

Practical, environment-benign and atom economic KOAc-catalysed deprotection of aryl TIPS ethers under mild fluoride-free conditions†

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A KOAc-catalysed, fluoride-free protocol not only effects chemoselective deprotection of phenolic TIPS ethers without affecting acetal, ketal, carbamate, *O*-acetyl and aliphatic silyl ethers, but also improves its atom economy by recycling the silanol byproduct.

Trialkylsilyls are widely used for the protection of phenols and alcohols.¹ Triisopropylsilyl (TIPS)² group is a representative of bulky and robust silyl protections.^{1,3} In addition, the steric effect of TIPS was often exploited to control the regio- and stereoselectivity, making it a useful directing group.³ For example, phenolic TIPS protection withstood the Snieckus lithiation and effectively directed the reaction away from the siloxyl group.⁴

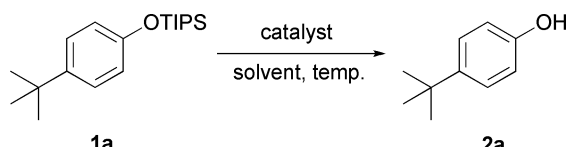
Compared to other members of the silyl family, TIPS often enjoyed greater stability under various conditions. In other words, the cleavage of TIPS ethers usually required harsh conditions such as excess fluoride sources (TBAF,^{5a-c} HF,^{5d-f} Et₃N·HF,^{5g,h} Py·HF,⁵ⁱ CsF^{5j,k}), strong acids (HCl,^{6a-c} TFA^{6d}) or strong base (KOH).⁷ Apparently, these protocols are incompatible with many sensitive functions and delicate structures, limiting the utility of TIPS in the synthesis of complex molecules.⁸ Furthermore, excess fluoride is not only ineconomical but also an environmental and operational concern, especially on an industrial scale.⁹ Efforts toward the development of a green deprotection method for TIPS have not been reported. Also, since TIPS was usually considered very robust, its preferential removal in the presence of other silyls has only been achieved in very special cases, where the steric or electronic factors were greatly biased.¹⁰ To our knowledge, no precedence has been documented for selective removal of phenolic TIPS ether without affecting another aryl silyl ether.

Traditionally, protective group chemistry is almost antithetical to atom economy.¹¹ This is exactly the case for fluoride-mediated desilylation, whose byproduct fluorosilanes are waste. However, we see alkali acetates, a class of mild Lewis base, as a solution to the above issues. As a part of our project on new chemistry of silyl protections,¹² herein we report a green and

atom economic deprotection protocol for aryl TIPS ethers, using an environment-benign catalyst KOAc under mild fluoride-free conditions.

Catalyst screening was carried out with an emphasis on reagent availability and cost, using 4-*t*-butylphenyl TIPS ether **1a** as the benchmark substrate (Table 1). To our delight, most alkali acetates as well as analogous quaternary ammonium salts were found to effect clean reaction (entries 1–5). Interestingly, in contrast to the deprotection of aryl TBS ethers,¹² the lower the cation Lewis acidity, the faster the reaction. Shifting the Lewis base to benzoate resulted in lower reaction rate, in line with the nucleophilicity of the anion (entry 6). Meanwhile, transition metal acetates such as Cu(OAc)₂, Pd(OAc)₂ and AgOAc were all inactive due to tight association of the cations to acetoxy anion, and **1a** was fully recovered. On consideration of environment-friendliness and economy, KOAc represented the best choice and was used throughout our subsequent study. With regard to the solvent, only DMF worked well, and the reaction did not proceed in other protic or aprotic solvents such as EtOH, THF and MeCN. Similar to the case of aryl TBS ethers, water was an essential additive to maintain the catalytic cycle (entry 9), otherwise a stoichiometric amount of KOAc and considerably longer reaction time is required. The optimum water content was determined to be 5 vol% (DMF–H₂O 20 : 1), which produced the highest reaction rate. Thus inexpensive and commercially available catalyst and solvent can be used as received, without

Table 1 Catalyst screening



Entry	Catalyst (mol%)	Solvent	T (°C)/t (h)	2a (%) ^a
1	LiOAc·2H ₂ O (20)	DMF–H ₂ O (50 : 1)	70/20	95
2	NaOAc (20)	DMF–H ₂ O (50 : 1)	70/20	83 (11)
3	KOAc (20)	DMF–H ₂ O (50 : 1)	70/20	96
4	CsOAc (20)	DMF–H ₂ O (50 : 1)	70/10	97
5	Bu ₄ NOAc (20)	DMF–H ₂ O (50 : 1)	70/6	95
6	NaOBz (20)	DMF–H ₂ O (50 : 1)	70/20	82 (12)
7	Cu(OAc) ₂ (50)	DMF–H ₂ O (50 : 1)	70/6	0 (>95)
8	KOAc (20)	EtOH–H ₂ O (10 : 1)	70/12	0 (>95)
9	KOAc (120)	DMF ^b	70/40	93
10	KOAc (20)	DMF–H ₂ O (20 : 1)	70/9	95
11	KOAc (20)	DMF–H ₂ O (10 : 1)	70/16	94
12	KOAc (5)	DMF–H ₂ O (20 : 1)	70/32	95

^a Isolated yields, recovery of **1a** in parentheses. ^b Anhydrous DMF.

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Table 2 KOAc-catalysed deprotection of aryl TIPS ethers

Entry	TIPS ethers (1)	<i>T</i> (°C)	Time (h)	2 (%) ^a
1	4-MeOC ₆ H ₄ OTIPS (1b)	70	8	91
2	4-H ₂ NC ₆ H ₄ OTIPS (1c)	70	22	90
3	4-BocNHC ₆ H ₄ OTIPS (1d)	70	6	93
4	2,4,6-Me ₃ C ₆ H ₂ OTIPS (1e)	70	20	90
5	1-Naph-OTIPS (1f)	25	14	96
6	4-BrC ₆ H ₄ OTIPS (1g)	25	5	91
7	2-O ₂ NC ₆ H ₄ OTIPS (1h)	25	1	92
8	3-NCC ₆ H ₄ OTIPS (1i)	25	14	96
9	2-OHCC ₆ H ₄ OTIPS (1j)	25	1.5	96
10	3-OHCC ₆ H ₄ OTIPS (1k)	25	13	92
11	4-OHCC ₆ H ₄ OTIPS (1l)	25	1	97
12	2-AcC ₆ H ₄ OTIPS (1m)	25	11	95
13	3-Py-OTIPS (1n)	25	4	89
14	3-Py-OTIPS (1o)	25	20	92

^a Isolated yields.

the need of meticulous pretreatment. The deprotection worked well under a catalyst loading as low as 5 mol% to give an uncompromised yield (entry 12), demonstrating the effectiveness of this catalytic process.

With the optimal conditions in hand, the scope of this catalytic desilylation protocol was examined (Table 2). The deprotection of electron-rich or highly hindered substrates was smoothly achieved at 70 °C (entries 1–4). Free amino group and the acid-sensitive *N*-Boc protection were both tolerated. The deblocking of substrates with halogens or EWG substituents can be carried out efficiently at RT in excellent yields (entries 5–12). In addition, TIPS derivatives of 3-hydroxypyridine as well as a base-labile enol were also cleanly removed (entries 13, 14). Thus 10 mol% KOAc effectively replaced stoichiometric amounts of fluorides in conventional procedures.^{5–7}

Next, we probed the chemoselectivity between TIPS and other common protective groups for hydroxyl including TBS, TBDPS and TES (Table 3). Gratifyingly, TBS protections of primary and allylic alcohols were both intact under KOAc catalysis (entries 1, 2). Moreover, phenolic TBDPS protection, which was reportedly far more base-labile than TIPS,¹³ could be retained during the deprotection of the latter (entry 3). Such counter-intuitive chemoselectivity is unprecedented and valuable. In addition, acetates of phenol and primary alcohol were also well-preserved (entries 4, 5). This is particularly noteworthy since phenol acetates are highly base-sensitive and incompatible with strong bases such as KOH or even alkali carbonates in alcoholic solvents.¹⁴ Furthermore, as anticipated, acid-labile THP and acetal protections were unaffected (entries 6, 7), thus complementing literature protocols using strong acids.^{5,6} Conceivably, other acetal-type protections such as MOM, MEM, BOM, acetonide and ketal can all be tolerated. It should also be mentioned that although acetoxy anion could serve as a nucleophile, in the present protocol terminal mono-substituted epoxide was intact (entry

Table 3 KOAc-catalysed chemoselective deprotection of aryl TIPS ethers^a

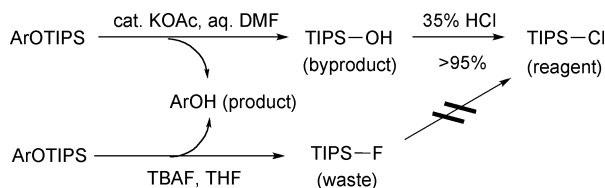
Entry	Aryl TIPS ethers (1)	<i>T</i> (°C)/time (h)	Yield (%) ^b
1	(1p) 	25/24	93
2	(1q) 	50/11	90
3	(1r) 	25/24	74
4	(1s) 	25/11	92
5	(1t) 	25/24	96
6	(1u) 	25/21	96
7	(1v) 	25/4	92
8	(1w) 	25/24	90
9	(1x) 	40/9	93

^a Arrow indicates selectivity for substrate bearing two silyl groups.
^b Isolated yields.

8). More significantly, orthogonal deprotection of phenolic TIPS in the presence of a secondary aliphatic TES ether was feasible (entry 9). To the best of our knowledge, such chemoselectivity is unprecedented.

The green and practicable aspect of our protocol is also demonstrated in the workup. In contrast to TBAF-mediated desilylation, our method is amenable to non-aqueous workup. This is a significant advantage, as aqueous workup could be tedious and produce a large volume of waste. For large-scale reactions, the solvent and the byproduct TIPSOH can be recovered by fractional distillation, while the crude product can be separated from KOAc by simply dissolving in a small volume of green solvent (EtOAc) followed by filtration. If desired, the recovered catalyst can also be reused directly.

Although protective group chemistry has been notoriously low in atom economy, this is no longer the case here (Scheme 1). The sole byproduct of this protocol, namely *i*-Pr₃SiOH, can be conveniently converted back to the protecting reagent TIPSCl in 99% yield by stirring with conc. HCl (no organic solvent needed).¹⁵ This is in stark contrast with fluoride-mediated



Scheme 1 Comparison of desilylation methods: recyclability of the silicon byproducts.

desilylations which yield TIPSF, a non-convertible waste. Hence our protocol renders TIPS a recyclable silyl protective group for solution-phase synthesis.

As alkali acetates exhibited different trends of activity in the deprotection of aryl TBS¹² and TIPS ethers, respectively, we reasoned that for the latter, Lewis base-catalysis was the predominant mechanism. The unique structural character of TIPS contributed to its vulnerability toward Lewis bases. The extraordinarily large cone angle (160°, typical 118–145°)¹⁶ and long Si–C bond (1.919 Å, typical 1.870 Å)¹⁷ of TIPS render the silicon atom geometrically exposed to external nucleophiles. Thus, a mechanism involving direct attack of the Si center by acetoxy anion, possibly with the assistance of hydrogen bonding between water and the outgoing aryloxy anion, is plausible (Fig. 1).

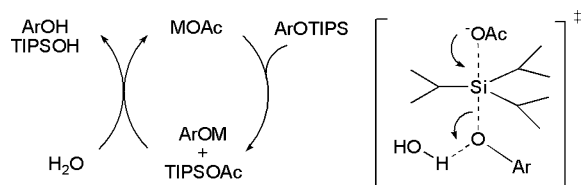


Fig. 1 Plausible catalytic cycle and transition state.

In summary, we have developed a green deprotection protocol for phenolic TIPS protection using catalytic amount of KOAc under fluoride-free conditions.¹⁸ The solvent, catalyst, and silanol byproduct can all be recycled, minimising waste production. Other notable benefits include operational simplicity, economy and environmental friendliness. Excellent functional group compatibility and chemoselectivity have been achieved. In particular, aryl TIPS ethers are orthogonally cleaved in the presence of alkyl silyl ethers, acetates, carbamates and epoxides. We believe that our protocol would significantly expand the utility of TIPS in both academia and industry. More detailed mechanistic study is in progress, and extension of Lewis base catalysis to other aspects of silicon chemistry is currently being pursued in this laboratory.

Acknowledgements

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