6	110	0.75	92
 **7** (70%)	A	1.1	110	3	70
	B[l]	0.6	65	2	94

[a] Unless otherwise noted, all reactions were performed in toluene with 4 equiv of methanol. [b] Numbers represent the yields of vanillin ethers. [c] A = Amberlyst-15; B = PTS-Si. [d] The lowest amount of acids required. [e] The lowest temperature required. [f] Isolated yield of vanillin. [g] Similar results were obtained in the presence and absence of methanol. [h] Vanillin was obtained in 98% yield under similar reaction conditions, using 1.1 equiv of acid (see ref 5b). [i] At room temperature, the reaction required 6 d (144 h) and provided vanillin in 91% yield. [j] Vanillin was obtained in 91% yield when 1.1 equiv of the acid was employed at 110 °C for 18 h. [k] The reaction proceeded to furnish vanillin in 93% yield at 65 °C for 3 h. [l] At 110 °C, the reaction required only 0.25 h to complete, providing vanillin in 90% yield.

Our proposed reaction mechanism for the deprotection of these ethers is shown in Scheme 1, which depicts the

Scheme 1. Proposed Mechanism for the Acid-Mediated Deprotection of Aromatic Ethers



(4) (a) Ballini, R.; Bigi, F.; Carloni, S.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1997**, *38*, 4169−4172. (b) Cappa, A.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696−5699. (c) Monoharan, M.; Lu, Y.; Casper, M. D.; Just, G. *Org. Lett.* **2000**, *2*, 243−246. (d) Papageorgiou, E. A.; Guant, M. J.; Yu, J.-Q.; Spencer, J. B. *Org. Lett.* **2000**, *2*, 1049−1051. (e) Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 4430−4432. (f) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149−1151. (g) Marković, D.; Vogel, P. *Org. Lett.* **2004**, *6*, 2693−2696. (h) Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513−1514. (i) Punna, S.; Meunier, S.; Finn, M. G. *Org. Lett.* **2004**, *6*, 2777−2779. (j) Fujioka, H.; Sawama, Y.; Murata, N.; Okitsu, T.; Kubo, O.; Matsuda, S.; Kita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11800−11801. (k) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930−5938. (l) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427−430. (m) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Sambri, L. *J. Org. Chem.* **2006**, *71*, 9580−9588. (n) House, S. E.; Poon, K. W. C.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 420−422. (o) Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K.-F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 9045−9050. (p) Aristegui, S. R.; El-Murr, M. D.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R. *Org. Lett.* **2006**, *8*, 5927−5929. (q) Fatakopoulou, I.; Barbayianni, E.; Constantinou-Kokotou, V.; Bornscheuer, U. T.; Kokotos, G. *J. Org. Chem.* **2007**, *72*, 782−786.

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(6) (a) Kotecha, N. R.; Ley, S. V.; Montegani, S. *Synlett* **1992**, 395−398. (b) Mayer, A. A.; Murphy, B. P. *Synth. Commun.* **1985**, *15*, 423−429. For compound **2**, see refs 4*l* and 4k. See the Supporting Information.

(7) Surface area of silica (Silicycle) is 500 m^2/g while that of Amberlyst-15 (Fluka) is 45 m^2/g.

protonated intermediate **8**, the desired product vanillin **9**, the carbocation resulting from the C−O bond cleavage **10**, and the byproducts **11**−**13** arising from the carbocation. Compounds **11** and **12** were formed via Friedel−Crafts-type C-alkylation reactions of **10** with vanillin (at the position *ortho* to the hydroxy group) and toluene, respectively, while olefins **13** were formed via loss of a proton on the carbon adjacent to the carbocation. The overall reaction time may not necessarily reflect the stability of carbocation generated from the C−O aryl bond cleavage but rather the overall combined rates of the C−O aryl bond cleavage and quenching of the resulting carbocation.

These vanillin ethers were next investigated for their competitive deprotection. As a model, the PMB ether of vanillin **5** was employed for selective deprotection either when mixed in equimolar amounts with the isopropyl ether **1** or with benzyl ether **4** in the presence of Amberlyst-15. Good to excellent selectivity could be observed and the results are summarized in Table 2. Between **1** and **5**, lowering

Table 2. Competitive Deprotection of Vanillin Ether **5** in the Presence of **1** or **4**[a]

ethers	equiv of acid[b]	temp (°C)	time (h)	yield of **9** (%)[c]	yield of **1** or **4** (%)[d]
MeO, CHO, *i*-PrO **1** + MeO, CHO, PMB O **5**	0.6	110	1	55	69 (**1**)
	0.6	65	4	99	94 (**1**)
	1.1	110	1	37	50 (**1**)
	1.1	65	3	99	99 (**1**)
MeO, CHO, BnO **4** + MeO, CHO, PMB O **5**	1.1	110	1	52	80 (**4**)
	1.1	65	2.5	92	99 (**4**)

[a] Unless otherwise noted, equimolar amounts of ethers were used. The reactions were allowed to proceed until one of the two ethers was completely consumed. [b] The acid employed was Amberlyst-15. [c] Isolated combined yield of vanillin mainly from the deprotection of **5**, with varying amounts of vanillin from partial deprotection of **1** or **4**. [d] Isolated yield of the remaining ether.

temperature resulted in much greater selectivity while requiring longer reaction time. The amount of acid used did not seem to affect the selectivity. Similar results were observed between **4** and **5**.

We next investigated the removal of similar as well as different protecting groups simultaneously present on the same aromatic ring in compounds **14**−**16** which were synthesized according to the standard procedures.[6] As shown in Table 3, use of solid-supported acids provided good selectivity in the removal of protecting groups.

Isopropyl ether of compound **14** was preferentially removed over the isopropyl ester in moderate to good yields to give compound **17**. Significantly higher yield was obtained when PTS-Si was used. The benzyl group in **15** was selectively removed while the isopropyl group remained virtually intact, furnishing **18** in moderate 58−60% yield. Such preference could arise from the difference in the rate of deprotection or the chelation provided by the adjacent carbonyl group of the ester.[8] In fact, when compound **16** was subjected to deprotection conditions, the isopropyl group *ortho* to the methyl ester was selectively and cleanly deprotected over the other at the *para* position, clearly suggesting the importance of the chelation effect. Only a small amount of byproducts **19** or **20** was detected.

Good selectivity could also be observed when similar or different protecting groups are present in the same molecule but on different aromatic rings. The unsaturated enone of the chalcone system in **21** (Figure 1) seemed incompatible

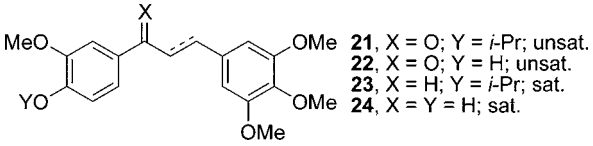


Figure 1. Chalcones and chalcone-derived compounds **21**−**24**.

with the reaction conditions as its deprotection reaction gave only low yields (13−22%) of **22**. However, when the unsaturated enone was completely reduced to aliphatic chain in **23**, the isopropyl group was smoothly removed, giving the corresponding product **24** in 93% yield.

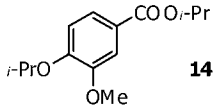
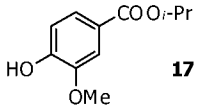
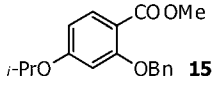
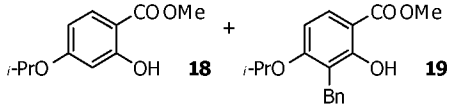
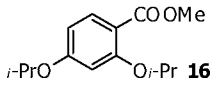
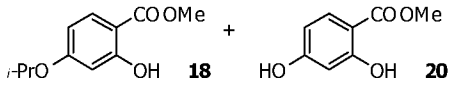
In addition, selective deprotections in the more functionalized nitroalkane compounds **25**−**30**[9] with Amberlyst-15 or PTS-Si occurred smoothly, furnishing the products **31a**−**f** in good yields (up to 91%) along with the bis-deprotected byproduct **32**.[10] Table 4 summarizes the results of our investigation. PMB was selectively removed over benzyl, isopropyl, and allyl groups.

The isopropyl groups on the biaryl system as part of the allocolchicine skeleton **33** and **34**[11] (Scheme 2) could be smoothly deprotected to the corresponding products **35** (68% and 69% yields with Amberlyst-15 and PTS-Si, respectively) and **36** (78% and 75% yields with Amberlyst-15 and PTS-Si, respectively) without the need for column chromatography on silica otherwise required for purifying the crude products with $AlCl_3$.[12]

In summary, we have developed a general and effective method for cleaving the C−O aryl bond using Amberlyst-15 and PTS-Si. The rate of C−O aryl bond cleavage under these reaction conditions was *tert*-butyl > PMB > di- and

(8) Demyttenaere, J.; Van Syngel, K.; Markusse, A. P.; Vervisch, S.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2163−2166.
(9) See the Supporting Information for their preparation.
(10) See the Supporting Information for its structure.
(11) (a) Besong, G.; Jarawicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. J. *Org. Biomol. Chem.* **2006**, *4*, 2193−2207. (b) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849−2852. (c) Seganish, W. M.; DeShong, P. *Org. Lett.* **2006**, *8*, 3951−3954.
(12) Deprotection of the isopropyl group(s) in **33** and **34** with $AlCl_3$ furnished **35** in 71% and **36** in 70% yields, respectively.

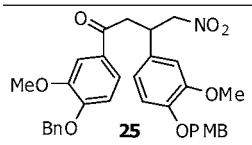
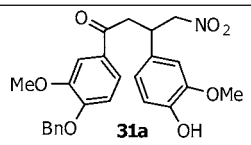
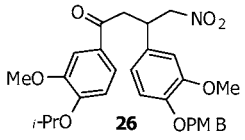
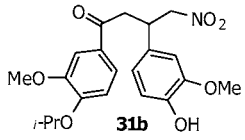
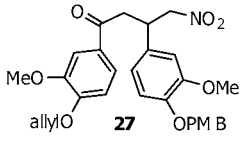
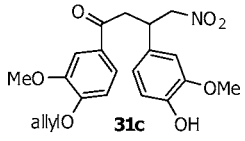
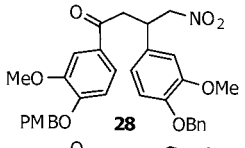
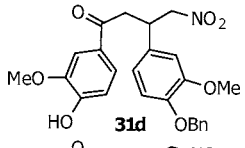
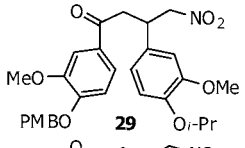
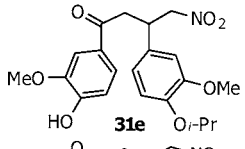
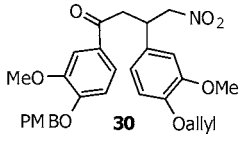
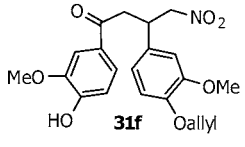
Table 3. Selective Deprotection of Aromatic Ethers **14**−**16**[a]

compound	product	acid[b]	temp (°C)	time (h)	yield (%)
 **14**	 **17**	A	65	72	37
		B	80	7	62
 **15**	 **18** + **19**	A	65	5	60
		B	65	3	58
 **16**	 **18** + **20**	A	80	3	80
		B	80	0.33	77

[a] Unless otherwise noted, the reactions were performed with 0.6 equiv of acids with no methanol added as additive. Solid-supported acids were removed when starting materials were completely consumed as evident by tlc. [b] A = Amberlyst-15; B = PTS-Si. [c] *C*-Benzylated byproduct **19** was isolated in 13% yield and 11% yield when Amberlyst-15 and PTS-Si were employed, respectively. [d] Methanol (4 equiv) was added as additive. [e] Compound **20** was isolated in 7% yield and 2% yield when Amberlyst-15 and PTS-Si were employed, respectively.

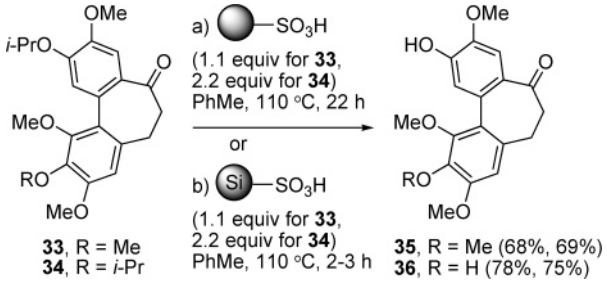
trimethoxylated benzyl > benzyl > allyl > isopropyl groups, which reflects both the stability of the carbocations and their reactivity toward quenching. Substoichiometric or stoichiometric amounts of acids are generally required to effectively cleave the aromatic ethers under relatively mild reaction conditions. Immobilization of acids on the solid supports provides good to excellent selectivity in the removal of protecting groups even when they were simultaneously present in the same molecule. Generality and selectivity of the solid-supported acids in the deprotection of aromatic ethers should be applicable in devising strategies for introducing and removing protecting groups in complex syntheses and thus should prove useful in protecting group manipulation.

Table 4. Selective Deprotection of Chalcone-Derived Aromatic Ethers **25**−**30** to Products **31a**−**f** [a]

compound	product	yield of **31** (%)[b]
 **25**	 **31a**	64[c], 87
 **26**	 **31b**	54[d], 62
 **27**	 **31c**	56, 62
 **28**	 **31d**	65, 91
 **29**	 **31e**	81, 90
 **30**	 **31f**	69, 75

[a] 1.1 equiv of Amberlyst-15 or PTS-Si in PhMe at 65 °C for 1−3 h. [b] Isolated yields (yields with Amberlyst-15, yields with PTS-Si). [c] 23% of **32** was obtained. [d] 5% of **32** was obtained.

Scheme 2. Deprotection of Isopropyl Groups on the Biaryl System of the Allocolchicine Skeleton



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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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