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Allylic Alcohols as Radical Allylating Agents. An Overall Olefination of Aldehydes and Ketones

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Not least of the advantages of radical reactions is the little tendency of many oxygen and nitrogen functions (alcohols, esters, amides, etc.) to undergo β-elimination when located vicinal to the radical center.[1] Radical **1**, for example, does not normally undergo elimination to give alkene **2** and a carbonyloxyl radical (Scheme 1).[2,3] Nonetheless, the possibility of converting an alcohol into a leaving group, in the radical sense, opens up many synthetic opportunities. As pictured in Scheme 1, this would correspond to an overall equivalent of the Wittig reaction: alkene **7**, formally derived from ketone or aldehyde **3** by reaction with hypothetical phosphonium ylid **9**, would be obtained via intermediates **4** and **5** by a radical addition−fragmentation on the latter.

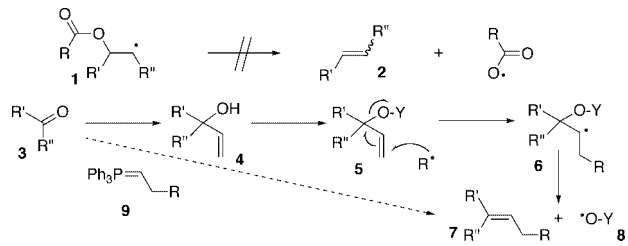
The key issue is finding an appropriate **Y** appendage that encourages rupture of the strong carbon−oxygen bond at a rate that is competitive with alternative pathways open to radical **6**. After some experimentation, we identified the 6-halopyridine motif as a suitable group; it is easy to introduce, and its elimination leads to a stabilized 2-pyridoxyl radical **8** (**Y** = 6-halopyridyl).[4] Furthermore, the electron-withdrawing pyridine nucleus speeds up the fragmentation by a favorable interplay of polar effects.[1]

In a preliminary experiment (Scheme 2), we found that butenyl derivative **10** underwent lauroyl peroxide mediated addition of xanthate **11** in refluxing 1,2-dichloroethane (DCE) to give adduct **13** in 78% yield but only traces of the desired olefin **14**. However, when adduct **13** was heated in chlorobenzene with di-*tert*-butyl peroxide, a smooth reaction took place to give olefin **14** in 63% yield as a 3:1 *E*:*Z* mixture. The possibility of returning from the adduct back to the intermediate radical (i.e., from **13** to **12**) is a key property of xanthate transfers: it provides the intermediate radical with enough accumulated lifetime to undergo what remains a relatively slow elimination.[5] The peroxide is required in stoichiometric amounts, as the expelled pyridyloxyl **15** does not propagate the chain but is converted mainly into 2-chloro-6-hydroxypyridine **16**, which could indeed be isolated.[6] Similarly, fluoropyridine analogue **17** reacted with xanthate **18** to give olefin **20** via intermediate **19**.

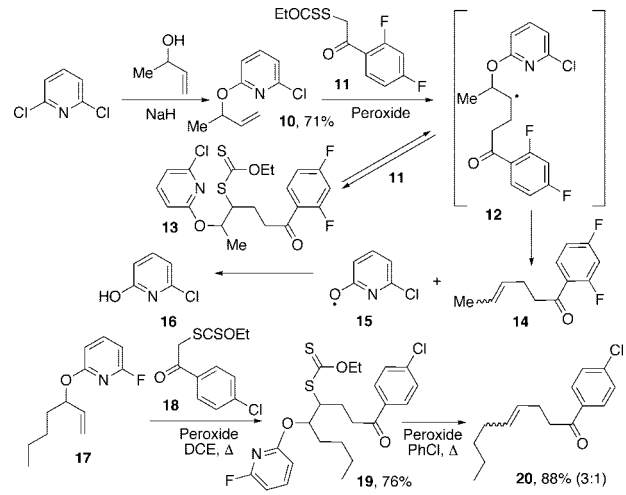
Because of their better accessibility, the fluoropyridine derivatives were selected for the remainder of the study. The starting allylic alcohol derivatives are readily obtained by reacting the allylic alcohol with 2,6-difluoropyridine in DMSO using sodium hydride as base.[7] The examples in Table 1 give an idea of the scope (FPy = 6-fluoropyridin-2-yl). We found that it was not necessary to isolate the xanthate adduct (e.g., **13** or **19**) nor was high temperature needed to promote the elimination step: treatment of the xanthate and the derivatized allylic alcohol with stoichiometric amounts of lauroyl peroxide in refluxing ethyl acetate was sufficient to bring about the desired transformation.

The reaction is successful with a broad range of allylic alcohol derivatives, and a variety of useful functions could be readily introduced.[8] In contrast to secondary allylic alcohol derivatives such as **10**, **17**, or **21**, where the xanthate adduct could be isolated, the final addition−elimination product was the only major compound

Scheme 1. Radical-Based Approach for the Olefination of Ketones



Scheme 2. Preliminary Experiments



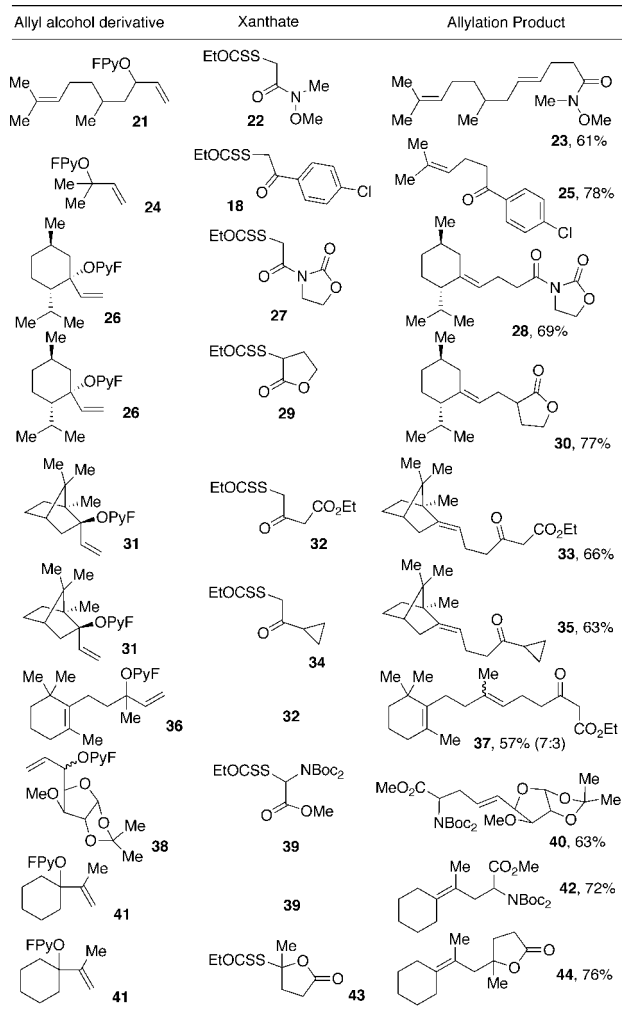
observed with derivatives of tertiary alcohols. Only the *E* isomer was formed in most instances, due in part to the milder reaction conditions. It is also worth underscoring the ease of formation of *tetrasubstituted* olefins as illustrated by the reaction of vinyl carbinol **41** with xanthates **39** and **43** to give the corresponding alkenes **42** and **44**.

Combining the xanthate addition to an ordinary olefin with the allylation results in an expedient and modular approach to complex frameworks (Scheme 3). Thus, addition of **27** and **22** to vinyl pivalate and 3-methyl-3-butenyl acetate provides xanthates **45** and **47**, and these in turn react with dimethylallyl derivative **24** to give imide **46** and Weinreb amide **48**, respectively. In the case of xanthate **51**, a ring closure was expected to precede allylation leading to **54**. In the event, the reaction with prenylating reagent **24** led mostly to the open chain derivative **52**. The ring-closed structure **54** could, however, be obtained by initial treatment of **51** with peroxide in the *absence* of olefin **24** to induce cyclization into **53**, followed by the allyation. The freedom to access at will open or cyclized structures such as **52** or **54** is noteworthy.

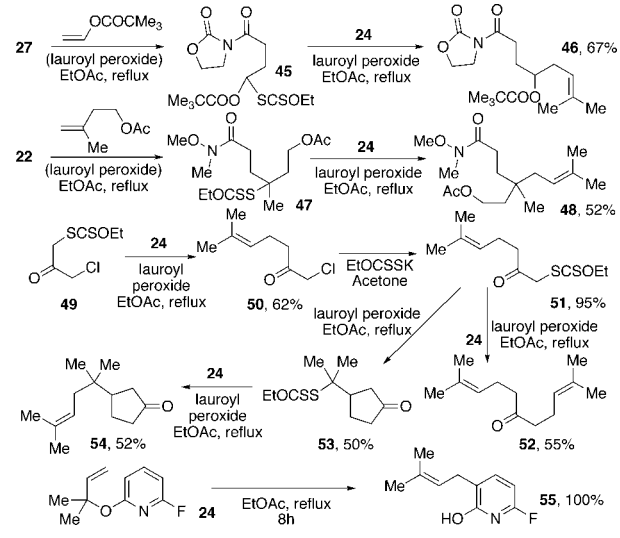
One final surprising observation deserves mention. We noticed that fluoropyridine derivatives of tertiary allylic alcohols gradually rearranged on heating; for example, **24** was quantitatively converted

10.1021/ja802899m CCC: $40.75

Table 1. Synthesis of Substituted Olefins by Radical Allylation



Scheme 3. Modular Construction of Substituted Olefins



into 3-prenyl hydroxypyridine **55** upon heating in refluxing ethyl acetate for 8 h. The rarely studied sigmatropic rearrangement of 2-allyloxypyridines normally requires much higher temperatures and results in migration of the allyl group on both the adjacent carbon and nitrogen.[9] This regioselective rearrangement under such mild conditions could have synthetic utility; it is nevertheless fortunate that it is slow enough to allow the desired radical process to proceed unhindered.

In summary, we have identified a convenient way to convert the hydroxy group of alcohols into a radical leaving group. As stated in the opening paragraph, the overall result is a formal olefination sequence. For instance, reagents **21**, **26**, **31**, and **36** derive initially from citronellal, menthone, camphor, and dihydro-β-ionone, respectively, yet it would have been difficult to access the corresponding olefinic products displayed in Table 1 by a direct classical Wittig reaction. In view of the critical importance of olefins in organic synthesis, the present strategy, which benefits from the considerable advantages associated with radical processes, nicely complements existing routes.

Acknowledgment. We thank Ecole Polytechnique for a fellowship to N.C. This paper is dedicated with respect to the memory of Dr. Ron Magolda.

Supporting Information Available: Experimental procedures as well as a compilation of spectral and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For a sole observation indicating that a phenoxyl radical could act as a leaving group under special circumstances, see: Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.

(5) For recent reviews of the xanthate transfer, see: (a) Zard, S. Z.; Quiclet-Sire, B. *Chem.—Eur. J.* **2006**, *12*, 6002. (b) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201.

(6) The possibility, raised by one of the reviewers, that the fragmentation could be heterolytic (see ref 2) leading to a radical cation and the anion of pyridone **16** appears unlikely for various reasons. The anion of pyridone **16** is not a sufficiently good leaving group as it is the conjugate base of a weak acid (see Bordwell, F. G.; Singer, D. L.; Satish, A. V. *J. Am. Chem. Soc.* **1993**, *115*, 3543.), and there are no groups in structure **12** to stabilize a radical cation. Furthermore, it is difficult to see how a radical cation could evolve cleanly into olefin **14** under our conditions. Note that the oxygen of the ketone in intermediate **12** is well positioned to react with a radical cation, should such an electrophilic species form.

(7) Surprisingly, ethanol appears to be the only alcohol previously made to react with 2,6-difluoropyridine: (a) Reiffenrath, V.; Bremer, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1386. (b) Schlosser, M.; Rausis, T. *Helv. Chim. Acta* **2005**, *88*, 1240.

(8) It is preferable that the radical derived from the xanthate be more stable than a simple secondary radical (such as **12**); otherwise, the radical addition step loses efficiency. See ref 5 for a detailed discussion.

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