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Allylic Alcohols: Ideal Radical Allylating Agents?

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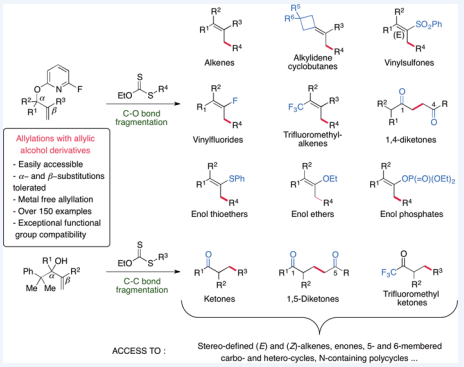
CONSPECTUS: Radical allylations represent effective routes to various alkenes, but to date they have relied chiefly on organostannane derivatives and still suffer from significant limitations with respect to the substitution pattern of the starting allylating agent. Indeed, while substituents at the β-position relative to the radical leaving group are well-tolerated, introduction of α-substituents induces a major complication due to the rapid and usually irreversible isomerization of the starting allylating agents. Although a number of research groups have made substantial efforts to develop heavy-metal-free radical allylations, methods compatible with α-substitution of the allylating agent are still scarce. Furthermore, quite a few systems are limited by the relative inaccessibility of the substrates. This Account summarizes our sustained efforts regarding the development of allylic alcohols into "ideal" radical allylating agents and presents published as well as some unpublished results. The systems we have developed combine the use of readily available xanthates and allylic alcohol derivatives under metal-free conditions to furnish not only alkenes but also aldehydes and saturated and unsaturated ketones through the virtually unprecedented homolytic cleavage of the normally strong C−O or C−C bond. The former route hinges on first converting the allylic alcohol into a 2-fluoro-6-pyridoxy derivative by reacting the corresponding alcoholate with 2,6-difluoropyridine, while the latter relies on attaching a cumyl group to the carbon bearing the free allylic alcohol. Either substrate is then exposed to the action of a suitable xanthate in the presence of a stoichiometric amount of a peroxide, usually lauroyl peroxide (DLP) in refluxing ethyl acetate or di-*tert*-butyl peroxide (TBHP) in refluxing chlorobenzene for the more difficult cases. Even though C−O or C−C bond homolysis leads to a stabilized 2-fluoro-6-pyridinyloxyl radical or a cumyl radical, respectively, the β-scission in both cases is relatively slow and at the lower limit of useful elementary radical steps. The kinetic barrier of the fragmentation can nevertheless be overcome because of the long relative lifetime of radicals generated by the degenerate transfer of the xanthate group, and this is a key element for success. This novel technology offers numerous advantages. The starting activated allylic alcohol derivatives are readily accessible in two steps from aldehydes or ketones. They can also be obtained by base-induced opening of epoxides. Numerous functional groups are tolerated under the mild reaction conditions for the radical addition−elimination, as nicely illustrated by over 150 examples of radical allylations, not all of which can be included in the present Account. In addition, substitution at both the α- and β-positions of the allylating agent is possible, a rare feature in this area.



INTRODUCTION AND CONTEXT

Radical allylations have hitherto relied heavily on organotin derivatives, especially allylstannanes **1**, which furnish alkenes **3** (Scheme 1).[1] Variations include the combination of allyl sulfones **4** with stoichiometric amounts of hexabutylditin. These methods are still popular but suffer from serious problems associated with stannanes, such as acute toxicity and severe difficulties in eliminating tin residues,[2] as well as intrinsic limitations regarding the substitution pattern of the allyl group. Thus, while substitution at the β-position is perfectly tolerated, substituents at the α-position relative to the leaving group, as in **5**, introduce a major complication due to the nondegenerate isomerization into the thermodynamically more stable but poorly reactive γ-isomer **7** (Scheme 1).

TIN-FREE RADICAL ALLYLATIONS

To overcome these limitations, four classes of allylating agents have been examined, relying on the homolytic cleavage of a carbon−sulfur, carbon−halide, or carbon−silicon bond.[1] The rate of fragmentation depends on the nature of the heteroatom and the substituents.

Allyl Sulfides

Barton developed the radical allylation of thiohydroxamic esters with allyl sulfides (**8** → **11**; Scheme 2a)[3] and later extended it to mixed oxalate/thiohydroxamate esters derived from tertiary alcohols.[4] Other methods include the allylation of halides with allyl tris(trimethylsilyl)silyl sulfide as reported by Curran.[5]

Allyl Sulfones

Following the pioneering work of Whitham[6] and Padwa,[7] Renaud devised an ingenious three-component hydroboration/radical allylation sequence (**12** → **15**; Scheme 2b).[8] Fuchs used trifluoromethyl allyl sulfones to allylate substrates bearing easily abstracted hydrogens.[9] We exploited both the α- and β-scission of alkylsulfonyl radicals to allylate iodides and xanthates with allyl sulfones.[10]

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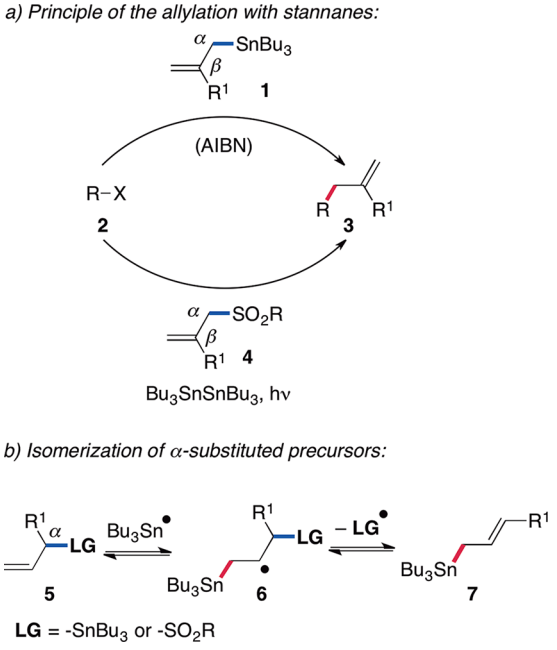
Scheme 1. Complications Associated with α-Substituted Precursors



Allyl Halides

Russell and Singleton pioneered the use of allyl halides as radical allylating agents.[11] More recently, Frejd[12] and Heinrich[13] developed aryl radical allylations using these reagents, while Ryu reported elegant allylation methods involving alkynes, allenes, or cyclopropyl alkenes in conjunction with allyl bromides (**16** → **18**; Scheme 2c).[14]

Allylsilanes

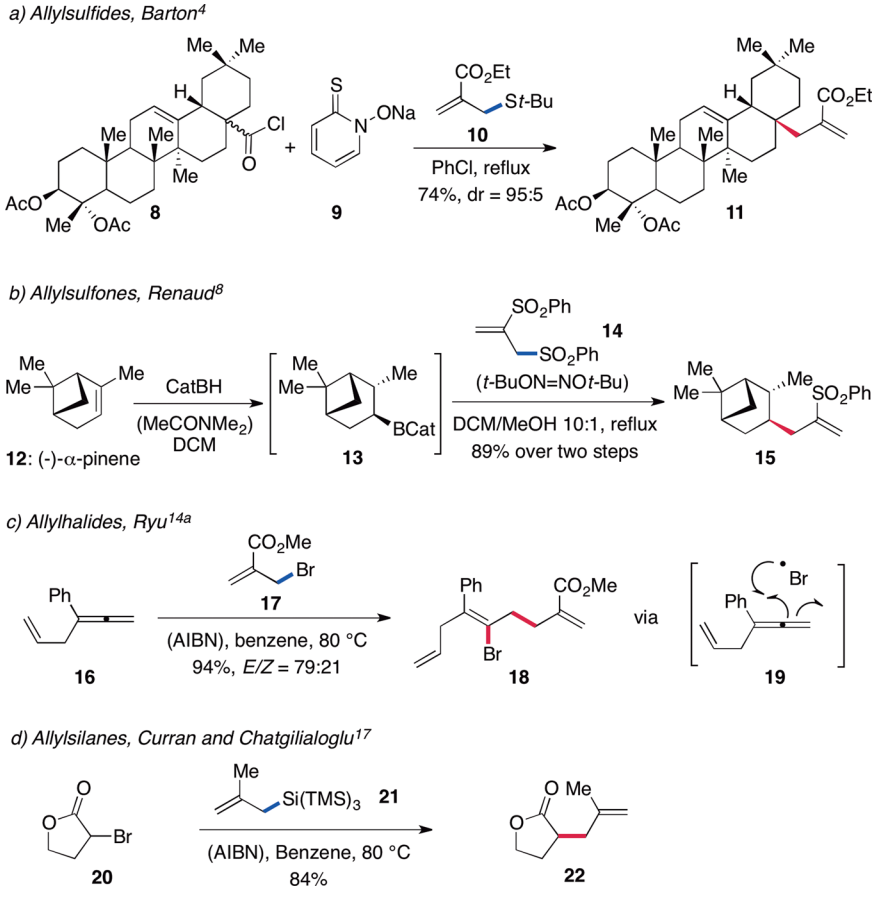
Guindon has shown that β-silylated radicals do not normally undergo fragmentation.[15] Consequently, most of the reported processes involving allylsilanes consist either of a radical addition followed by oxidation and ionic elimination of the silyl group or of a radical halide transfer followed by elimination of R_3SiX.[16] However, allylations involving purely radical species can be realized using allyl tris(trimethylsilyl)silane derivatives (**20** → **22**; Scheme 2d).[17]

Only a few reactions with α-substituted allylating agents are known. We described two such tin-free allylations of xanthates involving allyl sulfones[10c] and allylphosphine oxides[18] that are compatible with α-substituents (**23a** → **25** and **23b** → **27**, respectively; Scheme 3).[19] Despite their utility, the synthesis of complex allylating agents is sometimes problematic.

■ ALLYLIC ALCOHOLS AS RADICAL ALLYLATING AGENTS

Allylic alcohols could in principle act as ideal radical allylating agents; however, the carbon–oxygen bond is strong, and allylations involving allylic oxygen derivatives are virtually unknown.[20] One important exception is vinyl epoxides.

Scheme 2. Representative Examples of Tin-Free Allylations



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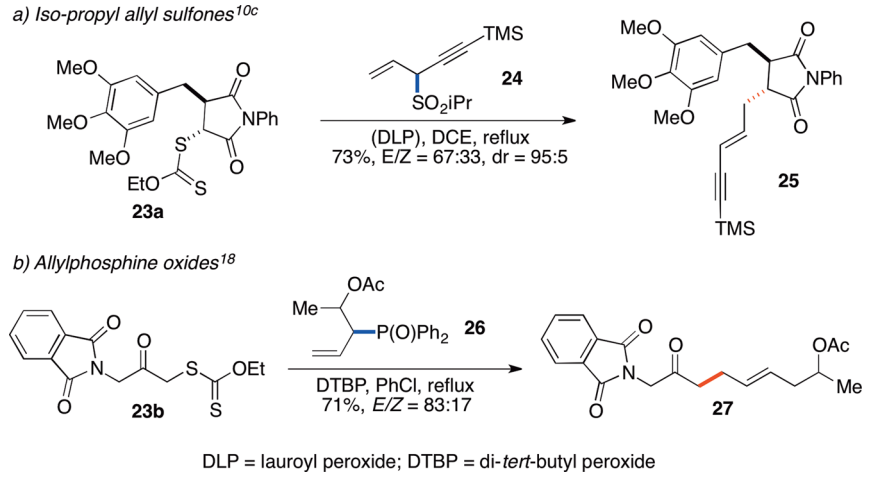
Scheme 3. Tin-Free Radical Allylation with α-Substituted Allylating Agents



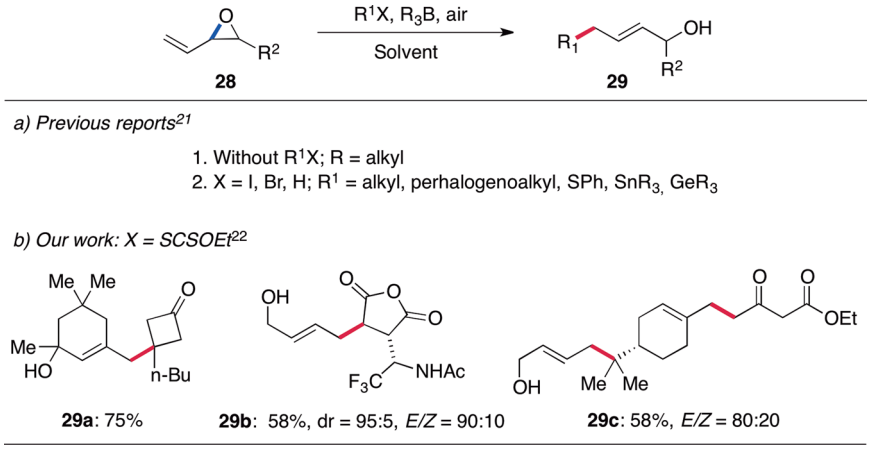
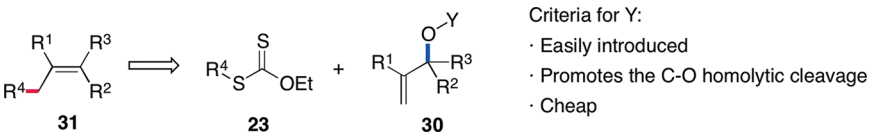
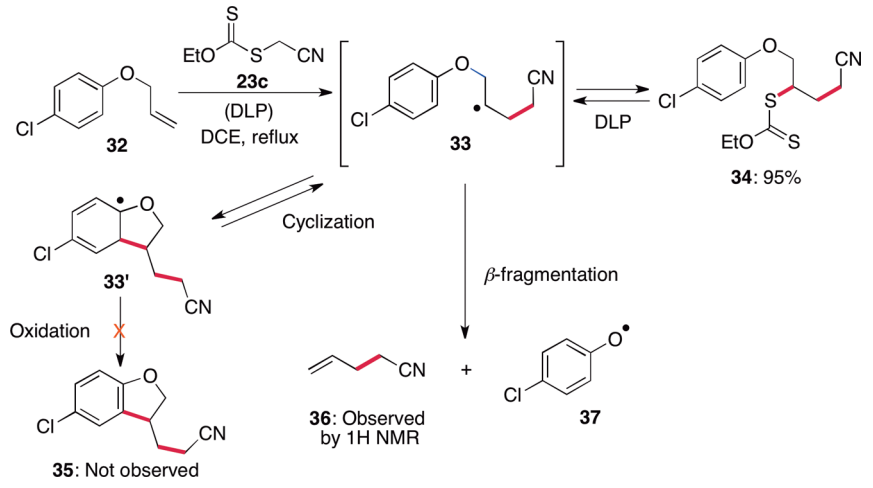


Figure 1. Allylations involving vinyl epoxides.

Scheme 4. Design of a New System Based on Allylic Alcohols



Scheme 5. Observation of C−O Bond Fragmentation



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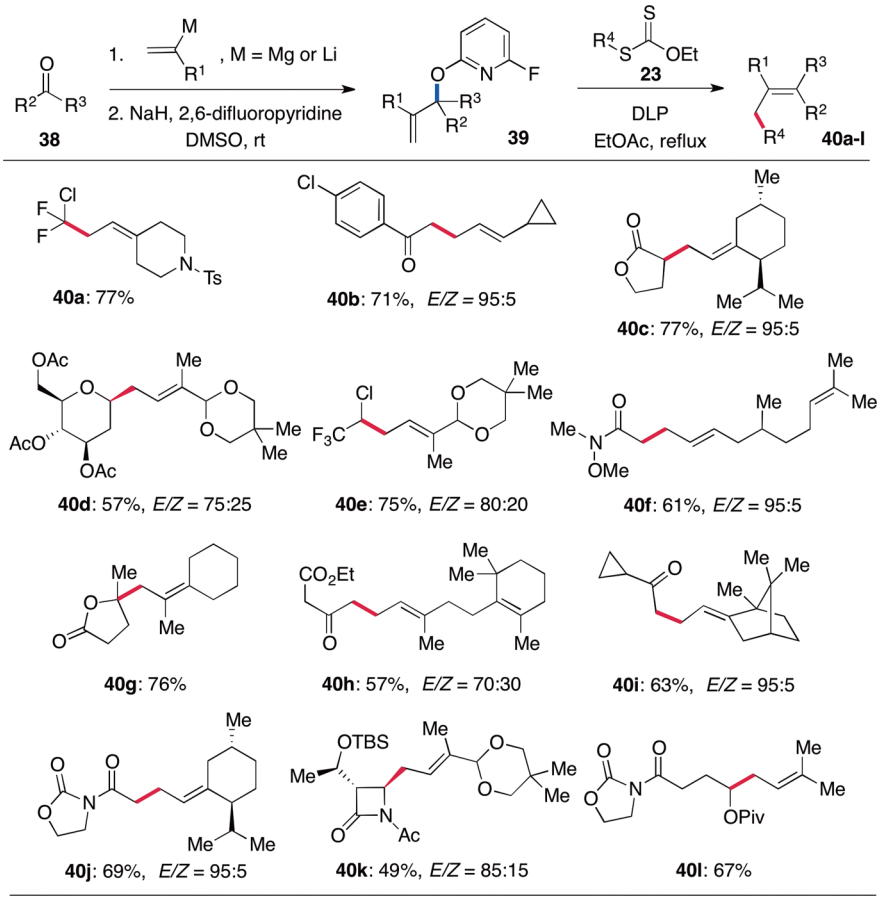
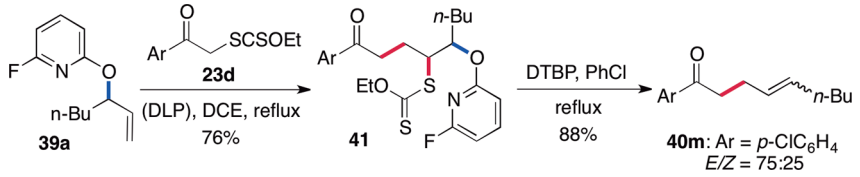


Figure 2. Sequence for the formation of functionalized alkenes.

Scheme 6. Stepwise Transfer and β-Elimination



Vinyl Epoxides

Vinyl epoxides **28** undergo ring opening to yield the corresponding allylic alcohols **29** upon triplet oxygen-induced reaction with organoboranes.[21] We significantly improved the scope of these transformations by combining the triethylborane/O_2 system with the wide variety of available xanthates (**29a–c**) (Figure 1).[22]

From an Experimental Observation to the Design of a New Radical Allylation Platform

For allylations using unbiased open-chain allylic alcohols, we needed to identify an easily introducible Y appendage that would render the C–O bond prone to radical fragmentation (**30**; Scheme 4). The answer emerged upon reconsidering an observation we made while attempting to construct dihydrobenzofurans by a radical addition–cyclization sequence (**32** → **35**; Scheme 5).[23] The expected dihydrobenzofuran **35** was not observed, but pent-4-enenitrile (**36**) was detected in the crude ^{1}H NMR spectrum. The β-fragmentation is clearly faster than either the reversible cyclization or the oxidation step. The driving force for the β-scission, apart from the gain in entropy, is presumably the relative weakness of the benzylic C–O bond and the ensuing formation of a stabilized phenoxyl radical (**37**).

Following this key observation, we proceeded to identify an aromatic moiety capable of facilitating β-fragmentation that is easily appended onto allylic alcohols. Our attention focused on 2,6-dihalogenopyridines, especially 2,6-difluoropyridine, since they readily undergo nucleophilic aromatic substitution by alcoholates. Indeed, a broad collection of α-mono- and α-disubstituted allylating agents **39** were prepared and afforded good yields of olefinic products **40** (Figure 2).[24] Importantly, this method tolerates substitution of the allylating agent at the α- and β-positions, which represents a genuine breakthrough.

The assembly of tetrasubstituted olefins is easily achieved (e.g., **40g**), and in all instances of di- and trisubstituted olefins, the (*E*)-alkene is obtained as the major stereoisomer and as the sole product when R^1 = H and R^3 is bulkier than R^2. Chlorodifluoromethyl adduct **40a** is interesting because its treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene gives a rare *gem*-difluorodiene.[24b] In all of these transformations, the addition–fragmentation was performed without isolation of the intermediate xanthate. While the rate of the fragmentation

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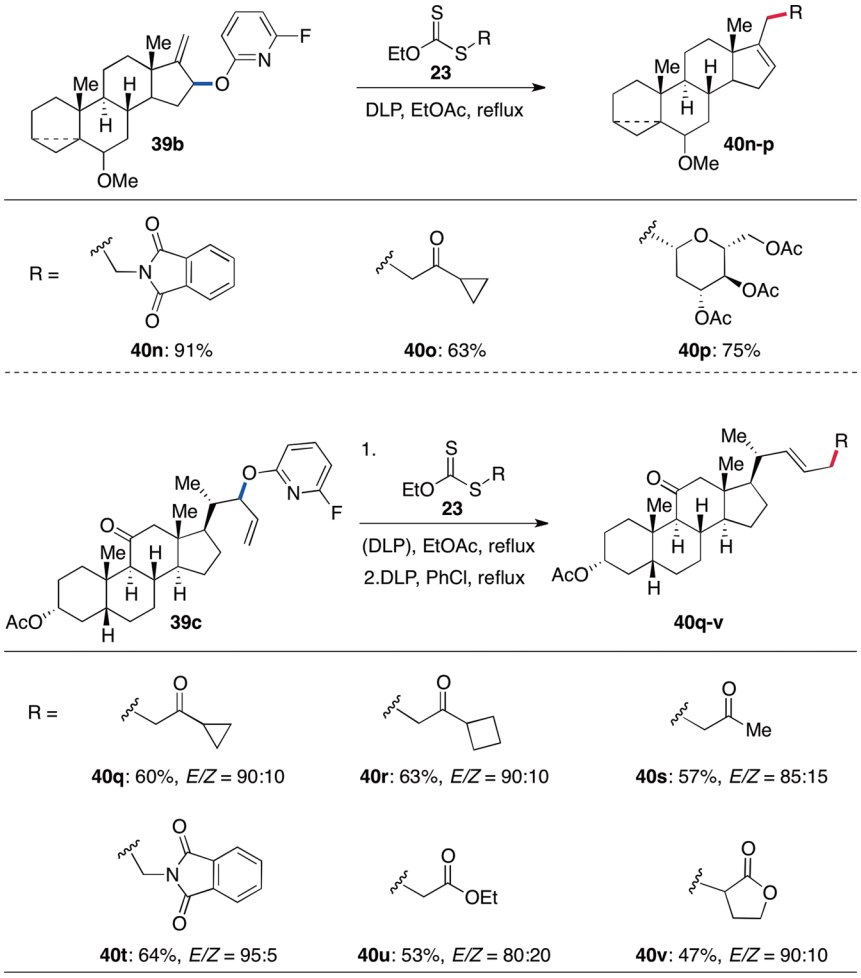

Figure 3. Allylation with steroids.

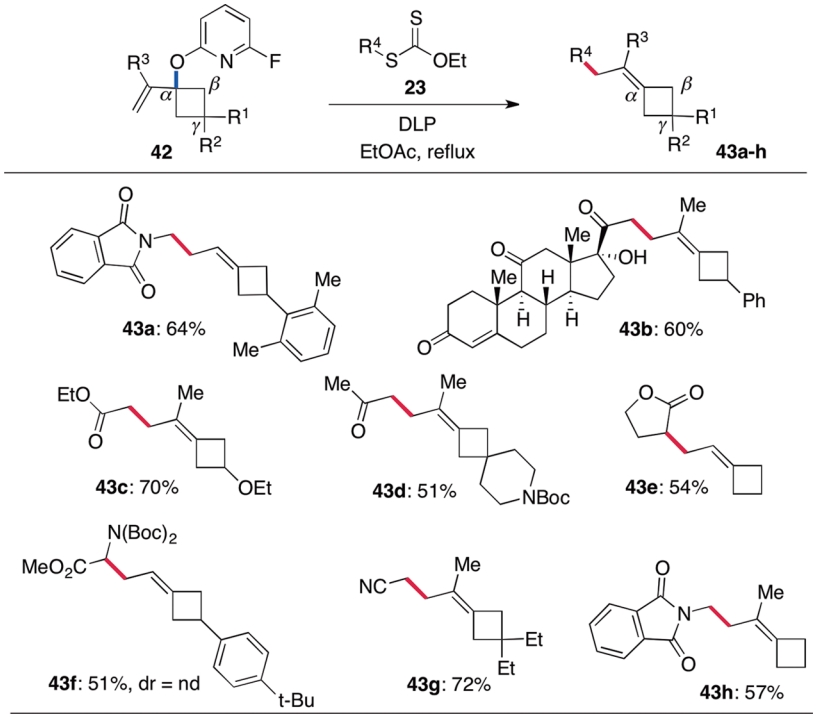

Figure 4. Access to alkylidenecyclobutanes.

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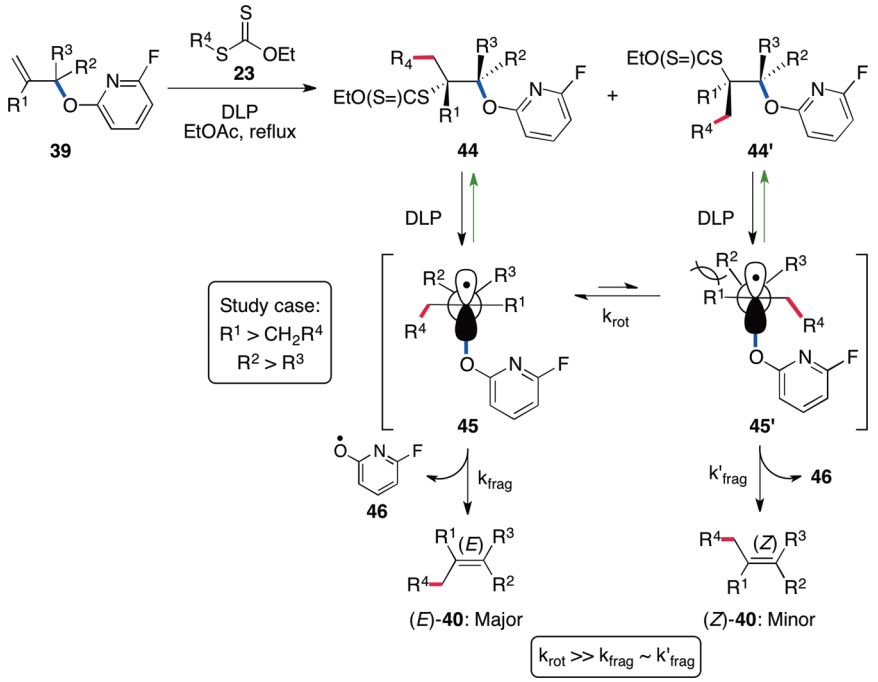
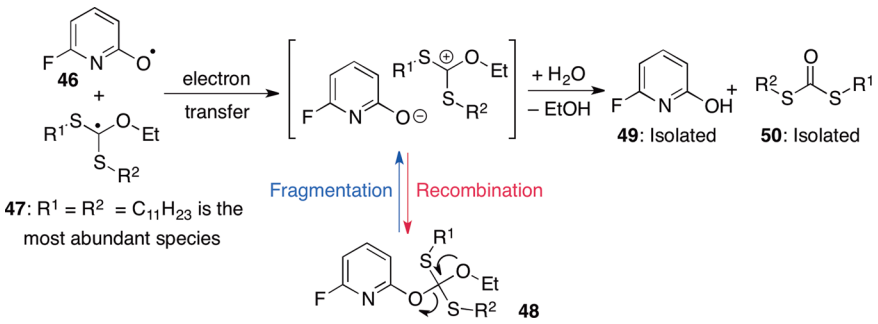
Scheme 7. Mechanistic Aspects



Scheme 8. Proposed Mechanism for the Formation of 2-Fluoro-6-hydroxypyridine



strongly varies with the structure, it is generally significantly slower than the reversible transfer of the xanthate group. Indeed, in substrates derived from unsubstituted secondary allylic alcohols, the intermediate xanthate **41** can be isolated (Scheme 6). The reversibility of the xanthate exchange ultimately forces the intermediate radical to collapse into alkene **40m**.[25] Indeed, the ability to keep going back to the intermediate radical by reversible transfer of the xanthate group is a key feature of the xanthate technology and underlies much of its synthetic potency. It provides a radical with a relatively long effective lifetime and allows it to overcome the kinetic barrier of slow transformations, as in the conversion of compound **41** into alkene **40m**, where the desired fragmentation is sluggish and needs to be further speeded up by an increase in the reaction temperature.

Even delicate steroids could be transformed (Figure 3). For steroid **39c**, it proved advantageous to carry out the reactions stepwise.

ALKYLIDENECYCLOBUTANES: EVALUATION OF THE ELIMINATION RATE

It also proved possible to access alkylidenecyclobutanes (**42** → **43**; Figure 4),[26] a class of strained alkenes with great synthetic potential. In this case, there is a competition between the desired homolytic fragmentation and the opening of the cyclobutane ring. The substituents on the cyclobutane play a crucial role in deciding the final outcome.[27] Thus, vinylcyclobutanol derivatives **42** (Figure 4), either un-, mono-, or disubstituted at the γ-position, furnished the expected addition−elimination products **43** in good yields. In contrast, β-substituted derivatives were more prone to ring opening and afforded significant proportions of ring-opened products.[28]

The rate of the C−O bond fragmentation in the 2-fluoropyridyl derivatives therefore appears to be comparable to that of the ring opening of cyclobutylcarbinyl radicals, i.e., on the order of 10^3−10^4 s^{-1} depending on the substitution pattern.[29] This estimation is consistent with the good levels of *E* selectivity observed for open-chain olefins and rationalized by the mechanistic manifold in Scheme 7. Thus, addition of xanthate **23** to olefin **39** generates a pair of diastereoisomers **44** and **44′** that evolve into different radical conformers **45** and **45′**, respectively. These are in equilibrium through rotation around the central C−C bond. The fact that the *E* isomer is formed as the major product implies that the interconversion between conformers **45** and **45′** is significantly faster than the fragmentation. Ultimately, the system allows the radical to adopt its most stable conformation **45**, wherein the larger substituents (R^1 and R^2) are anti to one another, prior to β-

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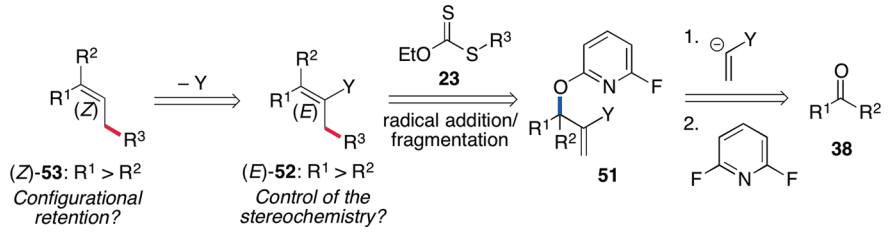
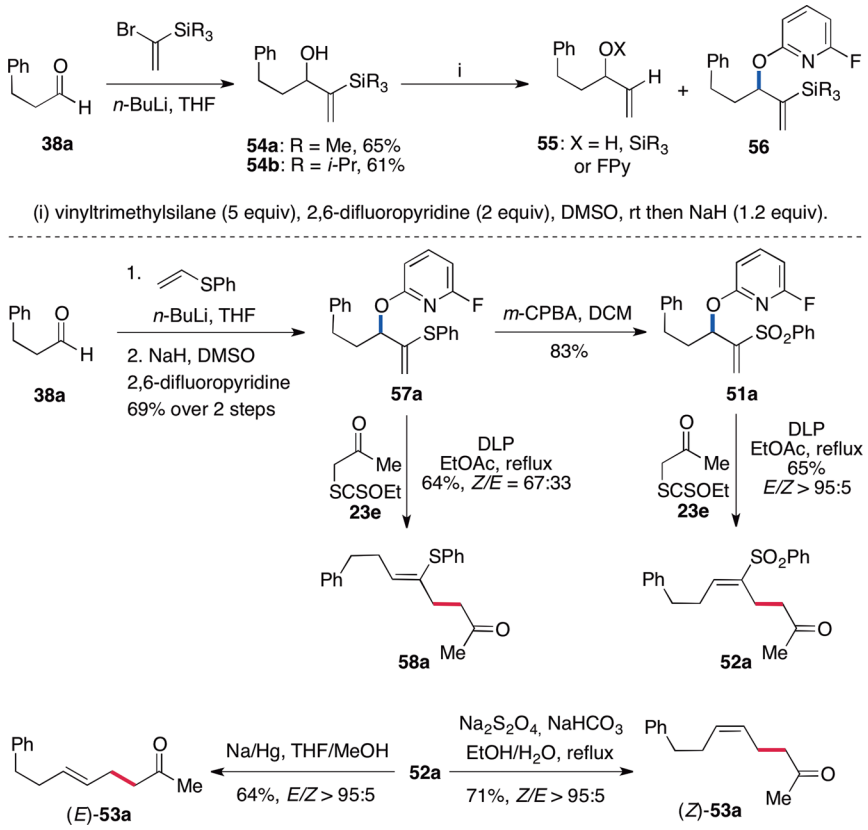
Scheme 9. Toward Stereodefined Alkenes



Scheme 10. Preparation of Stereodefined Alkenes



elimination. This aspect will acquire particular importance in a later section where the selective synthesis of alkenes is discussed.

Another facet that will prove equally crucial is the influence of the substituents on the rate of the homolytic scission. As expected, the more substituted the carbon bearing the fluoropyridoxyl group, the faster will be the collapse of intermediate radicals **45**. The release of strain due to steric congestion thus facilitates the synthesis of more highly substituted alkenes and nicely complements most of the earlier routes. A subtler but no less important effect concerns the influence of substituent R^1 on the carbon bearing the unpaired electron. An electron-donating group raises the energy level of the singly occupied molecular orbital (SOMO) and enhances its interaction with the σ^* orbital of the polarized C–O bond (the lowest unoccupied molecular orbital). An electron-withdrawing R^1 group has the opposite effect and ultimately slows the expulsion of the 2-fluoropyridoxyl radical.

The 2-fluoropyridoxyl radical **46** resulting from the fragmentation is mostly converted into 2-fluoro-6-hydroxypyridine (**49**) (Scheme 8). The former is a stabilized species that is unlikely to partake in hydrogen atom abstraction. However, it has significant electrophilic character and can therefore be reduced by electron transfer from the electron-rich radical **47**. This furnishes an ion pair that can recombine reversibly to produce dithio-orthoformate **48**, which ultimately reacts with water to give **49** and dithiocarbonate **50**. While there are various adduct radicals **47** in the medium at any given instant, by far the most abundant is the one where $R^1 = R^2$ = undecyl. This adduct radical is the most persistent simply because all of the available fragmentation pathways lead to high-energy primary radicals and therefore occur with much greater difficulty. This mechanistic proposal is reasonably supported by the isolation of dithiocarbonate **50** ($R^1 = R^2$ = undecyl).

FUNCTIONALIZED (*E*)-VINYL SULFONES: STEREOCONTROLLED SYNTHESIS OF OLEFINS

With the aim of controlling the alkene geometry, we considered the approach depicted in Scheme 9, whereby a bulky but stereoselectively removable Y group would direct the addition–fragmentation toward the formation of the *E* isomer (*E*)-**52**. Removal of the Y group with retention of configuration would finally deliver the targeted (*Z*)-alkene (*Z*)-**53**.[30]

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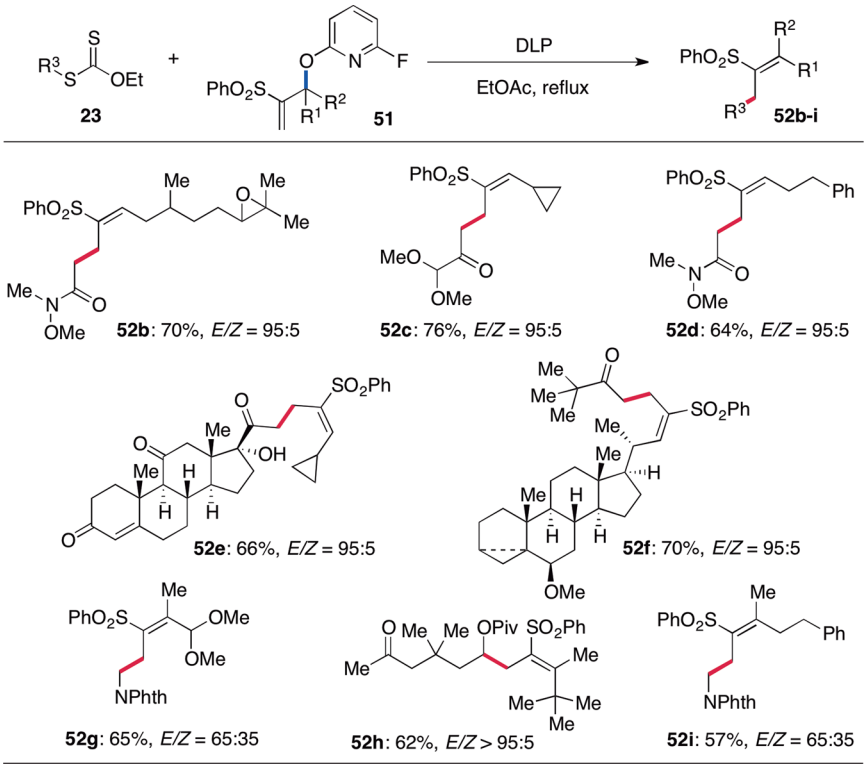
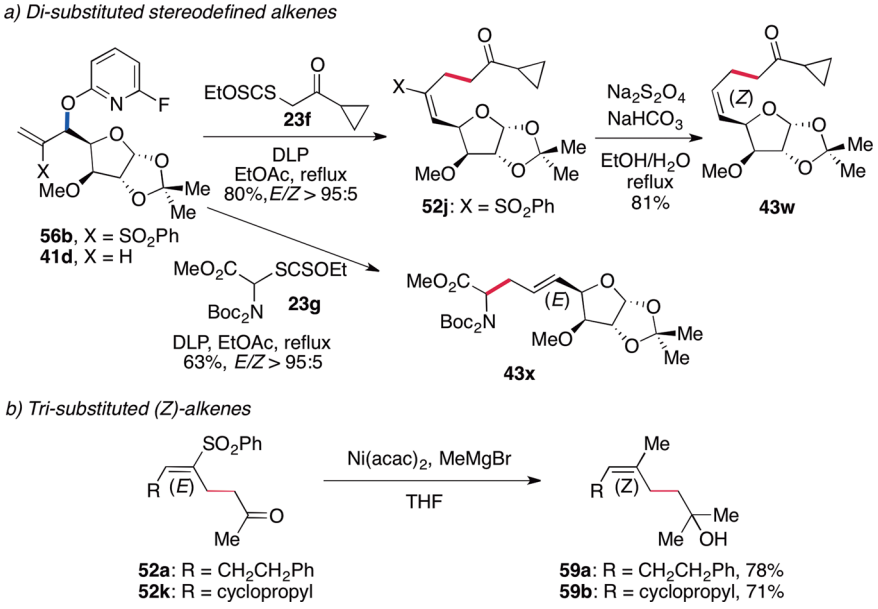


Figure 5. Stereoselective synthesis of (*E*)-vinyl sulfones.

Scheme 11. Routes to Stereodefined Alkenes



Two candidates for the Y group appeared promising from the outset: trialkylsilyl and arylsulfonyl substituents. All our attempts to obtain the silylated precursors resulted in the formation of mixtures of the desired allylating agent **56** and products **55** resulting from a Brook rearrangement of alcohol **54** and/or from the desilylation of the target fluoropyridyl ether **56** (Scheme 10). The use of the more robust triisopropylsilyl group (**54b**) in combination with a large excess of a fluoride trap such as vinyltrimethylsilane did shut down the desilylation pathway but did not affect the unwanted Brook rearrangement. In contradistinction, the synthesis of model precursor vinyl sulfide **57a** and sulfone **51a** was straightforward. Both olefins were exposed to xanthate **23e**, and to our surprise, the (*Z*)-olefin **58a** was obtained as the major isomer starting with vinyl sulfide **57a**. However, the bulkier sulfone group rendered the elimination highly stereoselective, and only the (*E*)-vinyl sulfone **52a** was detected by ^{1}H NMR spectroscopy. Stereoselective desulfonylation of vinyl sulfone **52a** under the conditions reported by Julia afforded the desired (*Z*)-alkene (*Z*)-**53a**.[31] Interestingly, reduction with sodium amalgam delivered the (*E*)-alkene (*E*)-**53a**.

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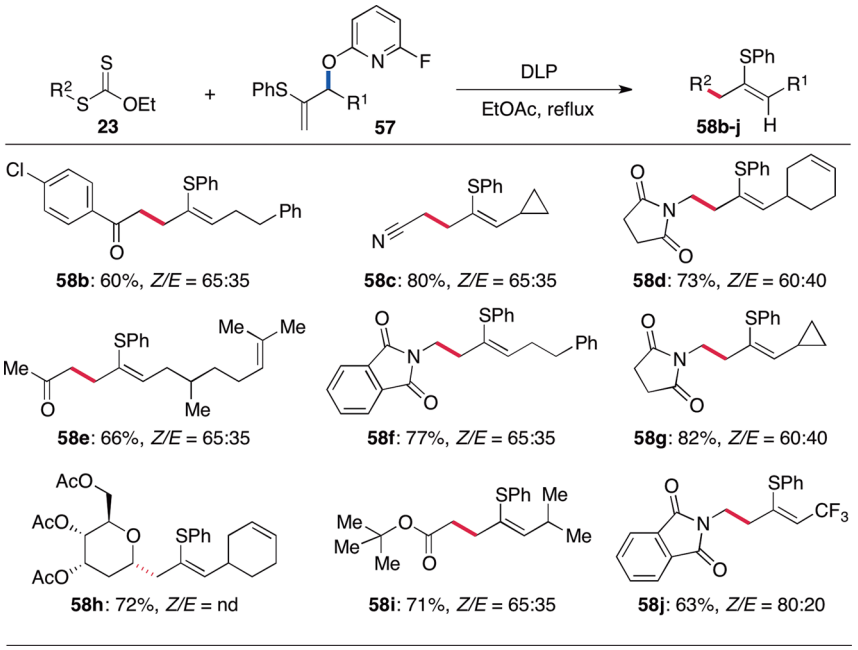

Figure 6. Synthesis of trisubstituted vinyl sulfides.

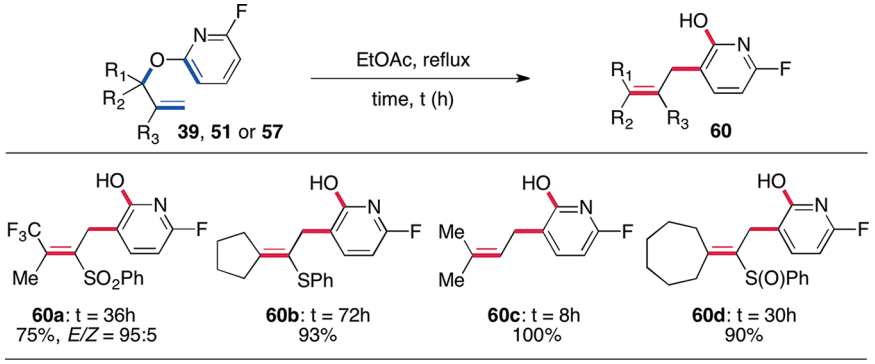

Figure 7. Claisen sigmatropic rearrangement.

We next proceeded to delineate the scope of the method (**51** → **52**; Figure 5). When the allylating agent **51** was derived from an aldehyde (R^1 = H), the reaction was highly stereoselective, and only the *E* isomer was isolated. With ketone-derived reagents, mixtures of geometric isomers were generally obtained (e.g., **52g** and **52i**), since the difference in the steric bulk of the substituents was too small to bias completely the equilibrium between the two diastereoisomeric rotamers. However, for substrates bearing substituents significantly different in size, complete *E* stereoselectivity was recovered (**52h**, R^1 = *t*-Bu and R^2 = Me).

The complementarity of these routes is illustrated by the synthesis of glucose-derived alkenes **43w** and **43x** (Scheme 11a). Whereas omission of the sulfonyl group cleanly yielded (*E*)-alkene **43x**, the less accessible *Z* isomer **43w** was made by desulfonylation of the corresponding (*E*)-vinyl sulfone **52j**. $Ni(acac)_2$-catalyzed cross-coupling of (*E*)-vinyl sulfones **52a** and **52k** with excess MeMgBr provided trisubstituted (*Z*)-alkenes **59a** and **59b** with high stereoselection (Scheme 11b).[32]

TRI- AND TETRASUBSTITUTED ENOL THIOETHERS

Enol thioethers are versatile building blocks that have been implicated in reactions involving thionium ions, in cyclo-additions, and in carbometalations. One of their prominent features is to behave as more stable enol ether surrogates, allowing them to react with proelectrophiles that, in our case, could be introduced through the xanthate partner. However, while the synthesis of di- and trisubstituted vinyl sulfides is well-documented,[33] efficient methods for the preparation of tetrasubstituted congeners are scarce. We could readily obtain trisubstituted vinyl sulfides **58**, albeit with moderate *Z* stereoselectivities (**57** → **58**; Figure 6). The smaller size of the sulfide moiety, due to the longer C−S bond compared with a standard alkyl group, presumably accounts for the preferential formation of the *Z* isomer.

In the more difficult case of tetrasubstituted vinyl sulfides, we were sometimes frustrated by the occurrence of a competing Claisen rearrangement of the starting material (**39**, **51**, or **57** → **60**; Figure 7), which diminished the efficiency of the process. This sigmatropic rearrangement, originally observed in our preliminary studies, takes place under remarkably mild conditions.[34] It is no doubt favored by the Thorpe−Ingold effect exerted by the R^1 and R^2 substituents, but it is probably also influenced by the geometry of the substrate and by the electronic nature of the vinylic substituent R^3 (examples in Figure 7).

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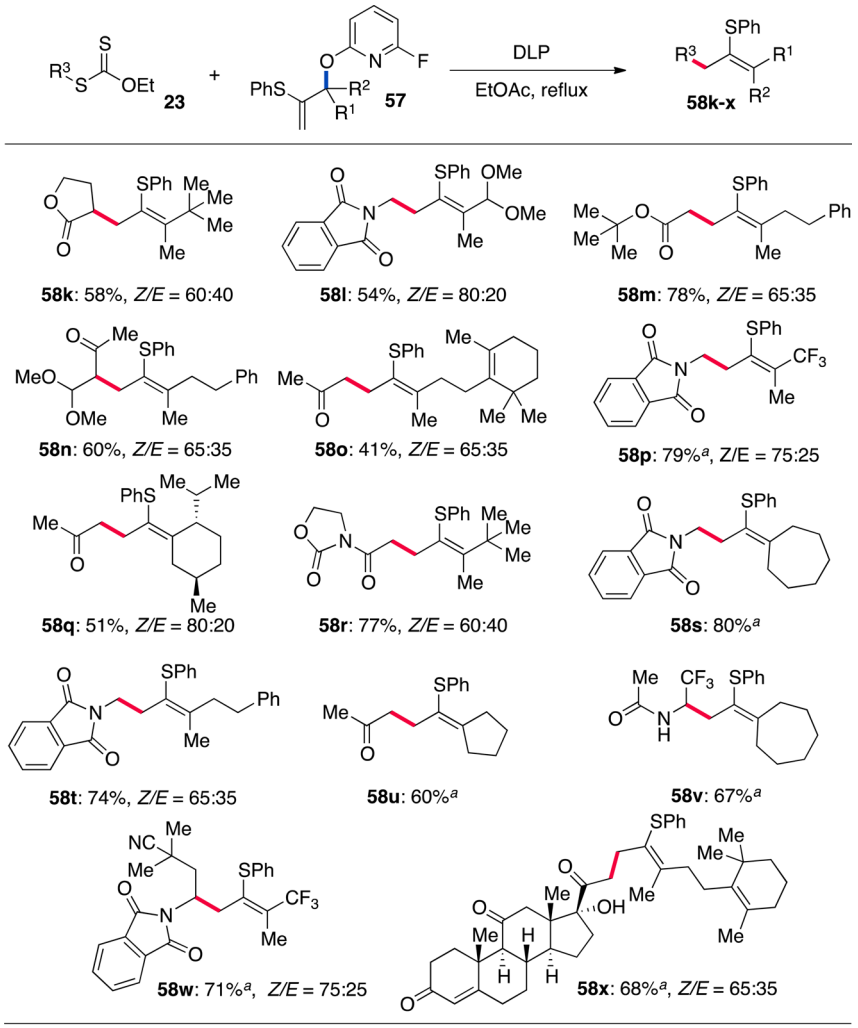
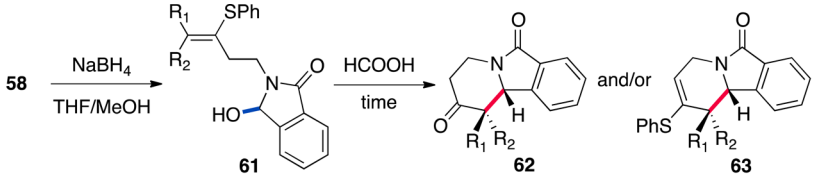


a The starting vinyl sulfide **57** rearranges in refluxing ethyl acetate and the reaction was carried out under modified conditions.

Figure 8. Access to tetrasubstituted vinyl sulfides.



substrate	Z/E	time	yield **62**	dr **62**	yield **63**	dr **63**
61a (90%)	95:5	12 h	(*cis*)-**62a** : 62%	≥ 95:5	**63a** : -	-
(*Z*)-**61b** (93%)	≥ 95:5	2 days	(*cis*)-**62b** : -	-	(*cis*)-**63b** : 61%	95:5
(*E*)-**61b** (93%)	≤ 5:95	2 days	(*trans*)-**62b** : 70%	≥ 95:5	(*trans*)-**63b** : -	-
61c (96%)	-	7 days	**62c** : 61%	-	**63c** : -	-
61ca (96%)	-	10 min.	**62c** : 20%	-	**63c** : 48%	-

a Reaction performed in DCM with 4Å molecular sieves.

Figure 9. Reaction of vinyl sulfides with *N*-acyliminium cations.

Overall, we were fortunate that in the case of most vinyl sulfides **57** derived from ketones, the rearrangement proved slow enough to enable the formation of the targeted tetrasubstituted vinyl sulfides **58** in useful yields (Figure 8). In the few problematic examples, shortening the reaction time by adding the peroxide in larger portions delivered the desired tetrasubstituted enol thioethers in yields comparable to those of the less substituted analogues.

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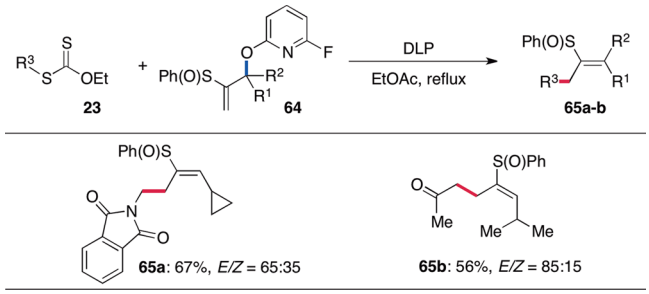


Figure 10. Synthesis of vinyl sulfoxides.

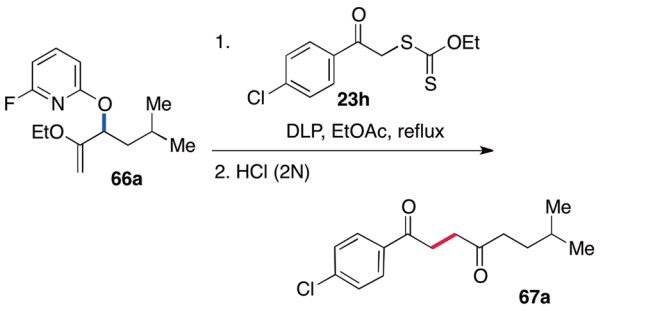
Vinyl sulfides **58** obtained starting from an α-ketoxanthate are in fact regioselectively protected and stable 1,4-dicarbonyl surrogates.[35] Furthermore, reactions of various π nucleophiles with thionium ions generated from vinyl sulfides have also been documented.[36] However, while enol thioethers have been used as π nucleophiles in reactions with a range of electrophiles, they have apparently never been exposed to *N*-acyliminium cations.[37] Chemoselective reduction of phthalimides **58f**, **58p**, and **58t** delivers hemiaminals **61a**, **61b**, and **61c** in quantitative yield, and upon exposure to formic acid, the in situ-generated *N*-acyliminium cations undergo smooth cyclization leading to the corresponding ketones **62** or vinyl sulfides **63** depending on the substitution pattern and the reaction conditions (Figure 9).

Vinyl sulfoxides **64** also proved to be competent partners in this radical allylation (**64** → **65**; Figure 10). The *E* isomer predominated, indicating that the sulfoxide is significantly bulkier than the sulfide but is still too small to prevent the formation of the *Z* isomer.

ENOL ETHERS: ACCESS TO 1,4-DICARBONYLS AND ENONES

We were also interested in expanding this strategy to the enol ethers themselves, as we were curious to see how the replacement

Scheme 12. Preliminary Results



of a sulfur atom by an oxygen atom would impact the feasibility and stereoselectivity of the reaction. However, while this would offer complementary synthetic opportunities, the premature hydrolysis of the more hydrolytically labile substrates might be in competition with the productive radical path.

Our first task was to identify suitable conditions for the allylation. Whereas all of the other variants presented in this Account were found to give synthetically useful yields under the first set of conditions developed for simple olefins, the presence of a β-oxygen substituent had a drastic effect on the transformation. Under the standard conditions, the reaction of

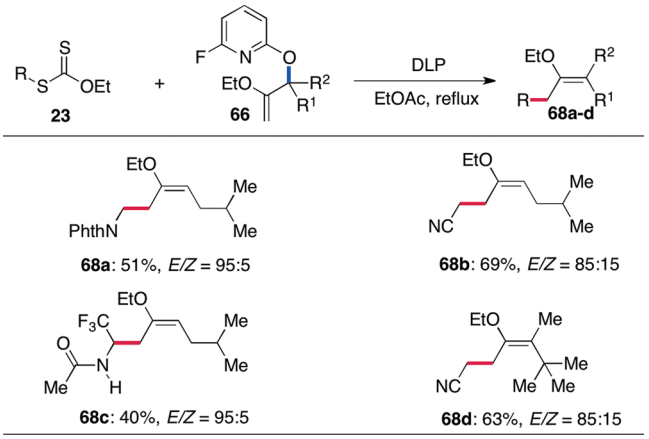
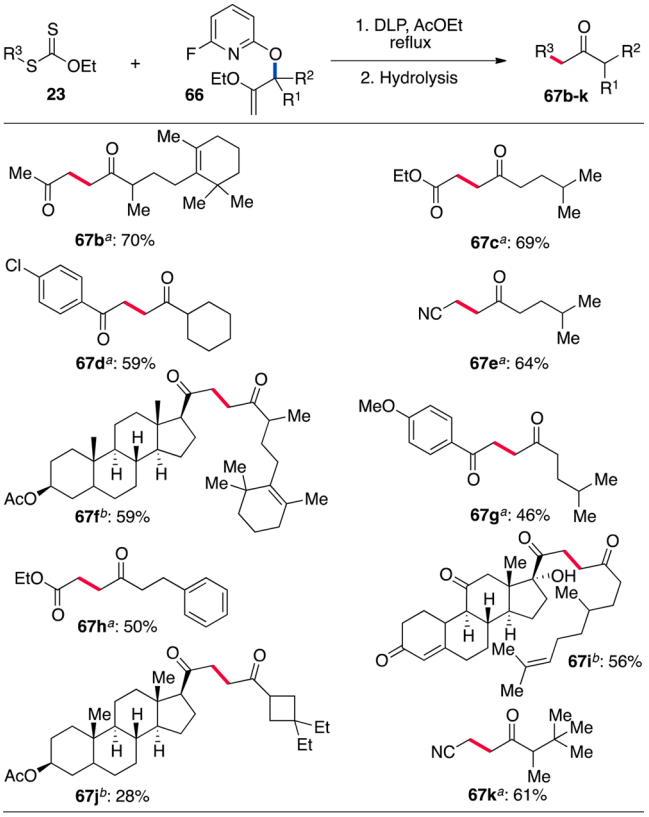


Figure 11. Preparation of enol ethers.



[a] The hydrolysis was realized using HCl (2N).
[b] Hydrolysis was carried out by adding silica to the crude reaction mixture.

Figure 12. Synthesis of ketones and 1,4-diketones.

enol ether **66a** with xanthate **23g** gave rise to 1,4-diketone **67a** in only 15% yield upon hydrolysis (Scheme 12). After careful optimization, we found that both the concentration and reaction time were critical parameters. Thus, dilution of the medium, addition of the peroxide in larger portions, and a 2-fold reduction of the reaction time allowed us to produce the desired diketone **67a** in 64% isolated yield.

It proved possible to isolate the intermediate tri- and tetrasubstituted enol ethers **68** by omitting the hydrolysis step (**66** → **68**; Figure 11). Surprisingly, the *E* isomer was obtained as the major product in all cases. The difference in selectivity observed between vinyl sulfides and their enol ether analogues

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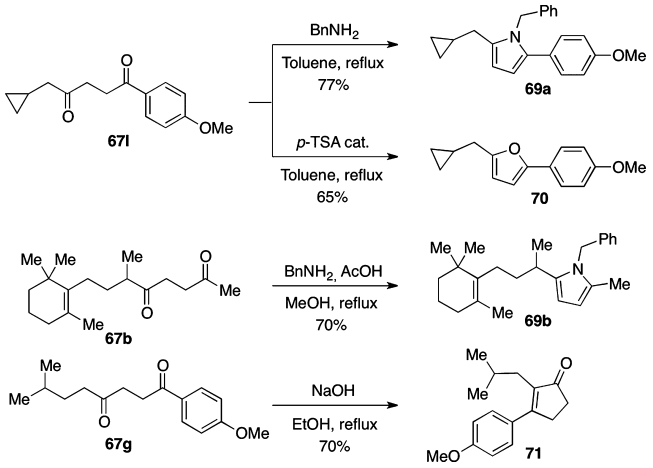
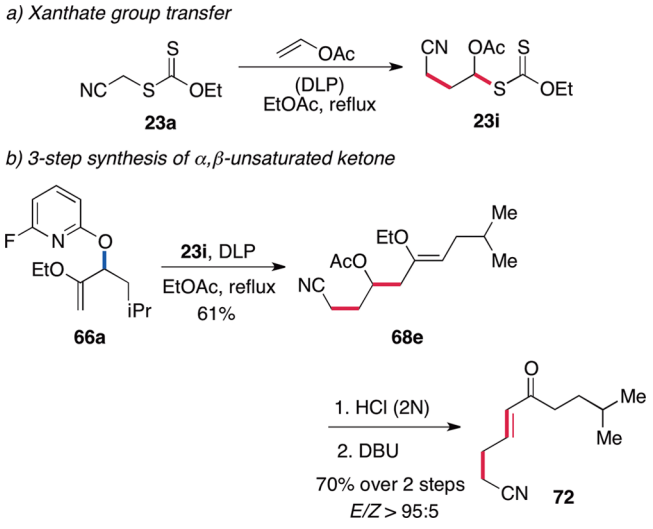
Scheme 13. Synthesis of Five-Membered Rings



Scheme 14. Formation of α,β-Unsaturated Ketones



probably reflects an increased steric effect due to the shorter C–O bond.

In contrast to vinyl sulfides, the hydrolysis of the enol ethers takes place under remarkably mild conditions (treatment with silica). The addition–fragmentation/hydrolysis thus gives access to a broad variety of ketones, in particular 1,4-diketones, as shown by the examples in Figure 12. 1,4-Diketones are classical precursors for numerous carbo- and heterocycles, some of which are of importance in medicinal chemistry and materials science. A few typical examples are displayed in Scheme 13.

A unique feature of the xanthate technology is the possibility of sequencing the intermolecular additions. In the present context, prior addition to vinyl acetate to give xanthates such as **23i** is particularly important because the subsequent addition–fragmentation leads to enol ether **68e**, which furnishes α,β-unsaturated ketone **72** upon hydrolysis and treatment with base (Scheme 14). Both saturated and unsaturated ketones may thus be readily accessed by this approach.

The allylation could be extended to the synthesis of enol phosphates, which are suitable partners in transition-metal-catalyzed cross-couplings.[38] The desired precursors **73** were readily obtained in two steps from the parent enol ethers, and their reaction with various xanthates afforded the targeted enol phosphates **74** in high yields but with disappointingly modest *E* stereoselectivities (Figure 13).

TRIFLUOROMETHYL- AND MONOFLUOROALKENES

Stereoselective access to haloalkenes, especially bromides and iodides, would be extremely useful for cross-coupling reactions. Unfortunately, the synthesis of the requisite precursors has proved elusive to date.[39] In contrast, modular, flexible routes to trifluoromethyl- and monofluoroalkenes, two classes of derivatives of importance for the pharmaceutical, agrochemical, and materials science industries could be established.

Various trifluoromethylalkenes were thus assembled by placing the trifluoromethyl group at either the α- or β-position relative to the fluoropyridyloxyl leaving group. The precursors were readily made from trifluoromethyl ketones or from the anion derived from 2-bromo-3,3,3-trifluoropropene, respectively. In fact, this dual strategy enables the preparation of trifluoromethylalkenes **76** and **78** that are regioisomeric to one another (Figure 14). The steric bulk of the CF_3 group translates into the preferential formation of the *E* isomer with good stereoselectivities. The complementarity of the two strategies is showcased by examples **76e** and **78c**. Indeed, while trifluoromethylalkene **76e** synthesized using strategy A was obtained with no control of the double bond geometry, strategy B allowed the placement of the bulky *t*-BuCH_2 group on the side opposite to the CF_3 group in **78c**.

The equally important vinyl fluorides can be reached by a similar strategy. Indeed, tri- and tetrasubstituted vinyl fluorides

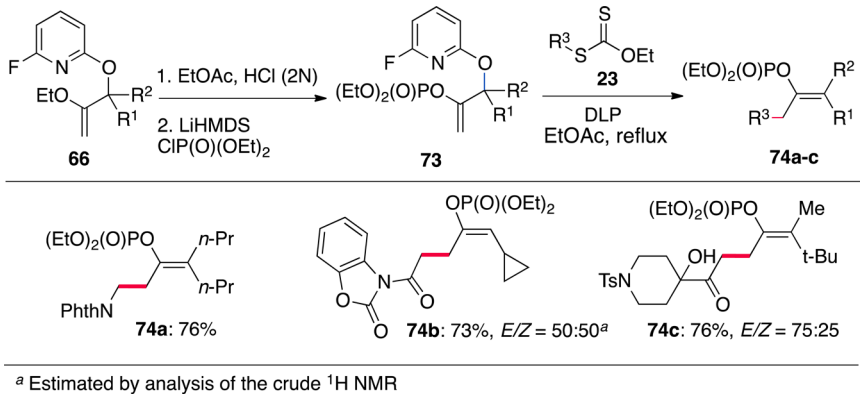


Figure 13. Synthesis of enol phosphates.

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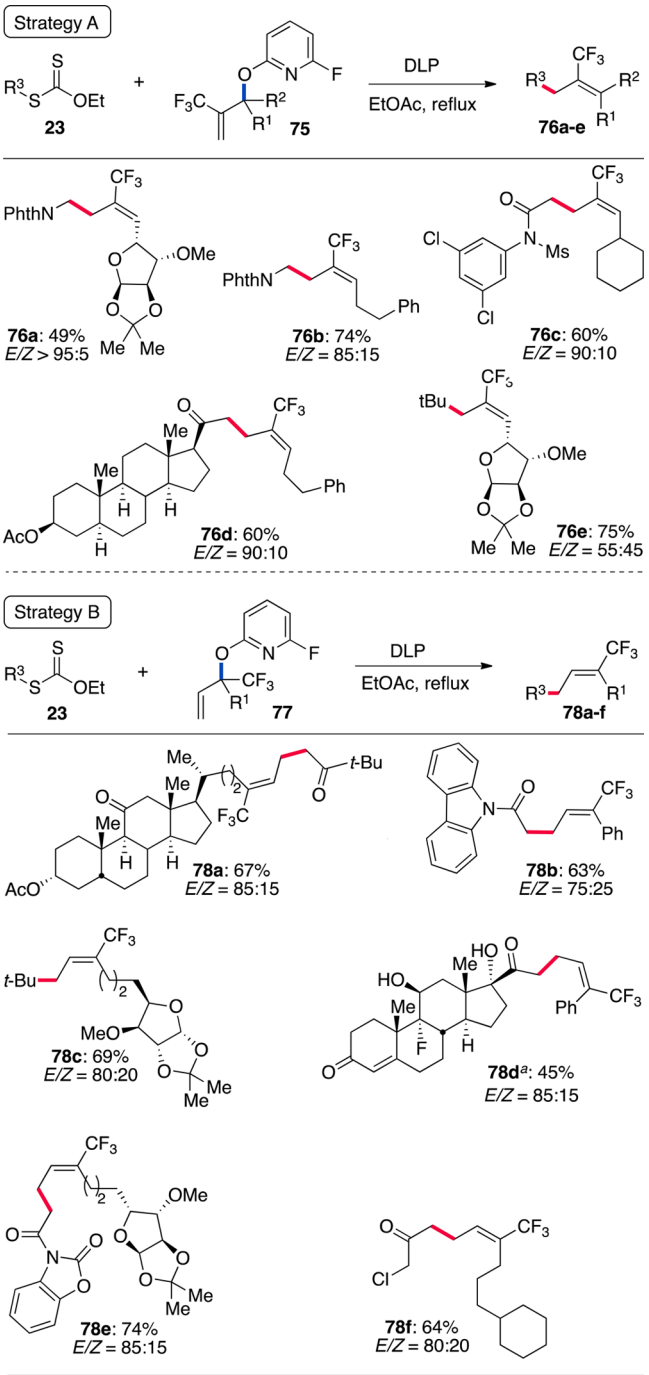

[a] The reaction was carried out in a 1:1 refluxing mixture of trifluoroethanol and 1,2-dichloroethane.

Figure 14. Synthesis of trifluoromethylalkenes.

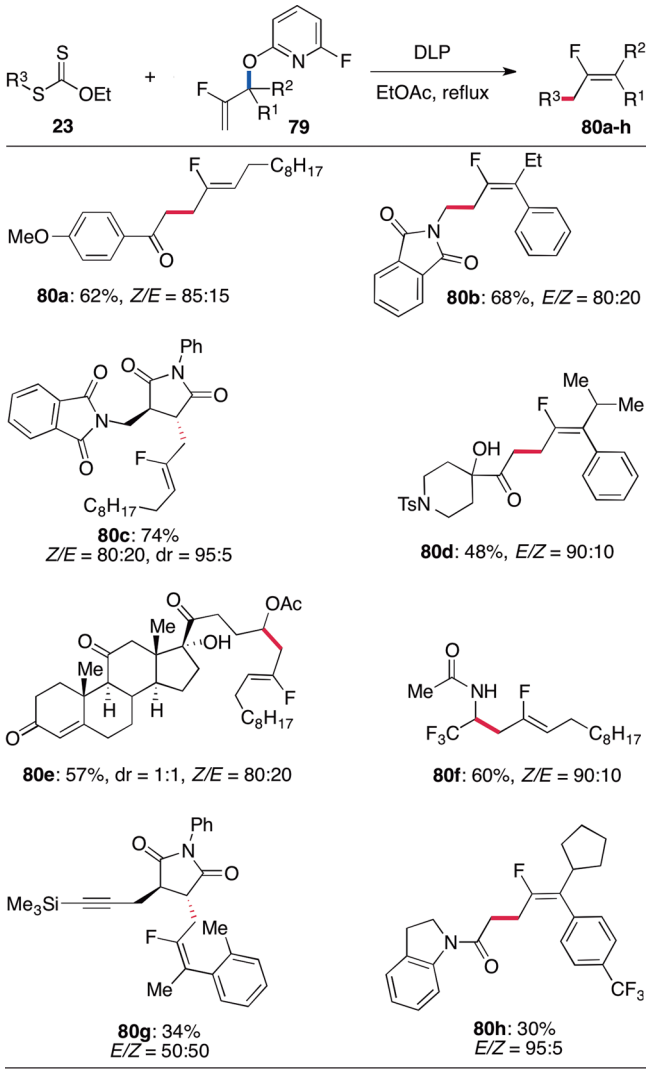

Figure 15. Synthesis of vinyl fluorides.

80 may be prepared from fluoropyridyl ethers **79** and xanthates **23** under identical reaction conditions (Figure 15).

The fluorine atom is the smallest substituent and tends to position itself cis to the bulkier R^1/R^2 group in the transition state to give the *Z* isomer preferentially. Surprisingly, when one of the substituents is an aryl group, the stereoselectivity of the reaction is reversed, and the *E* isomer is mainly obtained. This divergence in selectivity remains unexplained, since any kind of a π or agostic interaction with the aromatic substituent can hardly be invoked given the reaction temperature. Dipole minimization could be directing the stereochemistry, however, as suggested by one referee. In any event, the successful assembly of the more substituted analogues is remarkable in view of the challenges related to their stereoselective preparation explicitly voiced in a recent review.[40] Finally, we observed significantly lower yields in cases where one of the substituents is an aromatic ring (**80g** and **80h**), possibly because of a competing radical Smiles rearrangement (i.e., *ipso*-radical attack on the aromatic ring).

ALDEHYDES AND KETONES BY ALLYLATION VIA C−C BOND FRAGMENTATION

A striking behavior was observed when derivatives **81** were reacted with xanthate **23j** (Scheme 15). Substrates where the vinyl motif is substituted with an electron-donating group (Me, SPh), reacted as expected to give alkenes **83b** and **83d** (path A). In sharp contrast, those bearing an electron-withdrawing substituent (CF_3, SO_2Ph) unexpectedly underwent rupture of the benzylic C−C bond to furnish enol ethers **84a** and **84c** (path B).[41] Such clear-cut manifestations of polar effects are very rare in homolytic processes. While these effects have important synthetic consequences as discussed below, they also provide interesting information on our system. The electron-poor pyridine nucleus lowers the energy of the C−O σ^* antibonding orbital and favors the interaction with the high-lying SOMO of the electron-rich radicals. The β-fragmentation is thus

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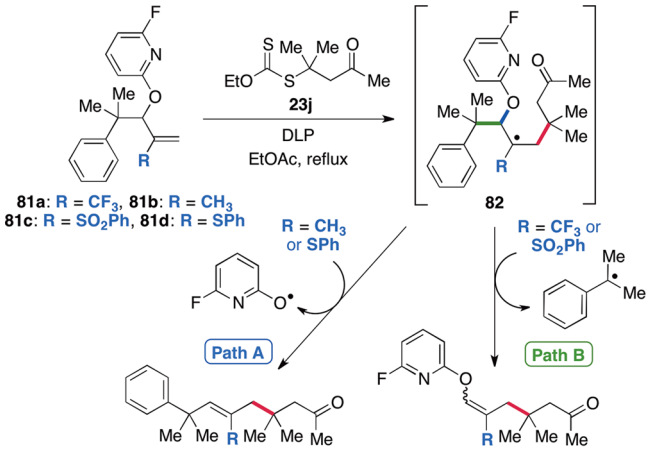
Scheme 15. C−O versus C−C Bond Fragmentation

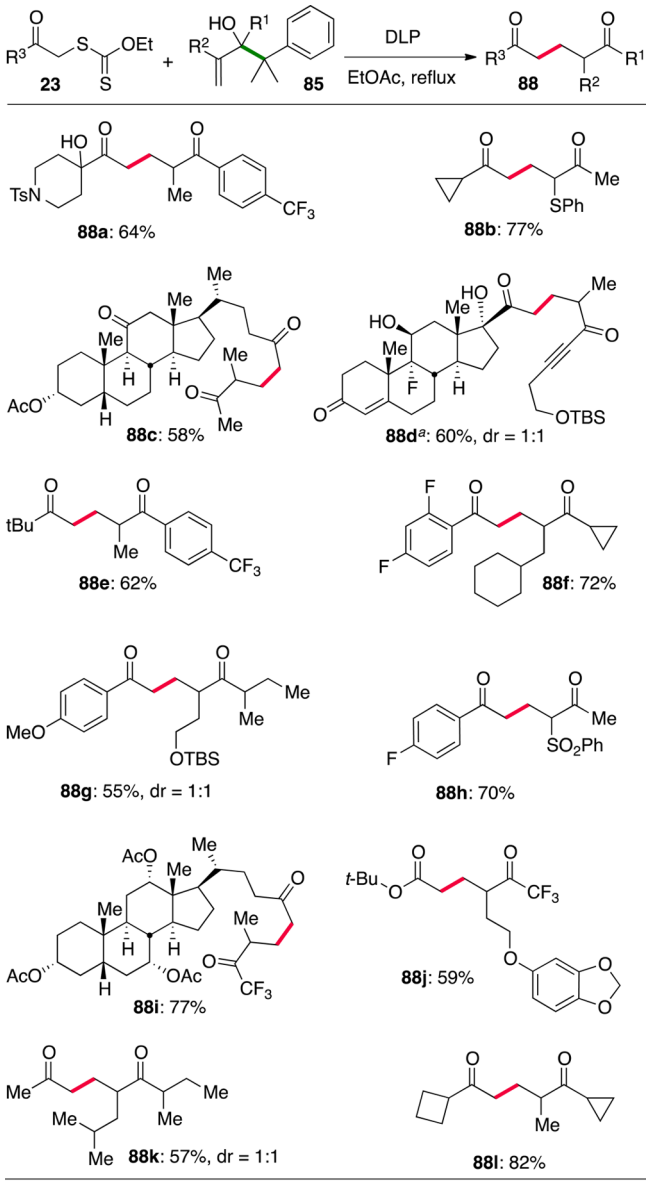


R = CF_3	**83a**: 0%	**84a**: 82%, *E*/*Z* = 50:50
R = CH_3	**83b**: 56%, *E*/*Z* = 96:4	**84b**: 0%
R = SO_2Ph	**83c**: 0%	**84c**: 75%, *E*/*Z* = 65:35
R = SPh	**83d**: 60%, *Z*/*E* = 80:20	**84d**: 0%

significantly faster for electron-rich-substituted allylating agents (Me, SPh) compared with the electron-poor-substituted precursors (CF_3, SO_2Ph). The good levels of *E* selectivity observed for vinyl sulfones and trifluoromethylalkenes are in fact partly a consequence of this polarity mismatch, which slows the elimination sufficiently to allow the intermediate radical to adopt its most stable conformation prior to fragmentation.

The homolytic fragmentation of C−C bonds from carbon-centered radicals in unstrained structures under such mild reaction conditions is rare and virtually unexploited in synthesis. We therefore considered the possibility of generalizing this unusual fragmentation as a new radical allylating process.[42] The fluoropyridyl group was first replaced by a simple acetyl group (**85**, R = $COCH_3$; Scheme 16). Unlike the fluoropyridoxyl group, an acetoxy group is very difficult to cleave homolytically, and only fragmentation of the C−C bond should occur. This was indeed the case, but another competing pathway emerged, namely, ring closure to give indane **87**. A practical solution to this complication was to use the free alcohol. The enhanced interaction between a lone pair on the oxygen atom of the free alcohol and the σ^* orbital of the benzylic C−C bond significantly weakens this bond by what may be viewed as an anomeric-type effect. This makes the fragmentation significantly faster than the undesired cyclization and opens a powerful route to ketones and aldehydes.

We first focused on the synthesis of 1,5-diketones (**85** → **88**; Figure 16) because of their value as intermediates for the preparation of various important six-membered-ring derivatives. The exceptional functional group tolerance of the process is demonstrated by the examples shown, especially the syntheses of



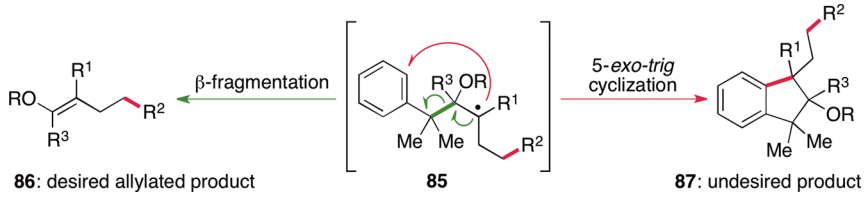
[a] The reaction was carried out in a 1:1 refluxing mixture of trifluoroethanol and 1,2-dichloroethane.

Figure 16. 1,5-Diketones by allylation via C−C bond cleavage.

ynone **88d** and α-substituted trifluoromethyl ketone **88i**. These compounds would be very tedious to prepare by ionic- or organometallic-based approaches. Particularly gratifying is the fact that allylic alcohols **85** bearing either electron-withdrawing or electron-donating groups at the β-position are competent substrates.

Complexity may also be introduced by combining this new ketone-forming reaction with the normal intermolecular addition

Scheme 16. Competition between Fragmentation and Cyclization



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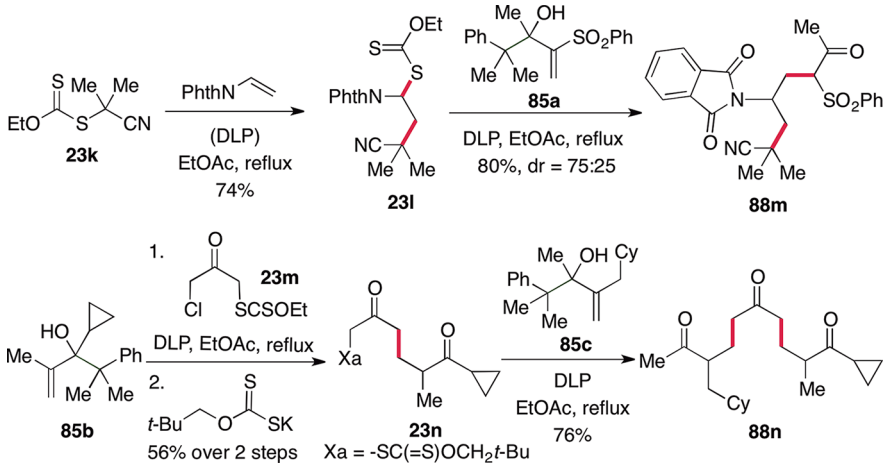
Scheme 17. Combinations of the Xanthate Transfer and Allylation



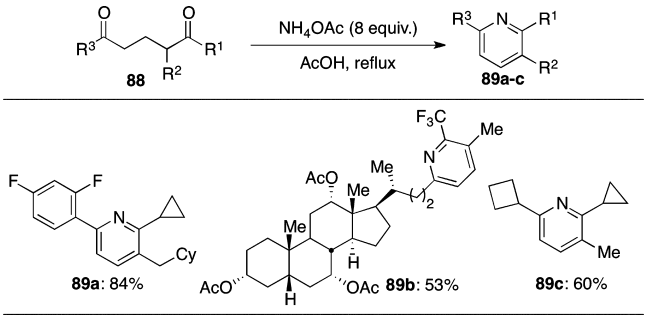


Figure 17. Synthesis of pyridines.

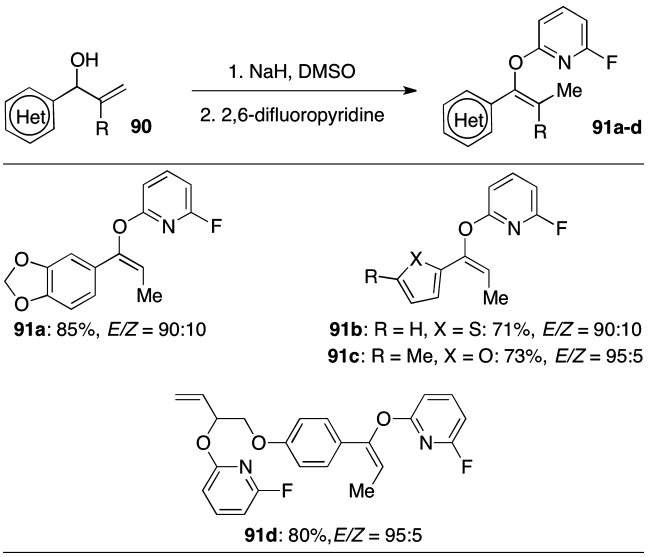


Figure 18. Isomerization during the activation step.

of xanthates to olefins (**23k** → **88m**; Scheme 17). Alternatively, complex triketones may be assembled by using chloroacetonyl xanthate **23m**. The product from the first allylation is easily converted into the new xanthate **23n**, which in turn can be reacted with a different allylating agent, **85c**, to provide functionalized unsymmetrical triketone **88n**.

1,5-Diketones are traditional precursors of pyridines. The present novel route therefore allows the assembly of trisubstituted pyridines **89** with unusual and otherwise difficult to access substitution patterns (Figure 17).

CONCLUSION

The possibility of using allylic alcohols as radical allylating agents in association with the powerful chemistry of xanthates opens up vast opportunities for the convergent, modular synthesis of alkenes, ketones, and aldehydes. Numerous functional groups are tolerated, and unusual retrosynthetic disconnections that were not hitherto feasible can now be conceived. Nevertheless, there remain some limitations related to the preparation of the starting allylating agents. Routes to fluoropyridoxyl precursors possessing halides and trialkylsilyl groups on the vinyl motif still need to be developed. The introduction of electron-withdrawing groups on the vinyl substituent has also proved to be problematic. Another difficulty arises from the base-induced migration of the terminal double bond in the course of the nucleophilic aromatic substitution when the starting alcohol is of the general structure **90** (**90** → **91**; Figure 18). Efforts to overcome these limitations as well as a better delineation of the scope are underway. For instance, the introduction of a boronate on the vinyl group would be highly desirable, as it would enable the application of the potent Suzuki−Miyaura coupling. Extension to the synthesis of dienes and implementation of internal hydrogen atom abstraction/elimination sequences must also be explored. This methodological study should ultimately be complemented by concise total syntheses of natural products in order to illustrate its utility.

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(28) The radical allylation using β-substituted precursors leads to the formation of substantial amounts of ring-opened derivatives, as in the example below taken from ref 27. The rate constant for ring opening of a substituted cyclobutylmethyl radical is estimated to be 10^3−10^4 s^{-1} (see ref 29).

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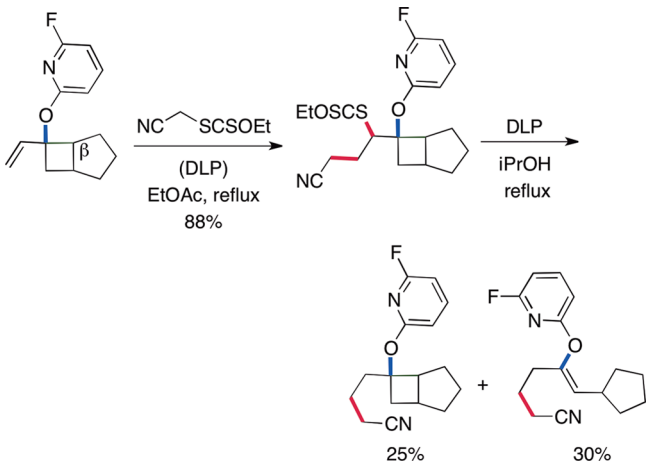

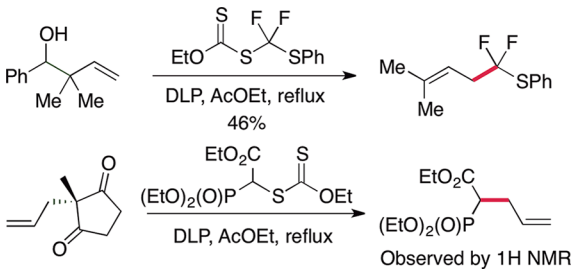

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