Synthetic Methods

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Alkene 1,2-Difunctionalization by Radical Alkenyl Migration

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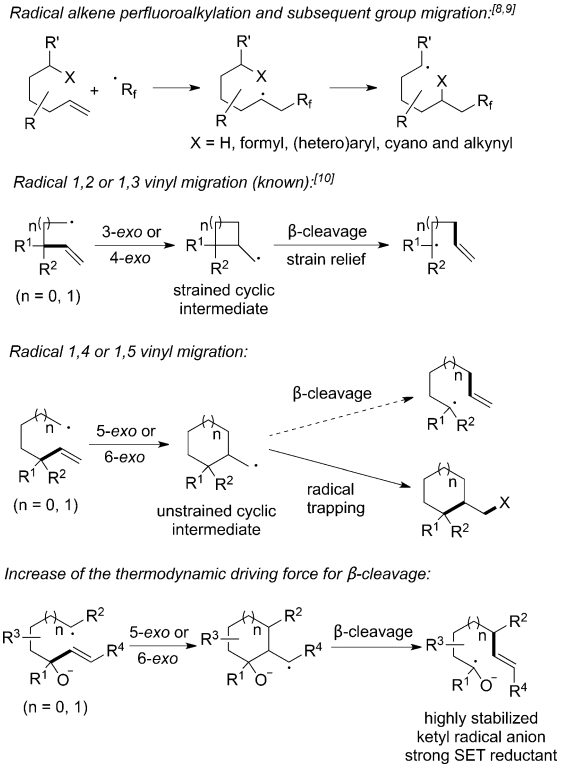
Abstract: *Transition-metal-free radical α-perfluoroalkylation with the accompanying vicinal β-alkenylation of unactivated alkenes is presented. These radical cascades proceed by means of 1,4- or 1,5-alkenyl migration by electron catalysis on readily accessed allylic alcohols. The reactions comprise a regioselective perfluoroalkyl radical addition with subsequent alkenyl migration and concomitant deprotonation to generate a ketyl radical anion that sustains the chain as a single-electron-transfer reducing reagent.*

Vicinal alkene difunctionalization is a very powerful strategy to increase complexity in organic compounds by a modular approach.[1] In the past decades, radical 1,2-difunctionalization of alkenes has attracted great interest and significant results have been achieved.[2,3] Radical alkene perfluoroalkylation with concomitant β-functionalization has received great attention,[4,5] owing to the fact that a perfluoroalkyl group (R_f) improves the solubility, bioavailability, lipophilicity, and metabolic stability of an organic compound.[6,7] Therefore, the development of methods for alkene perfluoroalkylation is of great importance.

Vicinal difunctionalization through radical perfluoroalkylation and subsequent intramolecular formyl,[8a] aryl,[8b] cyano,[8c] and heteroaryl[4e,8d] migration has been documented previously (Scheme 1). Moreover, Zhu and co-workers and our group reported cascade reactions involving a radical 1,4-alkynyl-group migration.[9] Although there are reports on radical 1,2- or 1,3-vinyl migrations,[10] the corresponding 1,4- or 1,5-vinyl migrations are not yet established in synthesis.[11] Considering the mechanisms of these reactions, 1,2- and 1,3-vinyl migrations proceed through radical 3-*exo* and 4-*exo* cyclizations that lead to highly strained three- and four-membered intermediates, which readily undergo ring opening by radical β-cleavage. Accordingly, 1,4- and 1,5-vinyl migrations have to proceed through 5-*exo* or 6-*exo* cyclizations to give thermodynamically more stable five- or six-membered cyclized radicals, which lack any strong driving force for ring opening. Indeed, 5-*exo* and 6-*exo* radical cyclizations are highly valuable in synthesis and belong to the most intensively studied radical processes to date. The β-cleavage of a cyclized radical resulting from a 5-*exo* process is only observed if trapping is very slow and if the ring-opened radical shows high thermodynamic stability.[12] Considering these prerequisites, we designed radical cascades comprising 5-*exo* or 6-*exo* cyclizations with subsequent ring opening leading to highly stabilized ketyl radical anions. These cascades should proceed in the absence of any efficient radical-trapping reagent, allowing the challenging β-C–C bond cleavage to occur. To suppress *endo*-type cyclization an R^4-substituent should be installed (Scheme 1).



Scheme 1. Intramolecular-radical-group migration.

Herein, we introduce a simple and efficient method for α-perfluoroalkylation with concomitant β-alkenylation of unactivated alkenes involving a radical 1,4- or 1,5-alkenyl migration.

(*E*)-3-Methyl-1-phenylhepta-1,6-dien-3-ol **1a** was chosen as a model substrate. The alcohol **1a** was first reacted with lithium hexamethyldisilazide (LiHMDS, 1.2 equiv) in 1.25 mL of 1,2-dimethoxyethane (DME) at room temperature for 0.5 h. After deprotonation, 1,4-diazabicyclo-[2.2.2]octane (DABCO, 1.5 equiv)[13] and perfluorobutyl iodide **2a** (1.8 equiv) were added sequentially and the mixture was stirred under visible-light irradiation [using a Philips Master HPI-T Plus (400 W) bulb] at 50 °C for 18 hours. To our

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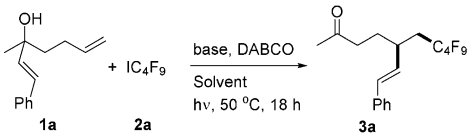
Table 1: Reaction optimization.[a]



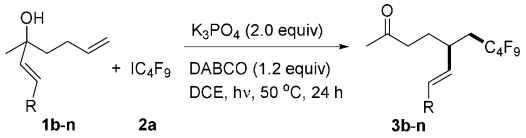
Entry	Base	Solvent	Amine	Yield of **3a** [%][b]
1	LiHMDS	DME	DABCO	34
2	LiOH	DME	DABCO	40
3	NaOH	DME	DABCO	25
4	KOH	DME	DABCO	27
5	Na_2CO_3	DME	DABCO	35
6	K_2CO_3	DME	DABCO	38
7	KO*t*Bu	DME	DABCO	16
8	K_3PO_4	DME	DABCO	41
9	K_3PO_4	1,4-dioxane	DABCO	34
10	K_3PO_4	DMA	DABCO	44
11	K_3PO_4	DMF	DABCO	–
12	K_3PO_4	DCM	DABCO	44
13	K_3PO_4	DCE	DABCO	52
14	K_3PO_4	DCE	TMEDA	21
15	K_3PO_4	DCE	DBU	10
16	K_3PO_4	DCE	TMPDA	–
17[c]	**K_3PO_4**	**DCE**	**DABCO**	**67 (63)**[d]
18	Na_3PO_4	DCE	DABCO	38
19	Li_3PO_4	DCE	DABCO	29
20	K_2HPO_4	DCE	DABCO	52
21	KH_2PO_4	DCE	DABCO	29
22[c,e]	K_3PO_4	DCE	DABCO	–
23[c,f]	K_3PO_4	DCE	–	3
24[c,g]	–	DCE	DABCO	10

[a] The reaction was conducted with **1** (0.1 mmol), **2a** (1.8 equiv), base (1.2 equiv), and amine (1.5 equiv) in 1.25 mL of solvent under visible-light irradiation [using a Philips Master HPI-T Plus (400 W) bulb] at 50 °C for 18 h. [b] Determined by ^{1}H NMR analysis by using 1-fluoro-4-methylbenzene as the internal standard. [c] K_3PO_4 (2.0 equiv) and DABCO (1.2 equiv) were used for 24 h. [d] Yield of isolated product in parenthesis. [e] The reaction was conducted without visible-light irradiation. [f] The reaction was conducted without DABCO. [g] The reaction was conducted without base. DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; DCM = dichloromethane.

delight, the 1,4-alkenyl migration product **3a** was obtained in 34% yield with complete *E* selectivity (Table 1, entry 1). The yield increased to 40% when LiOH was used as a base (Table 1, entry 2); however, with NaOH or KOH the yield decreased (Table 1, entries 3 and 4). In the presence of Na_2CO_3 or K_2CO_3 **3a** was formed in 35 or 38% yield, respectively (Table 1, entries 5 and 6), and KO*t*Bu was found not to be an efficient base to mediate this cascade (Table 1, entry 7). The highest yield in this series (41%) was obtained by using K_3PO_4 (Table 1, entry 8). A solvent screen revealed that dichloroethane (DCE) provided an improved result (52%) (Table 1, entries 9–13). Replacing DABCO by other amines, such as *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), afforded lower yields (Table 1, entries 14–16).[14] Varying the amount of base and DABCO showed that the highest yield (67%) was obtained by using **1a** (0.1 mmol), **2a** (1.8 equiv), K_3PO_4 (2.0 equiv), and DABCO (1.2 equiv) in 1.25 mL of DCE with stirring under visible light at 50 °C for 24 h (Table 1, entry 17). We also examined other phosphate salts, such as Na_3PO_4, Li_3PO_4, K_2HPO_4, and KH_2PO_4, but lower yields were obtained (Table 1, entries 18–21). Notably, the cascade reaction did not proceed without visible-light irradiation (Table 1, entry 22) and very low yields were achieved in the absence of K_3PO_4 or DABCO (Table 1, entries 23 and 24).

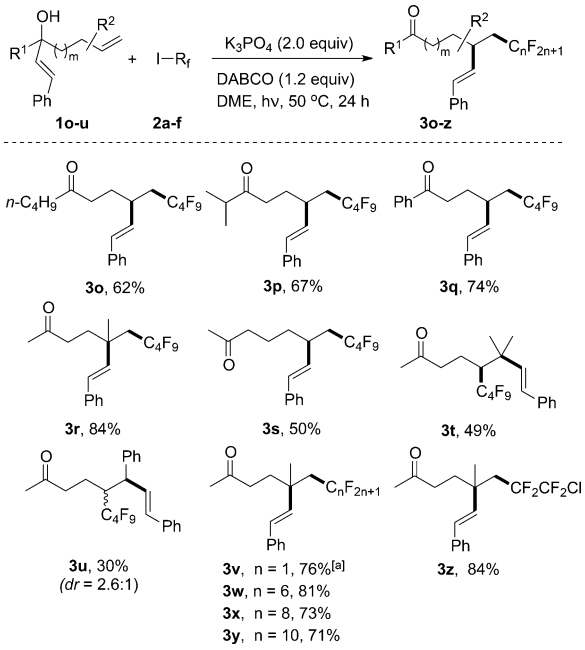
With the optimized reaction conditions in hand, we investigated the scope of the reaction by keeping perfluorobutyl iodide **2a** as the C-radical precursor and systematically varied the migrating styrenyl group (Table 2). Electronic effects at the *para* position in the aryl moiety are not pronounced and the corresponding products **3b**–**3f** were formed in moderate-to-good yields (Table 2, entries 1–5). The *meta*- and *ortho*-methyl substituted congeners **1g** and **1h** provided the targeted **3g** and **3h** in 61 and 52% yield, respectively (Table 2, entries 6 and 7). Alcohols bearing di- and trisubstituted styryl groups, such as **1i** and **1j**, afforded the corresponding ketones **3i** and **3j** in 51 and 53% yield (Table 2, entries 8 and 9), indicating that steric effects at the aryl moiety in the migrating styrenyl group do not play a major role. Notably, the 1-naphthyl and 2-pyridyl groups are both tolerated as substituents (see **3k**, **3l**, Table 2, entries 10 and 11). The silylated allylic alcohol **1m** also worked well and **3m** was isolated in 50% yield (Table 2, entry 12). Cyclohexyl-substituted allylic alcohol **1n** was also suitable for this migration reaction; however, only a moderate 23% yield of **3n** was obtained (Table 2, entry 13). Next, we studied the radical styrenyl migration on various alcohols of type **1** by varying the R^1 and R^2 substituents (Scheme 2). The butyl- and isopropyl-substituted allylic alcohols **1o** and **1p** worked well and ketones **3o** and **3p** were isolated in 62 and 67% yield, respectively. A higher yield was obtained with the tertiary

Table 2: Variation of the alkenyl substituent.[a]

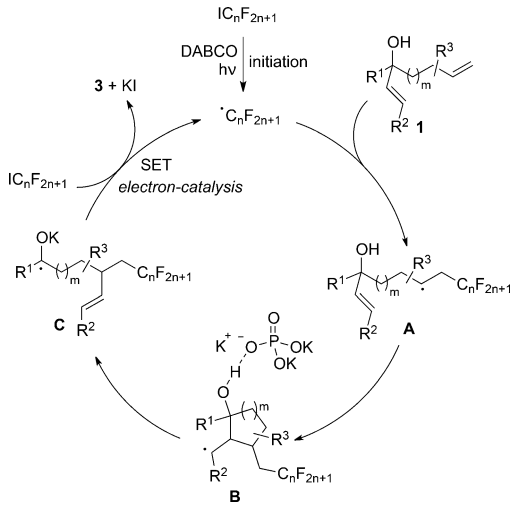


Entry	R	Product	Yield [%][b]
1	**1b**, 4-MeC_6H_4	**3b**	70
2	**1c**, 4-*t*BuC_6H_4	**3c**	69
3	**1d**, 4-MeOC_6H_4	**3d**	56
4	**1e**, 4-FC_6H_4	**3e**	50
5	**1f**, 4-ClC_6H_4	**3f**	72
6	**1g**, 3-MeC_6H_4	**3g**	61
7	**1h**, 2-MeC_6H_4	**3h**	52
8	**1i**, 2,4,6-$Me_3C_6H_2$	**3i**	51
9	**1j**, 3,5-$(MeO)_2C_6H_3$	**3j**	53
10	**1k**, 1-naphthyl	**3k**	45
11	**1l**, 2-pyridyl	**3l**	43
12	**1m**, *i*Pr_3Si	**3m**	50
13[c]	**1n**, Cy	**3n**	23

[a] The reaction was conducted with **1** (0.1 mmol), **2a** (1.8 equiv), K_3PO_4 (2.0 equiv), and DABCO (1.2 equiv) in 1.25 mL of DCE under visible-light irradiation [using a Philips Master HPI-T Plus (400 W) bulb] at 50 °C for 24 h. [b] Yield of isolated product. [c] The reaction was conducted at 0.2 mmol scale.



Scheme 2. Variation of the radical acceptor and the perfluoroalkyl iodides. [a] 3.6 equivalents of CF_3I were used.



Scheme 3. Proposed mechanism.

benzylic alcohol **1q** to give **3q** (74%). Notably, styrenyl migration also works for tertiary alkyl radicals, as documented by the successful preparation of **3r** bearing an all-carbon quaternary center (84%). Importantly, the reaction is not limited to the 1,4-alkenyl migration: The allylic alcohol **1s** reacted in 50% yield to provide the ketone **3s**, resulting from a 1,5-alkenyl migration. As expected, initial perfluoroalkyl radical addition on the trisubstituted alkene **1t** occurred at the less hindered site and the ketone **3t**, derived from a 1,5-alkenyl migration, was isolated in 49% yield. Phenyl-substituted alkene **1u** could also undergo this migration reaction and **3u** was obtained in moderate 30% yield as a 2.6:1 diastereoisomeric mixture.

Other perfluoroalkyl groups, including the important trifluoromethyl moiety, could also be introduced by this method as documented by the preparation of ketones **3v**–**3y**, which were isolated in good-to-excellent yields. The reaction of **1r** with ICF_2CF_2Cl provided **3z** (84%) and products derived from chloride fragmentation were not identified in this transformation. Other alkyl-radical precursors, such as ethyl 2-iodoacetate, 2-iodoacetonitrile, 2-iodo-2-methylpropanenitrile, 2-bromo-1-phenylethan-1-one, and 1-iodoadamantane were not suitable for this migration reaction.

Based on the above results, a plausible mechanism is suggested in Scheme 3. Initiation occurs by visible-light irradiation of the halogen-bond (XB) complex[14] formed between the perfluoroalkyl iodide and DABCO to give the corresponding perfluoroalkyl radical. This radical adds at the terminal position of the alkene in alcohol **1** to give the adduct radical **A**. The internal double bond is well shielded by the neighboring quaternary carbon center and, therefore, the internal double bond remains unreacted at this stage. Radical 5-*exo* or 6-*exo* cyclization leads to the cyclized radical **B**. Unlike our initial design in which the cascade reactions were planned to be conducted on deprotonated allylic alcohols, reaction optimization revealed that these transformations work most efficiently with K_3PO_4 in combination with DABCO. Both of these bases are too weak to deprotonate a tertiary alcohol. We assume that the phosphate anion undergoes hydrogen bonding with the tertiary alcohol and this leads to an activation of the β-C–C bond towards homolytic cleavage. This proposal is reminiscent of the β-C–H bond weakening in phosphate-complexed alcohols suggested by MacMillan and co-workers.[15] Radical β-C–C bond cleavage will then afford the ketyl radical anion **C**. Owing to the increase of the acidity of the hydroxy group in α-hydroxy-α-alkyl carbon radicals compared with that of the parent alcohols, we believe that deprotonation by K_3PO_4 occurs during β-C–C cleavage. As previously shown, such ketyl radical anions are very good single-electron transfer (SET) reducing reagents.[16] Hence, SET reduction of the perfluoroalkyl iodide will give the corresponding ketone **3**, along with the perfluoroalkyl radical sustaining the chain. The overall cascade is part of an electron-catalyzed process.[17]

In summary, we have developed a novel and efficient method for the radical perfluoroalkylation of unactivated alkenes with accompanying β-alkenylation. The radical cascade proceeds by a 1,4- or 1,5-alkenyl migration, a reaction that is currently not established in synthetic methodology. The chain reaction belongs to an electron-catalyzed process and does not require any transition-metal-based redox catalyst.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · alkenyl migration · alkenylation · perfluoroalkylation · single-electron transfer

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