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Base-Promoted C−C Bond Activation Enables Radical Allylation with Homoallylic Alcohols

Maximilian Lübbesmeyer, Emily G. Mackay, Mark A. R. Raycroft, Jonas Elfert, Derek A. Pratt,* and Armido Studer*

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ABSTRACT: The C_α−C_β bond in homoallylic alcohols can be activated under basic conditions, qualifying these nonstrained acyclic systems as radical allylation reagents. This reactivity is exemplified by photoinitiated (with visible light and/or blue LEDs) allylation of perfluoroalkyl and alkyl radicals generated from perfluoroalkyl iodides and alkylpyridinium salts, respectively, with homoallylic alcohols. C-radical addition to the double bond of the title reagents and subsequent base-promoted homolytic C_α−C_β cleavage leads to the formation of the corresponding allylated products along with ketyl radicals that act as single electron reductants to sustain the chain reactions. Substrate scope is documented and the role of base in the C−C bond activation is studied by computation.
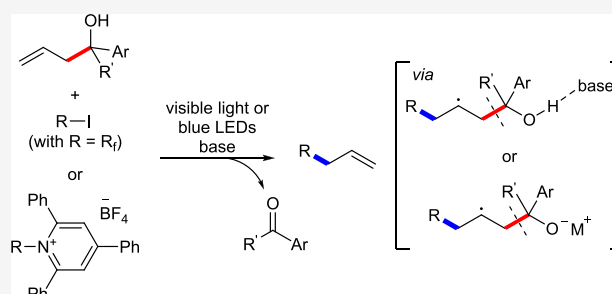
1. INTRODUCTION

The difficult activation of C−C bonds precludes its routine implementation as a strategic disconnection in retrosynthetic analyses.[1−3] Along these lines, efficient C−C bond cleavage is generally achieved only in strained cyclic systems where relief of ring-strain drives the fragmentation process. Indeed, σ-bond cleavage in nonstrained compounds remains a significant and largely unmet challenge.[2−5] Among developments in the context of the reactivity reported below, retroallylation of acyclic homoallylic alcohols by various metals, e.g., Li,[6,7] Mg,[7] Zn,[8,9] Ru,[10] Ga,[11] Rh,[12] Pd,[13−16] Ni,[17] and Cu,[18] is particularly relevant (Scheme 1a). The resultant organometallic species can then be added to various electrophiles. Since allyl groups are attractive structural entities that can be readily converted into a range of functional groups, we sought to develop homoallylic alcohols as radical allylation reagents (Scheme 1b).

Current methods for radical allylation rely on the homolytic cleavage of C−Sn,[19,20] C−S,[21−24] C−Si,[25,26] C−Cl/Br,[27−29] C−P,[30] or C−O[31−33] carbon−heteroatom bonds. To the best of our knowledge, the only radical allylations proceeding via C−C bond cleavage were achieved by Nishikata et al. using copper catalysis[34] and Zard and Debien, who discovered in the course of their studies on allylic alcohols and ethers as allylating reagents that α-substituted allylic alcohols can undergo carbon radical induced C−C-bond homolysis leading to functionalized ketones (after tautomerization).[35] Current methods typically require high temperatures and many involve the use of toxic reagents. Addressing these critical aspects, Weaver and Priya recently developed a mild photocatalytic prenylation of perfluorinated aryl radicals with allylic ethers.[33]

Herein, we disclose our results on the use of homoallylic alcohols as radical allylation reagents.

We were motivated by recent studies by Zhu and co-workers as well as some of our own successful radical alkene difunctionalizations, which proceed via intramolecular alkynyl and alkenyl migrations involving a C−C bond homolysis step.[36−40] We envisioned that either deprotonation of or hydrogen-bond donation from a homoallylic alcohol **1** would activate the C_α−C_β bond, enabling radical-mediated fragmentation as part of an overall allylation reaction. This activation mode, reminiscent of the "oxy-anionic substituent effect" in the oxy-Cope reaction,[41,42] has been leveraged for the activation of α-C−H bonds,[43−45] in selective C−H functionalization reactions[46] and efficient H-atom abstractions.[47,48] Such σ-bond activation relies on the interaction of the oxygen lone pair with the σ^*_{CC} or σ^*_{CH} orbital and, perhaps more importantly, by destabilizing the substrate (when involving ions in apolar solvents) while stabilizing the products resulting from σ-bond cleavage.

With regard to homolytic C−C bond cleavage, this effect is also known,[49,50] albeit less intensively explored, and applied in reverse pinacol coupling reactions,[51−54] cleavage of α,β-dihydroxyketones,[55] and the aforementioned intramolecular alkynyl and alkenyl migrations.[37,39] As a working model, we
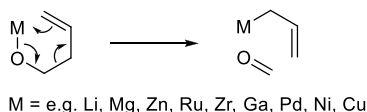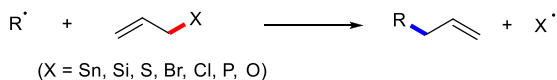
Scheme 1. Metal Catalyzed Retroallylation, Complementary Base-Promoted Radical Allylation, Existing Methodology, and Suggested Mechanism for the Allylation Using Homoallylic Alcohols
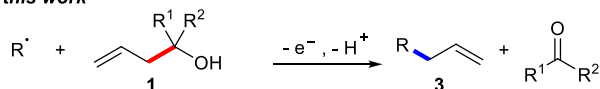
a) Retroallylation by C–C bond activation

M = e.g. Li, Mg, Zn, Ru, Zr, Ga, Pd, Ni, Cu

b) Homoallylic alcohols in radical allylations and established reagents
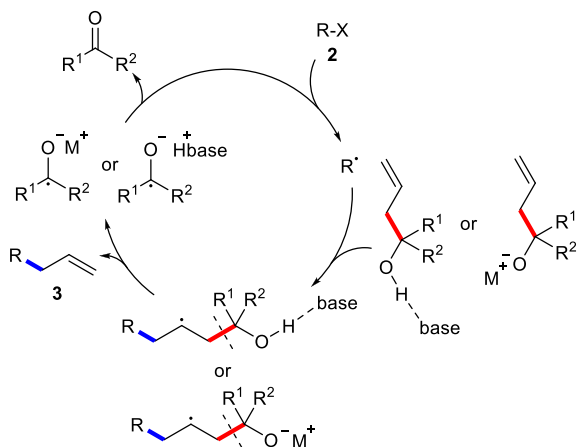
prior work

(X = Sn, Si, S, Br, Cl, P, O)

this work

c) Base-promoted radical allylation - suggested mechanism

envisioned that alkyl radical addition to a compound of general structure **1** would afford the allylation product **3** along with a ketyl radical anion that could be used to generate a new alkyl radical by dissociative electron transfer to a suitable precursor **2**, making possible a radical chain reaction as in Scheme 1c. Hence, this sequence qualifies as an electron-catalyzed process.[56,57] Due to the intrinsically strong C–C σ-bond, an S_H2'-type concerted addition/fragmentation was expected to be less likely.[58] The homoallylic alcohol could, in principle, be preactivated to C–C fragmentation either by deprotonation by a strong base or by an H-bonding interaction with a weak base. Given the acidity of the resultant α-hydroxyalkyl radical,[59,60] a ketyl radical is expected after/during fragmentation even in the presence of a weak base.

2. RESULTS AND DISCUSSION

To test our hypothesis, we chose perfluoroalkyl iodides **2** as radical precursors since their single electron reductive cleavage is well established and the corresponding perfluoroalkyl radicals are known to efficiently add to unactivated terminal alkenes.[37,39] Initiation with such radical precursors can be readily achieved by simple visible light irradiation. Moreover, fluoroalkyl substituents are privileged motifs in agricultural[61] and medicinal chemistry,[62,63] due primarily to their lip-

Scheme 2. Radical Allylation of Perfluorobutyl Iodide with 1a[a]

Method A
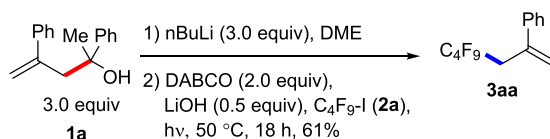
Method B
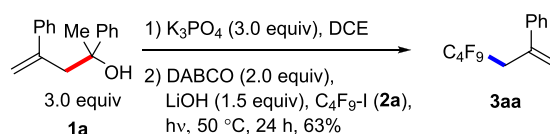
[a]The reactions were performed with **1** (3.0 equiv), C_4F_9I (1.0 equiv), nBuLi (1.6 M in hexane, 3.0 equiv) or K_3PO_4 (3.0 equiv), DABCO (2.0 equiv), LiOH (0.50 equiv or 1.5 equiv), DME or DCE (0.10 M). For visible-light irradiation, a Philips Master HPI-T Plus (400 W) bulb was used. Isolated yields are reported.

Table 1. Reaction of 2a with Various Homoallylic Alcohols: Variation of the Substituents R^1 and R^{2a}
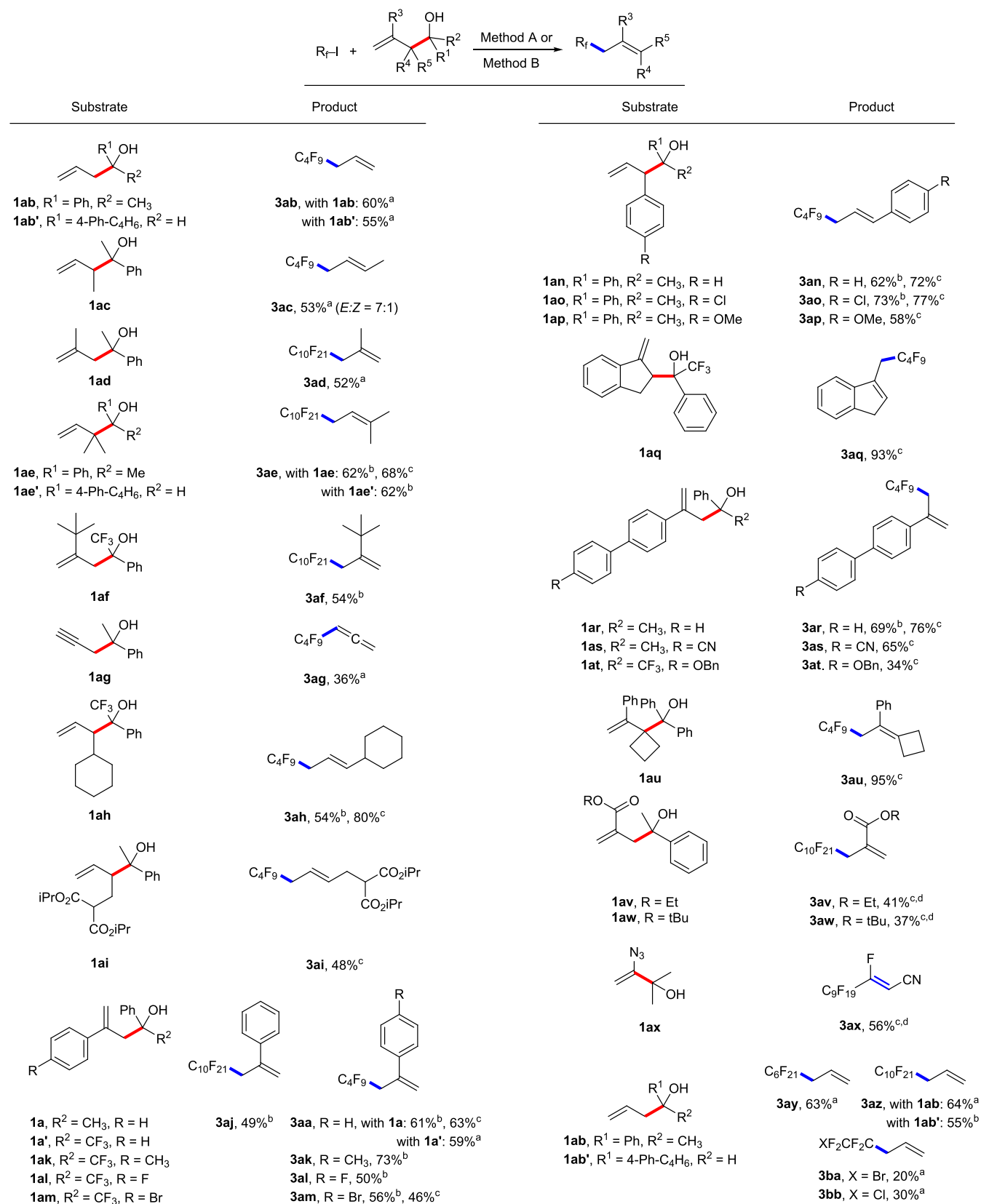

entry	R^1	R^2	yield (method A)	yield (method B)
1	H	H	nd	nd
2	H	Me	nd	15%
3	Me	Me	<5%	35%
4	H	Ph	62%	22%
5	H	$4-F-C_6H_4$	68%	27%
6	H	$4-NC-C_6H_4$	75%	13%
7	H	$4-Ph-C_6H_4$	85%	26%
8	H	$4-MeO-C_6H_4$	61%	36%
9	Me	Ph	65%	68%
10	CF_3	Ph	59%	35%
11	Ph	Ph	71%	77%

[a]Yields determined by ^{1}H NMR and/or ^{19}F NMR of the crude reaction mixture. 1,3,5-Trimethoxybenzene and benzotrifluoride were used as internal standards. nd: not detected.

ophilicity and metabolic stability, which enhance bioavailability.

The optimized reaction conditions are presented in Scheme 2 (see the Supporting Information for details on the optimization). Following an extensive screen of basic reagents, we found that the Li-alcoholate Li-**1a** generated by deprotonation of **1a** with nBuLi in 1,2-dimethoxyethane (DME) reacts with perfluorobutyl iodide (**2a**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and LiOH under visible light irradiation at 50 °C to yield the target compound **3aa** (61%, method A). While deprotonation with nBuLi was not necessary for the activation of **1a** (omission of nBuLi gave a similar yield), the addition of nBuLi was strictly necessary for the activation of several other substrates (e.g., **1ab**, vide infra). Alternatively, allylation with **1a** could be achieved under milder conditions using potassium phosphate to provide **3aa** (63% yield, method B). Without potassium phosphate, the desired product **3aa** was also formed, albeit in lower yield of 44%. These results indicate that the C–C bond cleavage can also be

Scheme 3. Reaction of Perfluoroalkyl Iodides with Various Homoallylic Alcohols

Substrate	Product	Substrate	Product

1ab, R^1 = Ph, R^2 = CH$_3$
1ab', R^1 = 4-Ph-C$_4$H$_6$, R^2 = H

3ab, with **1ab**: 60%[a]
with **1ab'**: 55%[a]

1ac

3ac, 53%[a] (*E:Z* = 7:1)

1ad

3ad, 52%[a]

1ae, R^1 = Ph, R^2 = Me
1ae', R^1 = 4-Ph-C$_4$H$_6$, R^2 = H

3ae, with **1ae**: 62%[b], 68%[c]
with **1ae'**: 62%[b]

1af

3af, 54%[b]

1ag

3ag, 36%[a]

1ah

3ah, 54%[b], 80%[c]

1ai

3ai, 48%[c]

1a, R^2 = CH$_3$, R = H
1a', R^2 = CF$_3$, R = H
1ak, R^2 = CF$_3$, R = CH$_3$
1al, R^2 = CF$_3$, R = F
1am, R^2 = CF$_3$, R = Br

3aj, 49%[b]

3aa, R = H, with **1a**: 61%[b], 63%[c]
with **1a'**: 59%[a]
3ak, R = CH$_3$, 73%[b]
3al, R = F, 50%[b]
3am, R = Br, 56%[b], 46%[c]

1an, R^1 = Ph, R^2 = CH$_3$, R = H
1ao, R^1 = Ph, R^2 = CH$_3$, R = Cl
1ap, R^1 = Ph, R^2 = CH$_3$, R = OMe

3an, R = H, 62%[b], 72%[c]
3ao, R = Cl, 73%[b], 77%[c]
3ap, R = OMe, 58%[c]

1aq

3aq, 93%[c]

1ar, R^2 = CH$_3$, R = H
1as, R^2 = CH$_3$, R = CN
1at, R^2 = CF$_3$, R = OBn

3ar, R = H, 69%[b], 76%[c]
3as, R = CN, 65%[c]
3at, R = OBn, 34%[c]

1au

3au, 95%[c]

1av, R = Et
1aw, R = tBu

3av, R = Et, 41%[c,d]
3aw, R = tBu, 37%[c,d]

1ax

3ax, 56%[c,d]

1ab, R^1 = Ph, R^2 = CH$_3$
1ab', R^1 = 4-Ph-C$_4$H$_6$, R^2 = H

3ay, 63%[a]   **3az**, with **1ab**: 64%[a]
with **1ab'**: 55%[b]

3ba, X = Br, 20%[a]
3bb, X = Cl, 30%[a]

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[a]Yields were determined by ^{19}F-NMR with benzotrifluoride as an internal standard. Method A was applied. [b]Isolated yields. Method A was applied. [c]Isolated yields. Method B was applied. [d]No LiOH was added.

Scheme 4. Radical Allylation of Various Katritzky Salts with Homoallylic Alcohols[b]

5a, 67%   5b, 49%

5c, 37%   5d, 36%   5e, 41%

Variation of the C-radical precursor

5f, 38%[a]

5g, 46%[a]

5h, R = H, 66%
5i, R = Me, 54%
5j, R = Cl, 67%
5k, R = CN, 64%

5l, 67%

5m, 39%   5n, 71%   5o, 57%   5p, 72% (dr = 1:1)

5q, 57%   5r, 67%   5s, 60%   5t, 57%
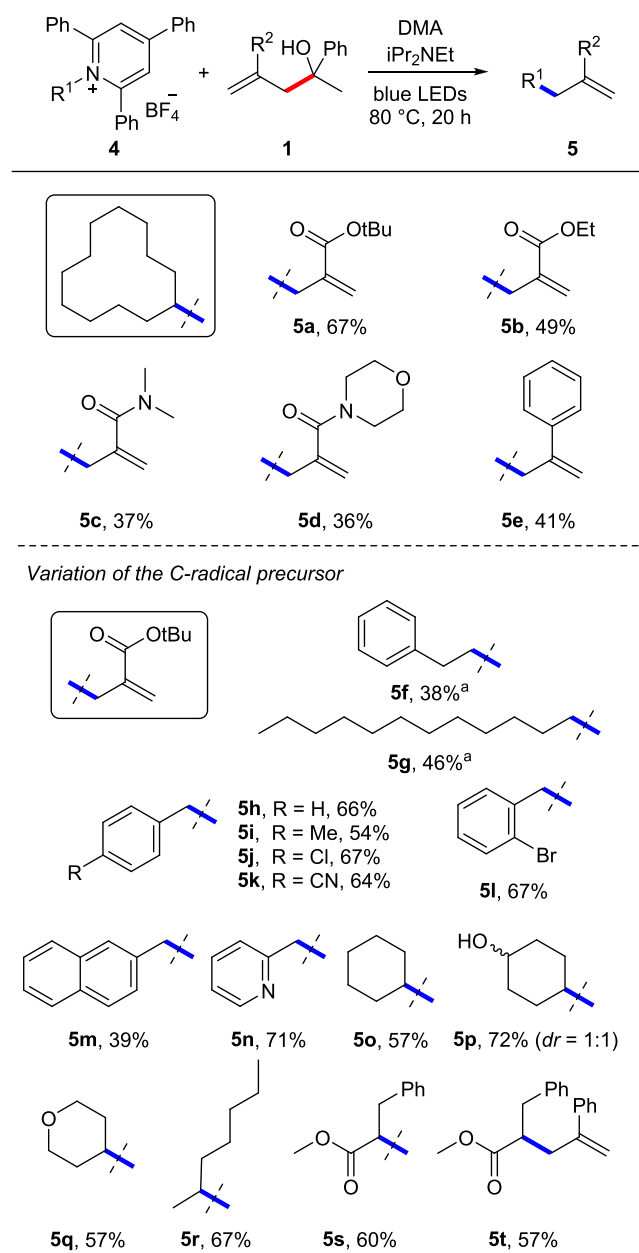
[a]Reaction performed at 120 °C instead of 80 °C. [b]The reactions were performed with 4 (1.0 equiv), 1 (3.0 equiv), iPr$_2$NEt (1.5 equiv), and DMA (0.10 M). The reaction tubes were heated in a beaker filled with paraffin oil and irradiated with two blue LEDs (5 W each, 465 nm). Isolated yields.

promoted by LiOH or DABCO. In the absence of any base, the product was not formed. For both protocols, DABCO significantly increased the yield, likely due to more efficient radical initiation.[64,65]

Since the stability of the ketyl radical leaving group should have an impact on the rates of both the fragmentation and the reduction of the radical precursor, we tested different homoallylic alcohols in the reaction with **2a**, varying the substituents R^1 and R^2 (Table 1). Little to no product formation was observed for the α-unsubstituted, monomethyl, or dimethyl substituted homoallylic alcohols (Table 1, entries
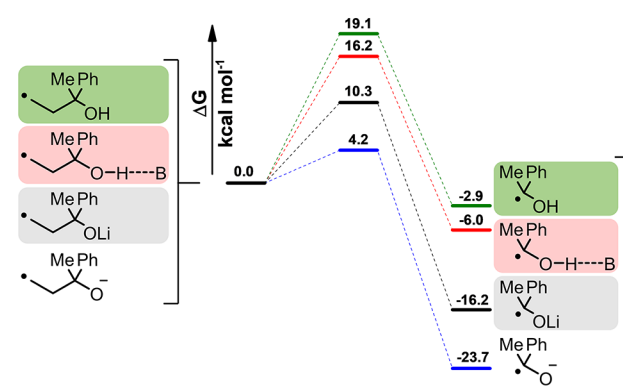
1−3). A stabilizing aromatic substituent appears to be required, as the monophenyl congener provided **3aa** in 62% yield using method A (Table 1, entry 4). Notably, when this homoallylic alcohol and all other secondary benzylic alcohols were tested as acceptors, method B afforded significantly lower yields (Table 1, entries 4−8). The electronics of the α-aryl substituent were found to be relatively unimportant; although slightly higher yields could be obtained with π-conjugating or electron-withdrawing substituents (e.g., 85% and 75% for para-biphenyl and para-cyanophenyl alcohols, respectively), electron-rich aryl substituents were still reasonable substrates (e.g., α-para-methoxyphenyl gave 61% yield). The highest yields using either method were obtained when tertiary homoallylic benzylic alcohols were used as the allylating reagent (Table 1, entries 9−11).

We next focused on the scope of the reaction and tested different homoallylic alcohols as substrates in combination with various perfluoroalkyl iodides (Scheme 3). Most of the acceptors were readily prepared from the corresponding allyl bromides by the Barbier reaction (see the Supporting Information). Since tertiary alcohols generally gave higher yields, we focused on α-methyl-α-phenyl and α-phenyl-α-trifluoromethyl homoallylic alcohols. While the former usually resulted in slightly higher allylation yields, the Barbier reaction providing the latter was more efficient. The promising α,α-diphenyl congeners were not considered in the scope study, since the Barbier reaction to form them was presumably less efficient. In selected cases (**3ab**, **3ae**, and **3az**), the corresponding secondary p-phenylbenzyl alcohols were tested; however, lower yields were observed compared to those obtained with the tertiary homoallylic alcohols.
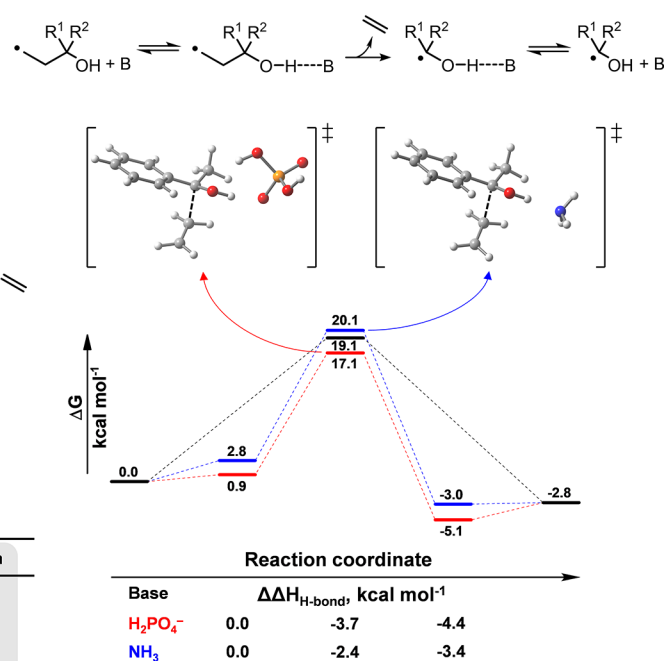
Homoallylic alcohol **1ab** was used to allylate perfluoroalkyl iodide **2a** to yield **3ab** in 60% yield using method A. Notably, we did not observe product formation with method B. We surmised that iodine atom transfer to the intermediate alkyl radical is faster than the desired fragmentation. Subsequent elimination of HI would lead to the corresponding alkene, which was observed by GC-MS. Alkyl groups in the β- and γ-positions of the homoallylic alcohol are tolerated and the allylated products **3ac**, **3ad**, **3af**, and **3ah** were obtained in 52−80% yield. Also, prenylation proved to be feasible (**3ae**, 68% yield). Starting with a homopropargylic alcohol, the allene **3ag** could be prepared, albeit in moderate yield (36%). The dialkylmalonyl moiety is compatible with method B (**3ai**, 48% yield). Aryl groups are tolerated in the γ-position as well as the β-position of the homoallylic alcohol (**3aa**, **3ak−3ap**, 50−77% yield). Also, α-biphenyl-substituted homoallylic alcohols were successfully alkylated with **2a** (**3ar−3at**, 34−76% yield). The functionalized indene **3aq** and the alkylidenecyclobutane **3au** were obtained in excellent yields (93% and 95%, respectively).

The perfluorobutyl iodide (**2a**) could be replaced with other perfluoroalkyl radical precursors, as demonstrated by the successful preparation of **3ad−3af**, **3aj**, and **3ax−3az**. ICF$_2$CF$_2$Br and ICF$_2$CF$_2$Cl reacted chemoselectively to give **3ba** and **3bb**, respectively, albeit in low yield. Surprisingly, even homoallylic alcohols bearing an electron deficient double bond reacted with electrophilic perfluoroalkyl radicals to give the allylated products **3av** and **3aw**, albeit in modest yields (41% and 37%, respectively). We also tested a cyanomethylation, which proceeds via radical addition to vinyl azide **1ax**, loss of dinitrogen and subsequent fragmentation of the iminyl radical.[66] The primary allylation product was found to be

A) Computed mechanisms of base-promoted C–C homolysis

B) Substituent effects on ΔG for C–C homolysis

	ΔG, kcal·mol⁻¹					
	OH		**OH---OPO₃H₂**		**OLi**	
R¹, R²	**Me, Me**	**Me, Ph**	**Me, Me**	**Me, Ph**	**Me, Me**	**Me, Ph**
SM	0.0	0.0	0.0	0.0	0.0	0.0
TS	21.3	19.1	20.1	16.2	12.6	10.3
P	7.2	-2.9	6.3	-6.0	0.1	-16.2

C) H-bond-promoted C–C homolysis

Base	ΔΔH$_{H\text{-bond}}$, kcal mol⁻¹		
H₂PO₄⁻	0.0	-3.7	-4.4
NH₃	0.0	-2.4	-3.4

Figure 1. (A) Computed (CBS-QB3) free energy barriers for C–C bond fragmentation in model intermediates featuring different electronics about the oxygen atom of the incipient ketyl radical. (B) Comparison of the reactivity involving H-bond assistance (with $H_2PO_4^-$) and lithium alcoholate formation to that of the unassisted alcohol using the computed free energies for C–C bond fragmentation when $R^1 = R^2$ = Me and R^1 = Me, R^2 = Ph. (C) Reaction pathway and corresponding free energy diagram depicting H-bond-assisted C–C bond fragmentation (black, no H-bond assistance; red, B = $H_2PO_4^-$; blue, B = NH_3) where R^1 = Me, R^2 = Ph. All computed values shown employ a CPCM solvation model for 1,2-dichloroethane.

unstable and underwent HF elimination under the reaction conditions to provide compound **3ax** in 56% isolated yield.

To demonstrate the general applicability of our allylation approach, we also investigated Katritzky salts as radical precursors, since they can be readily obtained from primary amines and efficiently undergo single electron reduction to yield alkyl radicals.[67−74] In contrast to the perfluoroalkyl radicals that are electrophilic, the Katritzky salts enable generation of nucleophilic alkyl radicals, thereby expanding the scope with respect to the electronics of the homoallyl alcohol acceptors.

We therefore chose the electrophilic *tert*-butyl acrylate **1aw** as a reaction partner. After careful reaction optimization (see the Supporting Information for full details), we found that 1-cyclododecyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **4a** could be allylated with **1aw** in 67% yield upon irradiation with blue LEDs at 80 °C in *N,N*-dimethylacetamide (DMA) using iPr₂NEt as the base (Scheme 4). Irradiation was essential for this transformation. At lower temperatures, the desired C–C bond homolysis was less efficient, and in the absence of iPr₂NEt the yield dropped to 44%. Notably, addition of nBuLi as the base led to decomposition of the starting homoallylic alcohol and potassium phosphate promoted its lactonization. With the optimized conditions in hand, we explored the reaction scope by first varying the electrophilic homoallylic alcohol component. Along with alkyl acrylates (see **5a** and **5b**), acrylamides (see **5c** and **5d**) and also a styrene derivative (see **5e**) engaged in the reaction with salt **4a** (36−67% yield). Keeping acceptor **1aw**, we next varied the Katritzky salt. For the more challenging generation of unactivated primary alkyl radicals from pyridinium salts **4f** and **4g**, the temperature had

to be increased to 120 °C and the respective allylated products **5f** and **5g** were obtained in moderate 38% and 46% yields. However, primary benzylic pyridinium salts turned out to be good substrates to afford the desired products in synthetically useful yields (54−67%). In these systems, methyl (**5i**), chloro (**5j**), bromo (**5l**), and cyano (**5k**) substitution at the phenyl moiety was tolerated. Also, naphthyl and pyridine moieties were compatible with the conditions and the corresponding products **5m** and **5n** were obtained in 39% and 71% yield, respectively. Secondary alkyl radicals could be allylated with **1aw** via our novel method to afford the products **5o − 5r** in 57−72% yield. Of note, a free hydroxy group (**5p**) was also tolerated. Moreover, the pyridinium salt **4s**, which was derived from phenylalanine methyl ester, could be used as a precursor, and the respective allylated products **5s** and **5t** were obtained in 60% and 57% yield, respectively.

To provide insight on the mechanism of the base-promoted C–C bond cleavage reaction, we turned to CBS-QB3 computations.[75] Specifically, we explored how deprotonation or H-bonding of the homoallylic alcohol promotes C–C bond fragmentation following radical addition to the terminal double bond. Model intermediates arising from radical addition to homoallylic tertiary alcohols with either two methyl groups ($R^1 = R^2$ = Me) or one methyl (R^1 = Me) and one phenyl (R^2 = Ph) group were selected to facilitate comparison to the foregoing experimental results. For each of these two models, transition state structures for C–C bond fragmentation were readily located for each of the alcohol, alkoxide, and lithium alcoholate as well as the alcohol H-bonded to either ammonia or monobasic phosphate anion. Calculations were carried out in the gas phase as well as a self-consistent reaction field[76]

parametrized to account for the effects of the 1,2-dichloroethane solvent employed in the experiments. Free energy barriers are shown for R^1 = Me, R^2 = Ph in Figure 1A.

Several trends are notable in the data. As the electron density on the alcohol(ate) increases (OH → OLi → O$^-$), the exergonicity of the reaction increases and the magnitude of the barrier decreases. The progressively earlier nature of the transition states (TSs) can be seen in the C−C bond lengths at the TS as well as in the degree of rehybridization of the carbon atoms shown in the TS structures (see the Supporting Information). This trend is presumably driven by SM destabilization, which is accentuated in the low polarity medium (1,2-dichloroethane (DCE), used in method B above). Reactions of model substrates with R^1 = R^2 = Me were computed to be endergonic, consistent with the lesser stability of alkyl ketyl radicals relative to their aryl counterparts (Figure 1B). Nevertheless, deprotonation and formation of the lithium alcoholate yields a barrier for fragmentation that is only slightly higher than in the highly exergonic reaction when R^1 = Me, R^2 = Ph.

The electron density on the incipient ketyl radical is more subtly manipulated by H-bonding, which also reduces the barrier to C−C bond fragmentation, but to a lesser extent than deprotonation. The calculations suggest that stronger H-bonding interactions lead to larger reductions in barrier height (Figure 1C). The stronger H-bonds found for $H_2PO_4^-$ compared to NH_3 reflect the higher H-bond basicity of phosphates than amines,[77] and the progressive increase in the strength of the H-bond on going from SM to TS to P (see bottom of Figure 1C) reflects the greater H-bond acidity of the ketyl radical compared to the alcohol.[60] It is interesting to note that the strengthening of the H-bond on going from the SM to TS to P is predicted to be larger in the solvent continuum. No transition states corresponding to a concerted proton-coupled C−C bond fragmentation were identified, presumably because the resultant ketyl radical is less acidic than the conjugate acid of the H-bond acceptor.[78] It is likely, however, that subsequent oxidation of the ketyl radical by the alkyl iodide or the Katritzky salt is facilitated by the coupled movement of the proton within the H-bond, turning over the catalytic cycle and producing the ketone along with the iodide of the conjugate acid of the H-bond acceptor or triphenylpyridine, respectively.

3. SUMMARY

We have explored the activation of C_α−C_β bonds in alcohols under basic conditions. In this context, we presented a carbon-radical induced C−C bond fragmentation in homoallylic alcohols, which is facilitated by the formation of an alkoxide anion or by hydrogen-bonding, reducing the energy barrier to the fragmentation and enabling propagation of a chain reaction. This rare example of a C−C bond fragmentation in a nonstrained acyclic system was exploited for the allylation of fluoroalkyl and alkyl radicals. We are convinced that this mode of activation will serve as inspiration for the development of new useful synthetic methods.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12343.

    Experimental procedures, optimization tables, analytical data, and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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