Thiol Catalyzed Aerobic Debenzylation of Alcohols and Amines

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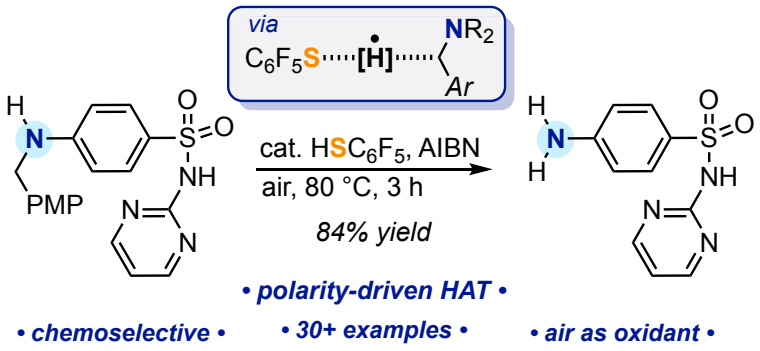


ABSTRACT: We report a radical method for the removal of benzyl and *p*-methoxybenzyl groups from amines and alcohols using a selective hydrogen-atom abstraction under aerobic conditions. The key usage of the strongly electrophilic thiyl radical derived from commercially available pentafluorothiophenol as the H-atom abstracting agent allowed for a chemoselective abstraction process leading to C-N or C-O bond cleavage. This approach is applicable to an array of alcohols and amines, operating under aerobic conditions with no need for further addition of a stoichiometric external oxidant or hazardous reagents.

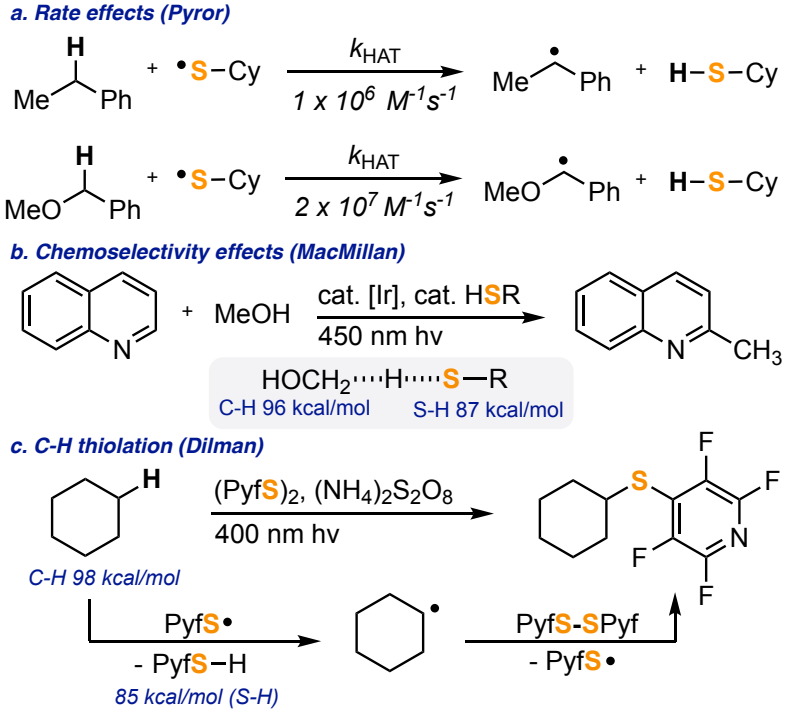
Introduction

Radical C-H abstraction has long been considered in C-H activation. Many free radical species undergo non-selective H-atom abstractions and consequently are implicated in cellular and DNA damage pathways.[1] However, increased reports that demonstrate the ability of tailored heteroatom-centered radicals to perform selective atom-abstractions highlights the potential of this activation strategy for chemical synthesis.[2] Thiols and their corresponding thiyl radicals are ubiquitous throughout radical chemistry,[3] serving as H-atom donors due to their relatively weak S-H bonds (80-90 kcal/mol)[4] and rapid rates of H-atom transfer (HAT ~10^5-10^8 $M^{-1}s^{-1}$).[3]

The electrophilic character of thiyl radicals favors abstraction of H-atoms from silanes (Si-H),[5] boranes (B-H),[6] aldehydes (OC-H),[7] and C-H bonds adjacent to heteroatoms.[8] Well-documented polarity effects in radical-mediated atom abstractions are evident in the relative rates of H-atom transfer to thiyl radicals as well as chemoselectivity.[9] Pryor and coworkers observed that cyclohexanethiyl radical abstracted the more electron-rich secondary benzylic H-atoms from benzyl-methyl ether 20x faster than from ethyl benzene (Scheme 1a).[10] MacMillan and

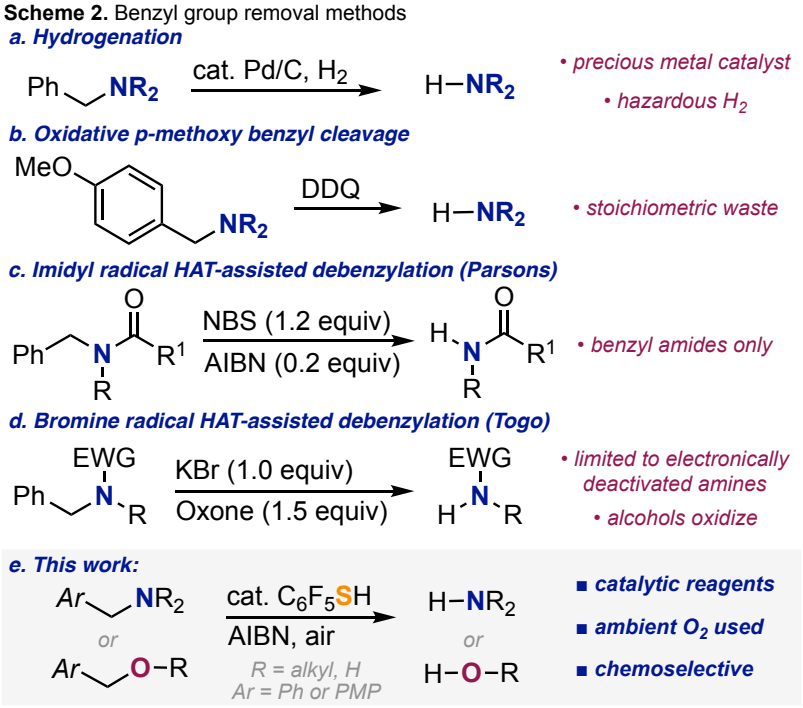
coworkers used ethyl-2-mercatopriopionate thiyl radical to abstract an electron-rich 1° methyl H-atom from methanol overcoming a ~9 kcal/mol uphill barrier to achieve arene alkylations (Scheme 1b).[11] Dilman and coworkers recently reported a radical-mediated thiolation of electronically unactivated alkanes.[12] Generated by purple-light-mediated homolytic disulfide bond cleavage, tetrafluoropyridinyl thiyl radical performed an estimated 13 kcal/mol uphill H-atom abstraction from alkane substrates after which the C-centered radical was rapidly trapped by a second equivalent of the disulfide reagent.

Scheme 1. Polarity effects of thiyl radical HAT



The strategic use of protecting groups is a common, and sometimes unavoidable, process in the construction of complex molecules,[13] with benzyl (Bn) and *p*-methoxybenzyl (PMB) being favorable for hydroxyl and amino groups due to the relative ease of installation and removal. However, common methods for the removal of Bn and PMB groups using heterogeneous palladium hydrogenolysis[14] (Scheme 2a) or stoichiometric oxidative cleavage[15] (Scheme 2b), respectively offer further sustainable chemistry development opportunities that would obviate the use of precious transition metals, hazardous hydrogen gas, or stoichiometric waste.[16] HAT-Mediated radical debenzylation strategies offer some sustainability benefits and potential functional group compatibility advantages but often require super-stoichiometric HAT reagent sources such as *N*-bromosuccinimide (NBS) (Scheme 2c)[17] or an Oxone/KBr couple (Scheme 2d),[18] are limited to electron deficient amino functionalities[17,18] and in the case of *O*-benzyl alcohols, may result in oxidation to the ketone following debenzylation.[18] Herein we report a HAT-mediated debenzylation protocol using a catalytic amount of a commercially available thiol and atmospheric O_2 as the terminal oxidant[19] that is applicable to a variety of functionalized alcohol and amine substrates (Scheme 2e). This approach operates with predictable chemoselectivity and is amenable to substrates that would be challenging for hydrogenolysis, oxidative cleavage, or acidic deprotection strategies.

Scheme 2. Benzyl group removal methods

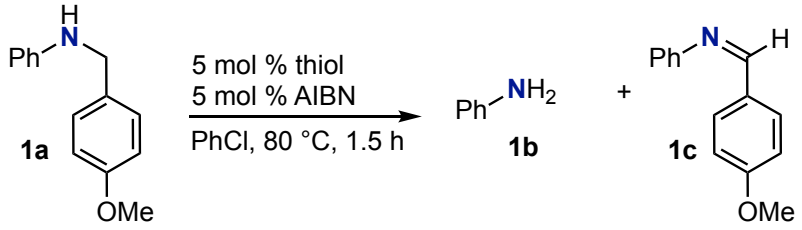


Results

Bertrand and co-workers had previously observed the formation of an *E*/*Z* mixture of 1-phenyl-*N*-(1-phenylethyl)ethan-1-imine from treatment of 1-phenylethan-1-amine to aryl thiols.[20] This was proposed to have formed via benzylic H-atom abstraction followed by oxidation and primary amine condensation, and we had also observed substantial production of *p*-anisaldehyde and *N*-methylaniline when *N*-(*para*-methoxybenzyl)-*N*-methylaniline was treated to 10 mol % each of *tert*-butyl hyponitrite and methyl thioglycolate in a 3:1 mixture of *tert*-butyl acetate and water at 60 °C. We followed this with an experiment using *N*-PMB-aniline (**1a**), 5 mol % methyl thioglycolate, and 5 mol % 2-2'-azobis(2-methylpropionitrile) (AIBN) heated to 80 °C in chlorobenzene for 1.5 h which resulted in only 29% consumption of **1a** and a 11% combined yield of aniline **1b** and imine **1c** (Table 1, entry 1). While the PMB group remained attached in **1c**, we hypothesized that its formation was the result of either a) direct formation under the reaction conditions, or b) the in-situ condensation of liberated aniline and *p*-anisaldehyde.

The use of thiophenol in place of methyl thioglycolate failed to improve **1a** conversion (entry 2). These low conversions were attributed to aerobic decomposition of thiols and sulfur-containing compounds at elevated temperatures.[21,22] However, the use of pentafluorothiophenol (PFTP) achieved 68% conversion and a 41% total yield (entry 3). Extending reaction time to 3 h and using 10 mol % PFTP resulted in 94% conversion and a total yield of 91% divided 17:74 **1b**:**1c**. Including an acidic workup effectively funneled all material to aniline **1b** as the sole product isolated in 95% yield as the HCl salt (entry 4).[23] The individual exclusion of AIBN (entry 5), thiol (entry 6), or O_2 (entry 7), resulted in only trace amount of debenzylation. Combined, these results support debenzylation via a radical rather than acid-mediated pathway[24] and that thiol and oxygen are required reagents.

Table 1. Reaction optimization

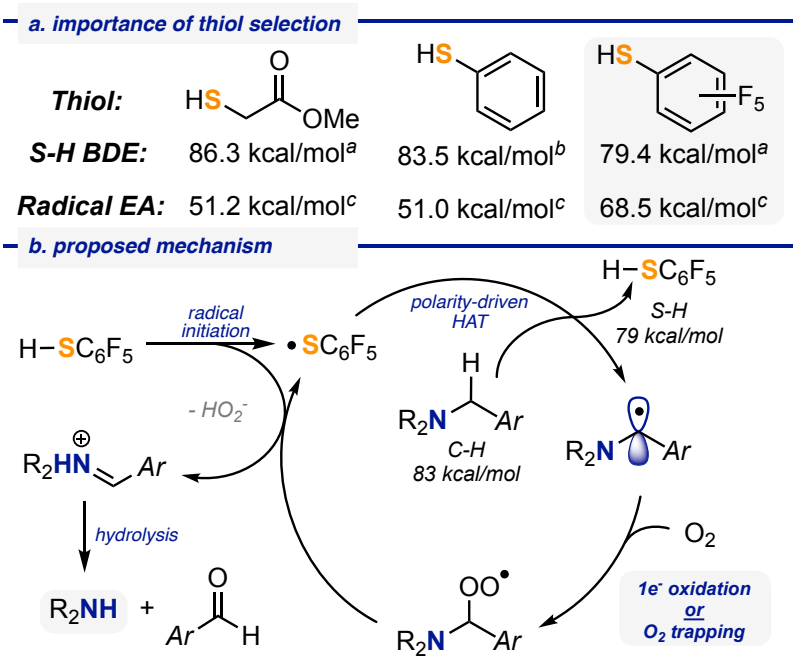


entry	reaction conditions[a]	**1a** conversion[b]	yield (**1b** : **1c**)[b]
1	methyl thioglycolate	29%	2% : 9%
2	thiophenol	33%	6% : 17%
3	HSC_6F_5	68%	9% : 32%
4	HSC_6F_5	94%	17% : 74%[c] (95% : 0%)[d]
5	HSC_6F_5, no initiator	7%	0% : 2%
6	no thiol	6%	0% : 3%
7	HSC_6F_5, degassed	20%	0% : 4%

[a]All reactions performed on a 0.2 mmol scale of **1a**. [b]Conversion and yields were determined by ^{1}H-NMR using dibromomethane as an internal standard from crude reaction mixtures. [c]10 mol % PFTP and 5 mol % AIBN used, with a subsequent addition of both every hour for a total reaction time of 3 h. [d] Yield following acid workup (See SI for details); **1b** isolated as HCl salt.

We turned to DFT to investigate the observed impact of thiol identity on debenzylation efficiency. We considered the S-H bond dissociation energies (BDE)[25] and the electron affinities (EA)[26] of the corresponding thiyl radicals of the three thiols investigated in Table 1 (Scheme 3a). These calculations indicated that PTFP had both the lowest S-H BDE (79.4 kcal/mol) and the greatest, most exothermic electron affinity (EA = 68.5 kcal/mol). While the inclusion of electron withdrawing groups often increases BDE, the presence of fluorine at the *ortho*- and *para*-positions of aryl thiols was demonstrated to decrease the S-H BDE, accounting for the ~4 kcal/mol S-H BDE difference between thiophenol and PFTP.[27] The electronegative nature of fluorine is likely responsible for the increased electron affinity of the pentafluorophenylthiyl radical relative to either methyl thioglycolate or thiophenol.[28] To further illustrate the importance of substrate electronics on the observed reactivity, we carried out side-by-side separate flask experiments using the benzyl and *para*-trifluoromethylbenzyl congeners of **1a** and observed significantly slower reactivity for these two substrates compared to the more electron-rich **1a** (see SI for details).

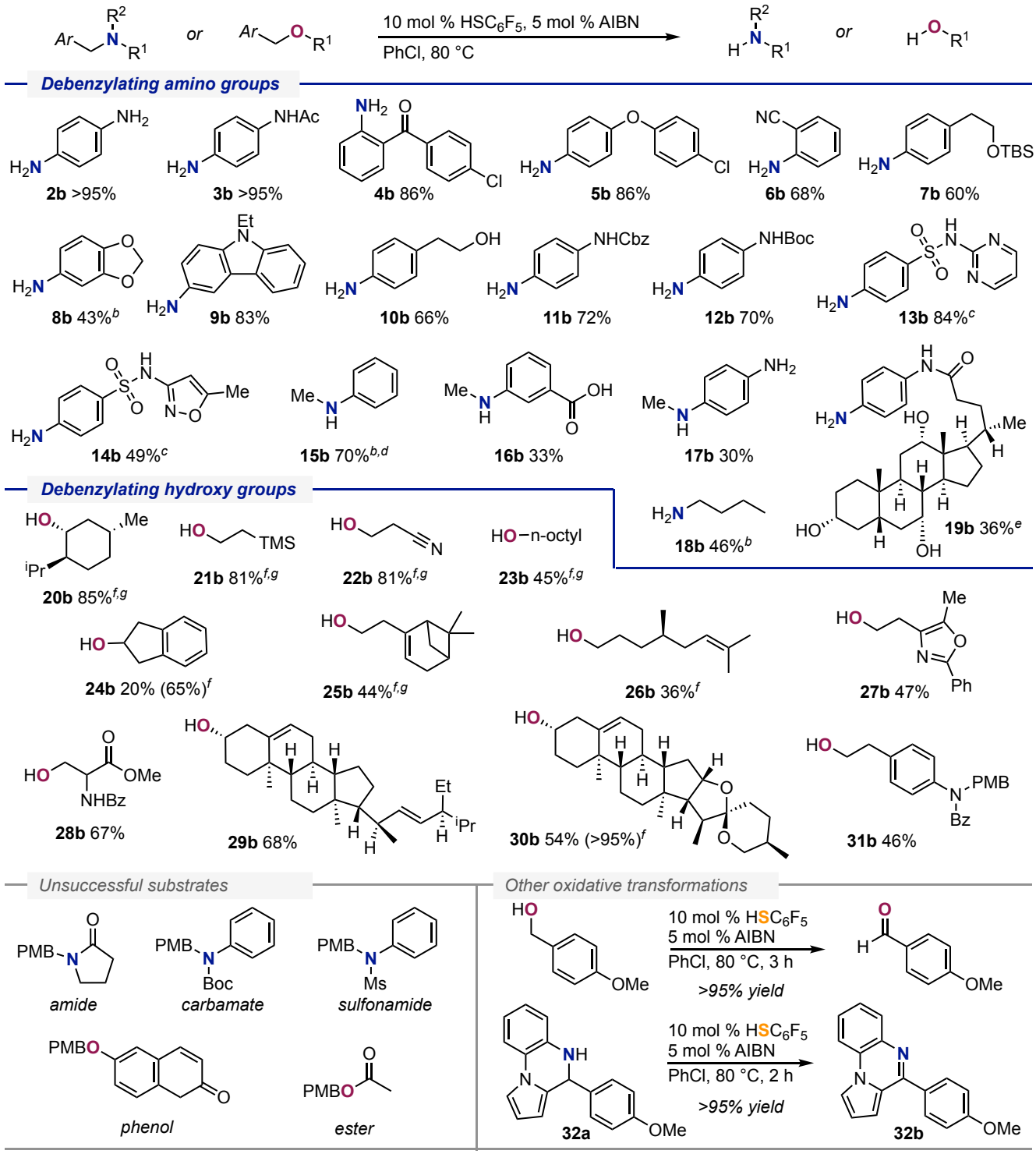
Scheme 3. Mechanistic considerations



[a]Thiol bond dissociation enthalpies were calculated at the wb97xd/6-311++g(d,p) level of theory and using the polarizable continuum model (integral equation formalism variant) with benzene as the solvent. [b]Value from ref. 27. [c]Radical electron affinity calculated at the B3LYP/6-311G(d,p) level of theory in the gas phase.

This collective data led to the proposed mechanism for thiol catalyzed, aerobic debenzylation shown in Scheme 3b. Radical initiation generates an electrophilic, thiyl radical from PFTP which then preferentially abstracts a relatively weak (~85 kcal/mol)[29], and electron-rich, benzylic H-atom from the substrate.[30] Notably, the most efficient thiyl radical precursor used contains the weakest S-H bond, making the proposed benzylic H-atom abstraction endothermic ($\Delta H \sim +4$ kcal/mol). Molecular oxygen may then either perform a single electron oxidation[31] or trap the benzylic α-amino C-centered radical[32] to generate a benzylic carbocation or peroxyl radical intermediate, respectively. Both pathways are kinetically and thermodynamically feasible and lead to a common benzylic peroxy radical intermediate.[33] Thiyl radical regenerating HAT from PFTP would generate a benzylic hydroperoxide from which elimination of hydrogen peroxide anion followed by hydrolysis furnishes the product.

Scheme 4. Debenzylation substrate scope[a]



[a]All reactions carried out using 1 equiv of benzylated amine or alcohol, 10 mol % pentafluorothiophenol, 5 mol % AIBN (refreshed every 1 h) at 80 °C in PhCl (1.0 M); 3 h total reaction time; yields are of isolated compounds following column chromatography. [b]Isolated as the hydrochloride salt. [c]MeCN used as solvent. [d]Obtained from the reaction with the benzyl starting material. [e]Reaction was performed with 2x thiol and initiator refreshes. [f]^{1}H-NMR yield determined using dibromomethane as internal standard from crude reaction mixture. [g]*t*-Butyl hyponitrite used as initiator at 50 °C.

We sought to explore the breadth and limitations of this selective thiyl radical H-atom abstraction for the removal of benzyl and PMB groups from amines and alcohols (Scheme 4). Primary, *para*-methoxybenzyl anilines were easily deprotected and were generally found to be the most efficient substrates. Aniline (**1b**) and phenylenediamine (**2b**) were isolated in near quantitative yields from their PMB analogs as was 4-amino acetamide **3b** without disruption of the acetamide group. Compounds containing potentially sensitive functionality such as ketones (**4b)**, bis-aryl ethers **(5b**), nitriles (**6b**), primary silyl ethers (**7b**), and acetals (**8b**) were similarly debenzylated in good yields. Carbazole **9a** underwent PMB removal to provide **9b** as did a substrate bearing a free hydroxyl group (**10b**). Carbamate functionality was well tolerated indicating that this approach chemoselectively removes PMB groups in the presence of Cbz which also contains α-amino benzylic C-H bonds (**11b**), and tolerates the acid labile Boc group (**12b**).[34] Debenzylation was successful to reveal sulfadiazine (**13b**) and sulfamethoxazole (**14b**), two potent antibacterial agents, as well as cholic acid derivative (**19b**), an essential component of bile acid synthesis. However, increasing the substitution at nitrogen generally decreased reaction efficiency (**15b**, **16b**, and **17b**), and *n*-butylamine (**18b**) was obtained in fair yield as it's HCl salt from *N*-(4-methoxybenzyl)butan-1-amine.

Alcohols including (-)-menthol (**20b**), acid sensitive 2-trimethylsilyl-1-ethanol (**21b**), and 3-hydroxypropanenitrile (**22b**) were similarly obtained from their PMB-derivatives in good yields. 1-Octanol (**23b**) and 2-indanol (**24b**) were analogously revealed from their corresponding benzyl-ethers. Unsaturated *O*-PMB ethers from (1*R*)-(-)-nopol (**25b**) and citronellol (**26b**) were successfully debenzylated in spite of the known propensity for thiyl radicals to participate in alkene additions.[35] Functionalized compounds including 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (**27b**), an *N*-benzoyl methyl ester serine derivate (**28b**), stigmasterol (**29b**), and diosgenin (**30b**) were all isolated from their *O*-PMB derivatives in good yields. Compound **31b** was isolated from its *O*-PMB congener leaving the *N*-PMB-amide intact, highlighting the chemoselectivity of this aerobic, thiol catalyzed approach.[36]

In contrast to previously reported HAT-mediated debenzylation protocols, electron deficient amino groups of amides, carbamates and sulfonamides were unreactive using this aerobic, thiyl radical approach, resulting in the recovery of starting material in each case.[17,18] The α-amino C-H bonds present in benzyl amides have significantly higher BDE[37] and decreased nucleophilicity compared to their amine analogs allowing for thiyl radical abstraction to discriminate between multiple, otherwise similar benzylic C-H bonds and provides complementary reactivity to existing stoichiometric HAT debenzylation approaches. Benzylated phenols and esters were not effectively cleaved. The electron-withdrawing properties of the ester acyl group is likely responsible for the disfavored H-atom abstraction. During our attempts to remove the PMB group from 6-hydroxycoumarin resulted in trace production of *p*-anisaldehyde along with the expected phenolic product suggesting that this small amount of phenol formed was sufficient to shunt reactivity and prevent additional conversion of the starting material.[38]

Further investigations revealed that these aerobic conditions allowed for the quantitative oxidation of *p*-methoxy benzyl alcohol to *p*-anisaldehyde and compound **32a** was easily oxidized to aromatic amine **32b**. Prior reports of this latter transformation required elevated temperatures (140 °C),[39] or strong oxidants ($KMnO_4$) to proceed.[40]

Reported herein is a mild, radical mediated method for the removal of benzyl and *p*-methoxybenzyl groups from amines and alcohols using commercially available pentafluorothiolphenol as a catalytic HAT-reagent. Combined experimental and computational mechanistic studies support a selective benzylic H-atom abstraction pathway. This process uses ambient air as the terminal oxidant with hazardous and/or stoichiometric reagents not required. Whereas thiols are most typically viewed as H-atom *donors* in radical processes, this approach hinges on the ability of a highly electrophilic thiyl radical to chemoselectively abstract electron-rich, benzylic H-atoms based on a combination of electronic and thermodynamic factors to achieve mild amine and alcohols debenzylations.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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[23] This reaction scaled to 1 mmol of 1a resulted in the isolation of **1b** as the HCl salt in 75% yield. See the SI for additional details.

[24] The pKa of pentafluorothiophenol has been determined to be 2.68 in H_2O as determined experimentally in: Jencks, W. P.; Salvesen, K. Equilibrium Deuterium Isotope Effects on the Ionization of Thiol Acids. *J. Am. Chem. Soc.* **1971**, *93*, 4433-4436. DOI: 10.1021/ja00747a016.

[25] The S-H bond dissociation enthalpies of pentafluorothiophenol and methylthioglycolate were calculated according to the method presented by Dilman in reference 12. The BDE for thiophenol was taken from Borges dos

Santosm R. M.; Muralha, V. S. F.; Correia, C. F.; Guedes, R. C.; Costa Cabral, B. J.; Martinho Simões, J. A. S-H Bond Dissociation Enthalpies in Thiophenols: A Time Resolved Photoacoustic Calorimetry and Quantum Chemistry Study. *J. Phys. Chem. A* **2002**, *106*, 9883-9889. DOI: 10.1021/jp025677i.

[26] The electron affinity of the methyl thioglycolate, thiophenol, and pentafluorothiophenol derived thiyl radicals were calculated according to the method presented in: Chandra, A. K.; Nam, P.-C.; Nguyen. The S-H Bond Dissociation Enthalpies and Acidities of Para and Meta Substituted Thiophenols: A Quantum Chemical Study. *J. Phys. Chem. A* **2003**, *107*, 9182-9188. DOI: 10.1021/jp035622w.

[27] Experimentally determined S-H BDE of thiophenol in benzene solution taken from: Borges dos Santos, R. M.; Muralha, V. S. F.; Correira, C. F.; Guedes, R. C.; Cabral, B. J. C.; Simões, J. A. M. S-H Bond Dissociation Enthalpies in Thiophenols: A Time-Resolved Photoacoustic Calorimetry and Quantum Chemistry Study. *J. Phys. Chem. A* **2002**, *106*, 9883-9889. DOI: 10.1021/jp025677i.

[28] We use electron affinity as an approximation for absolute electronegativity for two reasons: (a) electron affinity is directly correlated to absolute electronegativity as described in Mulliken, R. S. A New Electroaffinity Scale: Together with Data on Valence States and on Valence Ionization Potentials and Electron Affinities. *J. Chem. Phys. 2* **1934**, *2*, 782-793. DOI: 10.1063/1.1749394. (b) To the best of our ability, the heat of formation of the methyl thioglycolate cation could not be calculated due to the propensity for the molecule to fracture generating thioformaldehye and oxonium methyl ester cation ($^{+}$OCOMe). This value is necessary to determine the ionization potential for the methyl thioglycolate thiyl radical, which is in turn necessary to determine absolute electronegativity. The absolute electronegativity of the thiophenol and pentafluorothiophenol thiyl radicals were found to be 123 and 138 kcal/mol, respectively.

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