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Mild Two-Step Process for the Transition-Metal-Free Synthesis of Carbon−Carbon Bonds from Allylic Alcohols/Ethers and Grignard Reagents

Xinping Han, Yanhua Zhang, and Jimmy Wu*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received January 27, 2010; E-mail: jimmy.wu@dartmouth.edu

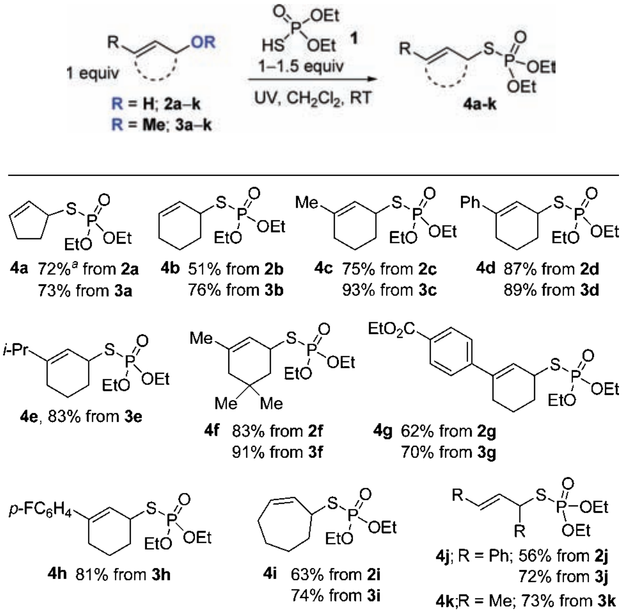
In contrast to the immense amount of effort devoted to developing transition-metal-mediated allylic substitution reactions with soft nucleophiles (the Tsuji−Trost reaction),[1] far fewer methods exist for allylic substitution reactions utilizing hard nucleophiles such as Grignard reagents.[2] Substitution reactions with Grignard nucleophiles are predominantly catalyzed by Cu(I) salts,[3] although variants promoted by other transition metals are also known.[4] Uncatalyzed reactions with Grignard reagents are rare and suffer from problems such as poor yields and regioselectivities.[5] In recent years, there has been an intense push toward developing chemistry that is more environmentally benign. A part of this larger goal is a reduction in the use of transition metals, which can sometimes be toxic, expensive, or difficult to properly dispose of in large quantities. *Herein we report a mild two-step procedure for the regioselective, transition-metal-free allylic substitution reaction between Grignard reagents and phosphorothioate esters prepared from the corresponding allylic alcohols and ethers.*

Recently, several groups have reported that under certain limited conditions, allylic alcohols and ethers can be used directly in substitution reactions with soft nucleophiles.[6] While there have been scattered reports of the direct use of allylic ethers as electrophiles, many of these examples required stoichiometric additives.[7] Grignard reagents have been used as nucleophiles with substrates containing heteroatom directing groups.[8] Because of their stability toward most reaction conditions, including those that are not compatible with typical leaving groups utilized in allylic alkylation reactions, such as acetates and carbonates, unactivated alkyl ethers could potentially serve as useful protecting groups for allylic alcohols. However, protecting-group strategies involving methyl ethers are less frequently seen in synthesis because their high stabilities often require the use of harsh deprotection methods (e.g., BBr_3, TMSI, $AlBr_3$, etc.) that may not be compatible with other functional groups in the rest of the molecule.[9]

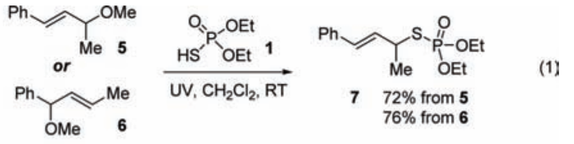
While attempting to carry out a photochemical thiol−ene[10] reaction between cyclopentenyl methyl ether and diethylphosphorothioic acid ($\lambda > 300$ nm, CH_2Cl_2, rt, 2 h), we were surprised that the expected saturated product was not obtained. Instead, we isolated **4a** (73% yield), in which substitution of the methyl ether had occurred. Furthermore, attempts to promote substitution reactions between allylic ethers and other sulfur nucleophiles (i.e., thioacetic acid) with *p*-TsOH resulted in decomposition. Intrigued by the mild conditions under which the allylic methyl ether had been removed, we decided to explore the scope of the substitution reaction.

A wide range of substituted acyclic and cyclic alcohols and ethers are compatible with the reaction (Table 1). Importantly, the use of trisubstituted alkenes furnished products **4c**−**h** as single regioisomers, while the reactions between **1** and either of the regioisomeric allylic ethers **5** or **6** furnished the same product **7** in good yields (eq 1). The scope of the allylic thiolation reaction was then expanded to include protecting groups commonly used for alcohols, such as benzyl, *tert*-butyldimethylsilyl (TBS), and benzoyl ethers (eq 2).

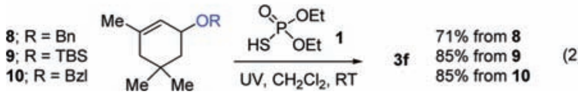
Table 1. Scope of the Alcohol and Ether Substitution Reaction



[a] Isolated yield after silica gel chromatography.

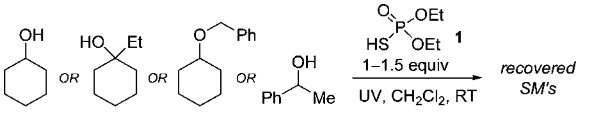


(1)



(2)

Attempts to carry out substitution reactions with various secondary and tertiary aliphatic and/or benzylic alcohols and ethers resulted only in the recovery of starting materials (eq 3). When we conducted a competition experiment between secondary, tertiary, and allylic alcohols, only the product resulting from substitution of the allylic alcohol was observed (eq 4). These results suggest that the thiolation reaction may be specific to allylic leaving groups.



(3)

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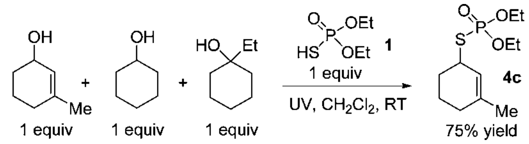


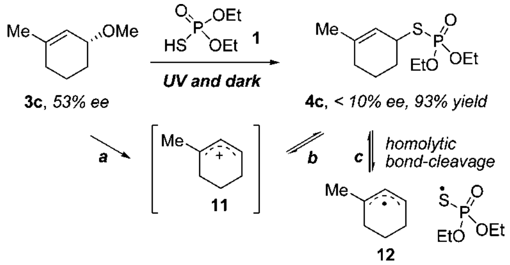
(4)

Conveniently, compound **1** is an odorless oil that can be prepared in multigram quantities from diethyl phosphite and S_8 in one step with no purification necessary. Furthermore, unlike secondary allylic phosphate esters, which are highly moisture sensitive,[11] phosphorothioate esters **4a**−**k** and **7** are robust compounds that can be chromatographed and stored for extended periods without any special precautions.

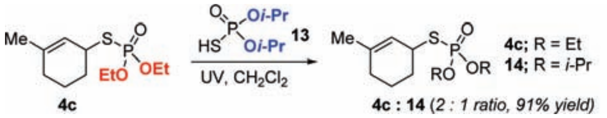
Control experiments indicated that although the use of UV light had an appreciable accelerative effect on the observed reaction rate, its presence was not required.[12] The reaction between **1** and 2-cyclohexen-1-ol was conducted in the presence and in the absence of UV light while maintaining the same internal temperature. The reaction conducted with UV light was appreciably faster than the corresponding dark reaction.

To determine whether or not the allylic thiolation reaction is stereospecific, we carried out the substitution reaction on scalemic allylic ether **3c**, which was prepared via Corey−Bakshi−Shibata reduction of the corresponding ketone followed by methylation. When **3c** was treated with **1** in the presence of UV light or in the dark, nearly racemic phosphorothioate ester **4c** was obtained (Scheme 1). The observation that racemization and convergence of regioisomeric allylic ethers to a single product occurs (eq 1) suggests the formation of prochiral common intermediates. Among other possibilities, we postulate that these intermediates can be either allylic carbocations derived from heterolytic ionization of starting materials/products (path a/b) and/or allylic radicals generated from homolytic photochemical cleavage[13] of the carbon−sulfur bond of the product (path c). We believe that the minimal amount of residual enantioenrichment that is observed may arise from the formation of tight or solvent-separated ion pairs.[14]

Scheme 1. Proposed Mechanism for Product Racemization

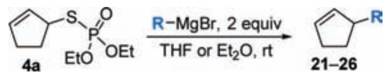


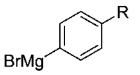
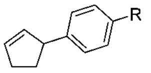
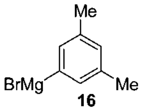
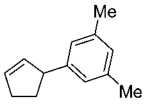
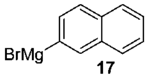
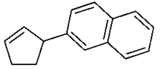
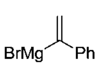
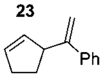
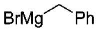
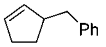
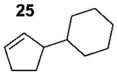
While it is possible that reactions via paths a, b, and c may all occur simultaneously, we conducted crossover experiments supporting the premise that allylic phosphorothioates are potentially photolabile functional groups (Scheme 1, path b/c). When a 1:1 mixture of **4c** and diisopropylphosphorothioic acid **13** was exposed to UV light (eq 5), we obtained a 2:1 mixture of diethyl and diisopropyl phosphorothioate esters (**4c** and **14**, respectively). **4c** was recovered nearly quantitatively when the reaction was conducted in the absence of UV light.



(5)

Table 2. Scope of the Grignard Coupling Reaction with **4a**



entry	Grignard	product	yield (%)[a]
			
1	**15a**; R = H	**21a**; R = H	83
2	**15b**; R = Ph	**21b**; R = Ph	81
3	**15c**; R = CF_3	**21c**; R = CF_3	78
4	**15d**; R = F	**21d**; R = F	79
5	**15e**; R = CN	**21e**; R = CN	59[b]
6	**15f**; R = CO_2Me	**21f**; R = CO_2Me	57[b]
7	**15g**; R = OMe	**21g**; R = OMe	77
8	 **16**	 **22**	71
9	 **17**	 **23**	75
10	 **18**	 **24**	56
11	 **19**	 **25**	89
12	 **20**	 **26**	75

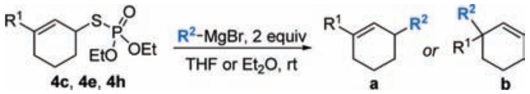
[a] Isolated yield. [b] Product coeluted with the protonated Grignard reagent. Yields were somewhat lower because of physical losses in the isolation process.

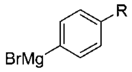
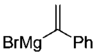
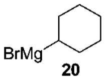
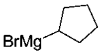
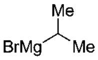
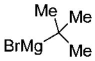
With allylic phosphorothioate esters in hand, we then proceeded to examine their effectiveness as electrophiles in uncatalyzed C−C bond-forming reactions with Grignard reagents. From Table 2, it is apparent that the alkylation reaction with **4a** is broadly applicable to a wide range of nucleophiles. The reaction is tolerant of both electron-withdrawing (entries 3−6) and donating (entry 7) groups as well as vinylic substrates (entry 10). Moreover, both primary and secondary alkyl Grignard reagents also participate in the substitution reaction (entries 11 and 12). To the best of our knowledge, the use of allylic phosphorothioate esters in C−C bond-forming reactions with Grignard reagents or any other nucleophile has not been previously reported.[15]

In principle, the reaction of *substituted* allylic phosphorothioate esters can proceed by either an S_N2- or S_N2'-type mechanism, each of which furnishes a different regioisomeric product. We therefore surveyed the alkylation reactions between **4c**, **4e**, and **4h** and a range of nucleophiles (Table 3). The use of aromatic and alkenyl nucleophiles resulted in S_N2-type displacements (entries 1−6). However, we were pleased that the use of secondary aliphatic Grignard reagents resulted in a reversal of regioselectivity in which S_N2'-type substitution reactions dominated (entries 7−12). These are highly sterically congested compounds that possess adjacent quaternary and tertiary centers. We were also able to demonstrate that *t*-BuMgBr is capable of participating in the coupling reaction in which one of the products possesses adjacent quaternary carbon centers (entry 12).

The divergent regioselectivities of the products obtained with aliphatic and aromatic Grignard reagents can be partially rationalized by invoking a radical-based mechanism in the former case.

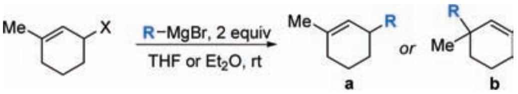
Table 3. Regioselective Grignard Coupling Reactions

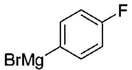
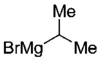


entry	R^1	Grignard	**a** : **b**[a]	major pdt	yield (%)[b]
1	Me	 **15a**; R = H	> 95 : 5	**30a**	--[c]
2	Me	**15c**; R = CF_3	> 95 : 5	**31a**	81
3	Me	**15d**; R = F	> 95 : 5	**32a**	75
4	*i*-Pr	**15d**; R = F	> 95 : 5	**33a**	70
5	*p*-FC_6H_4	**15d**; R = F	> 95 : 5	**34a**	70
6	Me	 **18**	> 95 : 5	**35a**	55
7	Me	 **20**	< 5 : 95	**36b**	81
8	*p*-FC_6H_4		15 : 85	**37b**	47
9	Me	 **27**	13: 87	**38b**	80
10	Me	 **28**	< 5 : 95	**39b**	86
11	*p*-FC_6H_4		15 : 85	**40b**	61
12	*p*-FC_6H_4	 **29**	1 : 1	**41a/b**	48

[a] Determined by ^{1}H NMR spectroscopy of unpurified material. [b] Isolated yield. [c] Yield could not be determined because of product decomposition (presumably via air oxidation) upon purification and standing in the rotary evaporator.

Table 4. Comparison Study with Other Allylic Electrophiles



entry	X	Grignard	product	**a** : **b**[a]	yield (%)[b]
1	**42;** X = Cl	 **15d**	**32a**	> 95 : 5	35
2	**43;** X = Br		**32a**	> 95 : 5	57
3	**42;** X = Cl	 **28**	**39a/b**	55 : 45	--[c]
4	**43;** X = Br		**39a/b**	60 : 40	--[c]

[a] Determined by ^{1}H NMR spectroscopy of unpurified material. [b] Isolated yield. [a] Yield could not be determined.

There is evidence that primary and secondary aliphatic Grignard reagents react with electrophiles such as allyl bromide via homolytic processes.[16] Zard and co-workers also observed S_N2' regioselectivity in the reactions between carbon-centered radicals generated from dithiocarbonates and allylic sulfones[17]/phosphonates.[18] In contrast, reactions with aromatic Grignards may proceed through a more ionic mechanism.

We then conducted a study comparing the efficiencies and regioselectivities of uncatalyzed C−C bond-forming reactions between Grignard reagents and secondary allylic chlorides and bromides[19] (Table 4) against C−C bond formation starting with phosphorothioate ester **4c**. Although the regioselectivities of the reactions using aromatic Grignard reagents remained high (entries 1 and 2), the yields were significantly reduced. The use of aliphatic Grignard reagents led to virtually unselective reactions (entries 3 and 4). While allylic halides **42** and **43** could be stored for short periods at room temperature, they were not stable toward silica gel and had to be used without purification. The disparate regioselectivities observed in alkylation reactions of **42** and **43** with aliphatic Grignard reagents and the operational difficulties associated with handling secondary allylic halides[20] in which the alkene is β,β-disubstituted differentiate our methodology from the use of other types of allylic electrophiles.

In conclusion, we have reported a simple two-step process for the transition-metal-free synthesis of sterically hindered quaternary and tertiary C−C bonds starting from a diverse set of allylic alcohols and ethers. A thorough investigation of the mechanistic and stereochemical aspects of both reactions is underway.

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

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