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$Ga(OTf)_3$-Catalyzed Direct Substitution of Alcohols with Sulfur Nucleophiles

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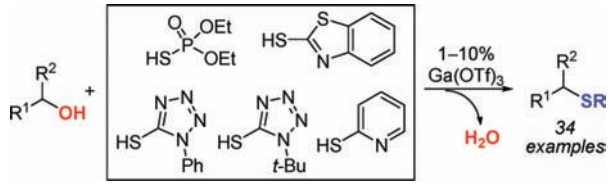
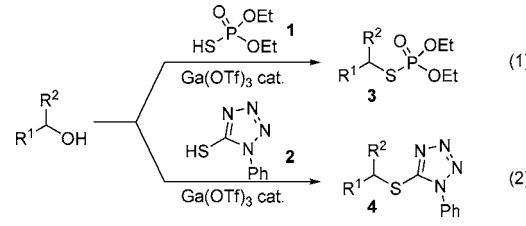
ABSTRACT



It is reported that $Ga(OTf)_3$ catalyzes the direct displacement of alcohols with sulfur nucleophiles. The products are versatile intermediates that can be utilized in carbon−carbon, carbon−sulfur bond formation or used in modified Julia olefination reactions. The only byproduct generated is water.

Sulfur-containing bioactive natural and pharmaceutical agents are prevalent and, among others,[1] include β-lactam and sulfonamide antibiotics, selective COX-II inhibitors, H_2-receptor antagonists,[2] pyrimidine thionucleosides,[3] penicillamine, glutathione, and immunoconjugates.[4] Because of the general availability and low cost of alcohols, the direct substitution of the hydroxyl functional group with sulfur nucleophiles is desirable. Although there are some examples of substitutions promoted by excess Brønsted acids, with the exception of a few reports,[5] these reactions are characterized by low yields, formation of undesired byproducts, and narrow substrate scope.[6] A limited number of Lewis acid promoted reactions are also known, but these typically require stoichiometric or near-stoichiometric amounts of catalyst.[7] The use of *catalytic* Lewis acids in the direct displacement of alcohols with sulfur nucleophiles is rare. Kagan and coworkers reported two examples in which $SmCl_3$ catalyzed the formation of thioethers from alcohols and thiols.[8] Hidai and Uemura demonstrated that cationic diruthenium complexes can promote the displacement of propargyl alcohols with thiols.[9]

Our own group reported the photochemically promoted substitution of alcohols with phosphorothioic acid **1**.[10] However, this transformation was limited to γ,γ-disubstituted allylic alcohols. Primary, secondary, and tertiary aliphatic alcohols and benzyl alcohols did not participate.



Herein we report that $Ga(OTf)_3$ catalyzes the direct displacement of a wide range of alcohols with phosphorothioic acid **1** and phenyltetrazole **2** (eqs 1, 2). $Ga(OTf)_3$ is an inexpensive, hydrolytically stable, oxygen-tolerant Lewis

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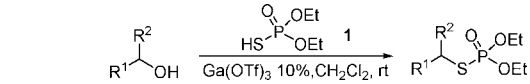
acid that was first utilized by Olah and Prakash,[11] then Kobayashi,[12] in a variety of transformations. The present work was inspired by Baba and co-workers who demonstrated that In(III) salts are effective catalysts for the direct substitution of alcohols with various carbon nucleophiles.[13] We have previously shown that phosphorothioic esters **3** are useful intermediates in transition-metal-free allylic alkylations[10] with Grignard reagents and one-step syntheses of thioethers.[14] Furthermore, compounds **1** and **3** are odorless, bench-stable compounds that are compatible with column chromatography. Others have demonstrated that phosphorothioate esters can be transformed to the corresponding alkenes[15] or converted to thiols via hydrolysis[16] or reduction.[17] Sulfides **4** are valuable because they can be oxidized to the corresponding sulfones and applied to Julia olefination reactions.[18]

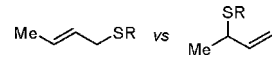
We selected benzyl alcohol (**5a**) and diethyl phosphorothioic acid (**1**) as the initial test substrates for optimization. When **1** and **5a** were aged at rt in the presence of 10 mol % $Ga(OTf)_3$, no reaction was observed. However, increasing the temperature to 60 °C in dichloroethane generated the desired product in good yield. A control reaction in which $Ga(OTf)_3$ was omitted furnished no observable product. The use of various In(III) catalysts resulted in inferior yields. With optimized conditions in hand, we surveyed the scope of the transformation (Table 1). The reaction is tolerant to oxygen, sulfur, and nitrogen heterocycles (entries 5−6, 9−10). Both primary and secondary alcohols are compatible if at least one of the substituents is aromatic or allylic. This method is amenable to both electron-donating and -withdrawing substituents (entries 2−6). Alcohols with all alkyl substituents participated only if they are tertiary (entry 14). For more active substrates, heating was not necessary.

Table 1. Scope of Substitution with Phosphorothioic Acid, **1**



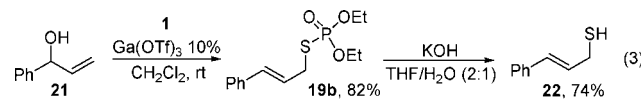
	alcohol	product[a]		alcohol	product[a]
1[b]	**5a**; R = H	**13a**; 80%	9[c]	**9**	**17**, 94%
2[b]	**5b**; R = 4-Cl	**13b**; 60%	10	**10**	**18**, 65%
3[b]	**5c**; R = 4-F	**13c**; 74%	11[b]	**11a**; R = Me	**19a**; 78%[e]
4	**5d**; R = 4-OMe	**13d**; 89%	12	**11b**; R = Ph	**19b**; 79%
5[c]	**6a**; X = O	**14a**; 63%[d]	13[c]	**11c**; R = 4-MeO-Ph	**19c**; 54%
6[c]	**6b**; X = S	**14b**; 89%	14[b]	**12**	**20**, 79%
7	**7a**	**15a**; 76%			
8	**8**	**16**, 64%			

[a] Isolated yield. [b] Conducted in dichloroethane at 60 °C. [c] 1% Ga $(OTf)_3$ used. [d] Product decomposes upon standing. [e] Isolated as a 3:1 mixture of regioisomers:



Other than **6a**, the alcohols in Table 1 do not undergo the photochemically promoted substitution described in our earlier publication.[10] In that report, we observed more facile substitution reactions for substrates in which cleavage of the carbon−oxygen bond results in highly stabilized carbocationic or radical intermediates. We suspect that the highly electron-rich nature of the furan ring in **6a** is why it is able to successfully undergo photolytic displacement. When geraniol (**8**), a γ,γ-disubstituted allylic alcohol, was subjected to the UV-promoted substitution, significant decomposition was observed.

Interestingly, the use of regioisomeric alcohols (**21** vs entry 12, Table 1) furnished identical products (eq 3). We also demonstrated that phosphorothioate esters can be efficiently hydrolyzed to the corresponding thiol with KOH in aqueous THF.



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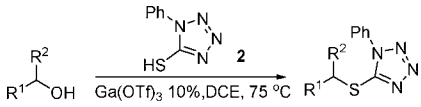
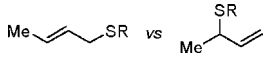
The substitution was extended to include phenyltetrazole **2** as the nucleophile (Table 2). As with phosphorothioic acid

Table 2. Scope of Substitution with Phenyltetrazole, **2**



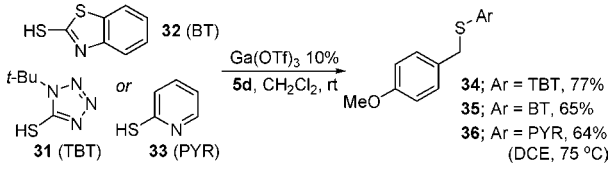
alcohol	product[a]		alcohol	product[a]
1	**5a**; R = H	**24a**; 75%	11 **9**	**27**, 92%
2	**5b**; R = 4-Cl	**24b**; 72%		
3	**5c**; R = 4-F	**24c**; 75%		
4[b]	**5d**; R = 4-OMe	**24d**; 94%		
5	**5e**; R = 2-NH_2	**24e**; 59%		
6	**5f**; R = 4-CO_2Me	**24f**; 61%		
12 **10**				**28**, 82%
7[b]	**6a**; X = O	**25a**; 52%	13	**11a**; R = Me **29a**; 64%[c]
8[b]	**6b**; X = S	**25b**; 84%	14	**11b**; R = Ph **29b**; 58%
			15[b]	**11c**; R = 4-MeO-Ph **29c**; 75%
9[b]	**7a**; R = H	**26a**; 64%	16[b] **23**	**30**, 91%
10[b]	**7b**; R = F	**26b**; 71%		

[a] Isolated yield. [b] Conducted in DCM at rt. [c] Isolated as a 3:1 mixture of regiosomers:



1, the reaction exhibited broad generality for a range of alcohols. Electron-donating and -withdrawing functionality as well as oxygen, sulfur, and nitrogen heterocycles, free amines, and esters were well tolerated (entries 5−6). Three other thiols commonly utilized in sulfone olefination reactions were also examined (Scheme 1). In principle, this

Scheme 1. Substitution with Other Julia Olefination Thiols

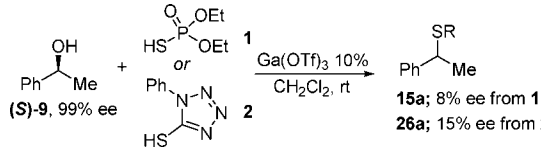


methodology can be extended to sulfur nucleophiles other than **1**−**2** and **31**−**33**. These results will be reported in a full paper.

The products obtained in Table 2 and Scheme 1 are important because they can be further oxidized to the corresponding sulfones for use in Julia-type olefination reactions. Conventional methods for synthesizing these sulfides typically employ the Mitsunobu reaction[19] between an alcohol and **2**. However, the Mitsunobu reaction is an inherently nonatom economical process which produces stoichiometric amounts of hydrazine dicarboxylate and triphenylphosphine oxide byproducts, of which the latter can sometimes be difficult to separate from the desired product. In contrast, the only byproduct generated in our method is water.

We then performed the $Ga(OTf)_3$-catalyzed sulfur substitution reaction on enantioenriched alcohol (*S*)-**9** with both phosphorothioic acid **1** and phenyltetrazole **2** under optimized conditions (Scheme 2). In both instances, the expected

Scheme 2. Substitution with Enantioenriched Alcohol, (*S*)-**9**



product was isolated in good yield but in nearly racemic form. These results, taken together with the fact that regioisomeric starting materials converge to a single product (eq 3 vs Table 1, entry 12), provide strong evidence that prochiral carbocationic intermediates are involved in the reaction.

In summary, we have described the direct substitution of alcohols with phosphorothioic acid **1**, phenyltetrazole **2**, and other heteroaromatic thiols catalyzed by $Ga(OTf)_3$. Broad versatility has been demonstrated with respect to the alcohols that participate in the reaction. This method provides an alternative means for preparing two useful classes of sulfur-containing compounds.

Acknowledgment. The authors are grateful to Dartmouth College and the Walter and Constance Burke Foundation for their generous financial support.

Supporting Information Available: Experimental procedures and spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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