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From Light-Driven to Dark Synthesis: Streamlining Perfluoroalkyl Selenide Ether Formation

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Two complementary and operationally simple methods enable the efficient perfluoroalkylation of organodiselenides: (i) direct visible-light irradiation at 395 nm in aqueous MeCN with R_F–I, requiring no photocatalyst, and (ii) a base-promoted protocol using KOH in MeCN under dark conditions. Both furnished perfluoroalkyl selenoethers in excellent yields, while only the photoinduced protocol delivered good to excellent yields of perfluoroalkyl thioethers from organodisulfides. The direct irradiation approach also enables the preparation of Se- and S-perfluoroalkylated derivatives of selenocysteine and cysteine, highlighting the applicability to biologically relevant substrates. Both protocols feature excellent chemical selectivity, good functional group tolerance, mild conditions, and simple operation. Compared with existing photocatalytic and thermal methods, these approaches provide greater versatility and operational simplicity, exemplified by the gram-scale synthesis of a perfluoroalkyl selenoether in excellent yield.

1. Introduction

The construction of Se—C bonds has undergone significant progress in the last few years.[1]

The trifluoromethyl selenide CF_3Se— group, and perfluoroalkyl selenide R_FSe— ($R_F = C_nF_{2n+1}$) groups in general,[2–7] have distinctive features, such as being highly lipophilic as revealed by the Hansch constants (π $CF_3Se = 1.61$) and moderately electronegative substituents according to Hammet *para* substituent constants (σ_p $CF_3Se = 0.53$[8,9] vs. σ_p $CF_3S = 0.50$). These groups have become attractive to the pharmaceutical industry for enhancing bioavailability and metabolic stability of the substituted drug, as observed from the bioactive examples depicted in **Figure 1**. For example, trifluoromethylselenomethionine was shown to display potent methioninase-induced cytotoxicity to colon cancer cells compared with selenomethionine.[10] The trifluoromethylselenolated nonsteroidal anti-inflammatory drugs (NSAIFDs-$SeCF_3$) were also shown to bear anticancer activity against different cancer cell lines.[11,12]

Fluoroalkyl selenide ethers can be synthesized through direct and indirect strategies. Direct methods rely on the direct installation of the R_FSe moiety using nucleophilic fluoroalkylselenating reagents such as $[Me_4N][SeCF_3]$, $Hg(SeCF_3)_2$, $CuSeCF_3$, $[(bpy)CuSeCF_3]_2$, and $AgSeCF_3$,[13–26] and electrophilic reagents $ClSeCF_3$, $CF_3SeSeCF_3$, and $TsSeCF_3$.[27–37] There exist review articles that illustrate these processes.[13,15,38–40] These methods are very convenient from the viewpoint of late-stage installation of the R_FSe— moiety. However, they necessitate the prefabrication of the reagent, which could entail sensitive environmental and harsh chemical reaction conditions or multistep syntheses.

In contrast, indirect approaches rely on the combination of a selenium-containing source and a perfluoroalkyl precursor to construct the desired perfluoroalkyl selenoether. The selenocontaining source is either a selenol, a diselenide, or a selenocyanate,[41–49] whereas the fluoroalkyl source can be a perfluoroalkyl iodide R_F–I, $CuCF_3$, or $TMSCF_3$ reagents. The indirect methods for obtaining perfluoroalkyl selenoethers reported in the literature are illustrated in **Scheme 1**.

On the one hand, when selenocyanates are the starting materials for the indirect syntheses of perfluoroalkyl selenoethers, reagents such as $CuCF_3/CHF_3/^tBuOK$,[43,49] $TMSCF_3/Cs_2CO_3$,[42] or $TMSCF_3/Bu_4NF$[47] are employed (Scheme 1).

On the other hand, starting from diselenides, the indirect methods to obtain perfluoroalkyl selenoethers can employ Rongalite precursor NaO_2SCH_2OH and a perfluoroalkyl iodide R_F–I in DMF as solvent (Scheme 1A),[46] *tetrakis*-(dimethylamino)ethylene (TDAE) and CF_3–I in DMF (Scheme 1B),[44] Bu_4NF/CF_3SiMe_3 in THF as solvent (Scheme 1C),[48] or, more recently, our results from the Eosin Y-green light-photocatalyzed perfluoroalkylation of diselenides with R_F-I in aqueous MeCN (Scheme 1D).[41]

We herein present our new results to obtain perfluoroalkyl seleno- (and thio-) ethers without the use of photocatalysts,

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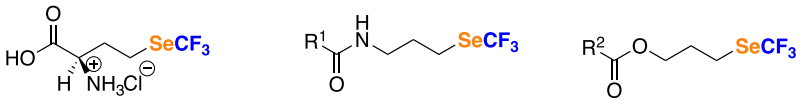
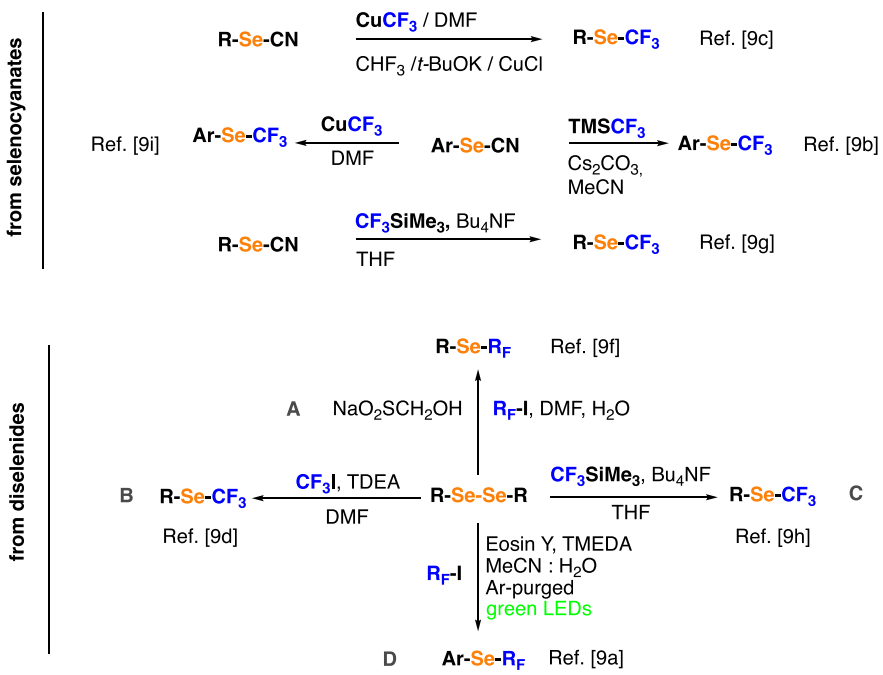


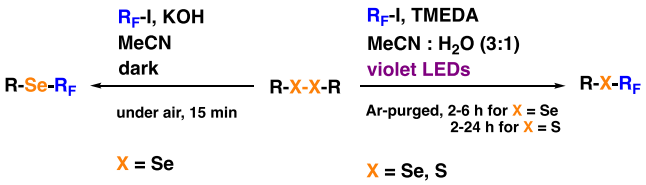
trifluoromethylseleno methionine hydrochloride

R^1, R^2 = *from* NSAID$_s$

Figure 1. Examples of trifluoromethylselenolated compounds with biological activity.



Scheme 1. Indirect methods for obtaining perfluoroalkyl selenoethers.



Scheme 2. This work.

according to either a direct visible-light irradiation or a dark simplified procedure, illustrated in **Scheme 2**.

2. Results and Discussion

Very recently, Li, Zhou, and colleagues[50] informed the photocatalyst-free green light-assisted (510 nm) selenation of alkenes and alkynes from diselenides in the presence of Hantzsch ester to afford alkyl(aryl) seleno- and alkenyl aryl seleno- ethers, respectively, in high yields. Being the λ_{max} of diphenyldiselenide around 335 nm in MeCN as solvent (see Figure S1, Supporting Information), we envisaged that direct homolysis of PhSe—PhSe bond[51] by absorption of light would initiate a radical chain process by allowing arylselenyl radicals to react with R_F-I. The optimization of the reaction conditions is depicted in **Table 1**.

The optimum wavelength for total conversion of diphenyl diselenide to product **1** resulted to be 430 nm (entry 2, Table 1) from blue light-emitting diode (LEDs) or 395 nm (entry 3) from violet LEDs, in the presence of *N,N,N,N′*-tetramethylethylenediamine, TMEDA, in an Ar-deoxygenated mixture of MeCN: H_2O, 3: 1 for 2 h (entries 2 and 3, Table 1). We chose to pursue 395 nm as irradiation wavelength as this wavelength would result in better product yields and shorter irradiation times from the majority of organodiselenides (and disulfides) studied.

The reaction in the absence of light, or absence of TMEDA, did not afford product (entries 4 and 5, Table 1). With one equivalent of TMEDA, a drop in product **1** yield is observed (entry 6, Table 1). In previous works, we determined the association constant between TMEDA and C_4F_9–I in MeCN as solvent, resulting to be 8 M^{-1}.[52,53] This association between TMEDA and R_F–I (Electron Donor Acceptor complex,[54] EDA, in the form of halogen-bonding interaction[55,56]) was held responsible for weakening the C—I bond in $R_F'F_2C$—I, facilitating an electron transfer process and the production of R_F radicals by irradiation. UV–vis data (Figure S2, Supporting Information) confirm 395 nm absorption by the complex, consistent with R_F-radical formation via this route;[55,56] nevertheless,

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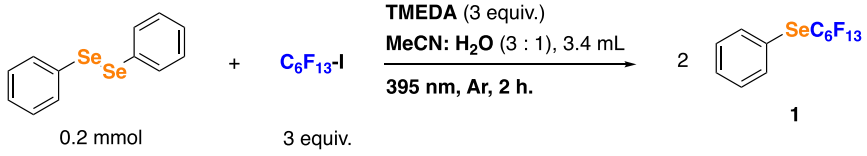
Table 1. Optimization of the reaction conditions. Change of standard reaction conditions. % Yields from ^{1}H-nuclear magnetic resonance (NMR) integration.



Entry	Change of standard reaction conditions	Yield of 1, [%]
1	535 nm,[a] 2 h	15[b]
2	430 nm,[c] 2 h	99
3	**No change**	**99**
4	Without light	0
5	Without TMEDA	0
6	1 equiv. TMEDA	81
7	Without Ar, under air	94
8	With triethylamine[d] (no TMEDA)	83
9	With triethanolamine[d] (no TMEDA)	35
10	With Cs_2CO_3[d] (no TMEDA)	93
11	Without H_2O (in pure MeCN)	93
12	With KOH,[d] without TMEDA in pure MeCN	99
13	With KOH,[d] without TMEDA in pure MeCN, 15 min	76
14	**With KOH,[d] without light, without TMEDA in pure MeCN [1 mL], 15 min**	**99**

[a]Green LEDs, 3 W; [b]99% yield of **1** after 20-h reaction; [c]blue LEDs, 3 W; [d]3 equiv.

under our conditions, diphenyldiselenide captures nearly all the incident light.

The reaction carried out in MeCN as solvent, in the presence of KOH instead of TMEDA, provided **1** in 99% yield (entry 12, Table 1) upon irradiation for 2 h and in 76% yield when irradiating for 15 min (entry 13, Table 1). In the absence of light, presence of KOH (3 equiv.), in MeCN (1 mL) during 15 min, a quantitative yield of **1** is obtained (entry 14, Table 1). Further exploration for optimization of the reaction conditions utilizing the dark system KOH/MeCN is illustrated in Table S2, Supporting Information.

The optimization studies summarized in Table 1 revealed two equally effective sets of reaction conditions for the perfluorohexylation of diphenyldiselenide, enabling the synthesis of perfluorohexyl phenyl selenoether **1**: one involving visible-light irradiation without a photocatalyst (entry 3, Table 1), and the other a KOH-mediated reaction carried out in the dark (entry 14, Table 1) in pure MeCN as solvent.

Given the best reaction conditions either for direct visible-light irradiation (entry 3, Table 1) or dark KOH/MeCN (entry 14, Table 1) conditions, we proceeded to investigate the scope of the perfluoroalkylation reaction of organodiselenides, according to **Table 2**.

As observed from Table 2, the direct irradiation (395 nm) of organodiselenides in the presence of TMEDA afforded excellent yields of perfluoroalkyl-(hetero)aryl or perfluoroalkyl-alkyl selenoethers under both *conditions 1* and *2*.

Regarding perfluoroalkylation of di(hetero)aryl diselenides under *conditions 1*, those with electron-donating groups such as 1,2-bis(2-methoxyphenyl)diselane, 1,2-bis(4-methoxyphenyl) diselane, and methylated diaryldiselenides rendered the perfluoroalkyl aryl selenide ethers **3–5**, **8–10** in fairly good yields (84%–96%) under direct irradiation at 395 nm wavelength (*conditions 1*).

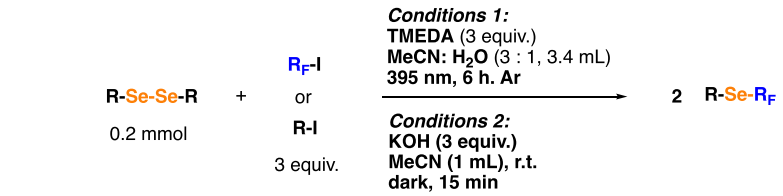
Di(hetero)aryl diselenides with electron-withdrawing groups such as 4,4′-diselanediyldibenzaldehyde, 1,2-bis(2-nitrophenyl)diselane, and 1,2-bis(pyridin-3-yl)diselane rendered products **12–14** in 97%, 82%, and 96% yields, respectively. 1,2-Bis([1,1′-biphenyl]-4-yl) diselane and 1,2-bis(thiophen-3-yl)diselane afforded products **7** and **15** in 85% and 94% yields, respectively, under *conditions 1*.

Dialkyldiselenides also showed excellent reactivity toward 395 nm-irradiation in the presence of perfluoroalkyl iodides (*conditions 1*). 1,2-Dipentyldiselane and 1,2-dihexyldiselenide afforded products **16** and **17** quantitatively.

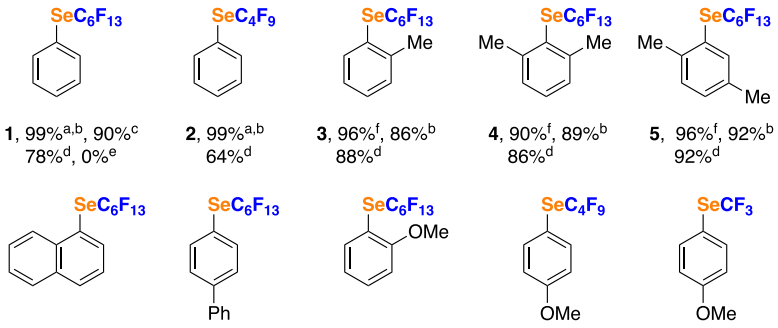
The dark reaction, under *conditions 2*, also afforded very good yields of perfluoroalkyl selenide ethers in only 15 min-reactions. Diselenides with electron-donating groups afforded products **3–5**, **8–10** in yields ranging from 86%–97%. Diselenides with electron-withdrawing groups rendered products **12–14** in excellent yields as well (>85%). Under *conditions 2*, 1,2-bis([1,1′-biphenyl]-4-yl)diselane and 1,2-bis(thiophen-3-yl)diselane furnished products **7** and **15** in 92% and 99% yields, respectively. The perfluoroalkylation of dialkyldiselenides under *conditions 2*, afforded products **16** and **17** in quantitative manner, as observed under *conditions 1*, albeit in 15 min-reactions.

The reaction of diphenyldiselenide with C_4F_9–I was carried out in a larger scale (2 mmol) under *conditions 1*, and product **2** was obtained in 67% (1.0 g) isolated yield (^{1}H nuclear magnetic resonance [NMR] yield 99%). These results demonstrate the good scalability of the direct irradiation protocol.

Table 2. Scope of the perfluoroalkylation of organodiselenides under photochemical and thermal conditions. % Yields from ^{1}H-NMR integration or otherwise noted.



from R_F-I and Ar(Het)-Se-Se-Ar(Het):



1, 99%[a,b], 90%[c] 78%[d], 0%[e]

2, 99%[a,b] 64%[d]

3, 96%[f], 86%[b] 88%[d]

4, 90%[f], 89%[b] 86%[d]

5, 96%[f], 92%[b] 92%[d]

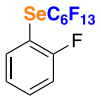
6, 87%[f], 93%[b] 81[d]

7, 85%[f], 92%[b.] 81%[d.]

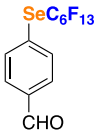
8, 94%[f], 91%[b] 89%[d]

9, 88%[f], 97%[b] 72%[d]

10, 84%[g], 96%[b] 57%[h]

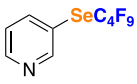


11, 97%[b,f], 85%[d]

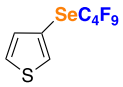


12, 97%[f], 85[b] 92[d]

13, 82%[f], 86%[b] 77[d]

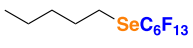


14, 96%[f], 95%[b] 78[d]

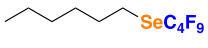


15, 94%[f], 99%[b] 71[d]

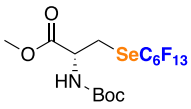
from R_F-I and Alkyl-Se-Se-Alkyl:



16, 99%[b,f], 65%[d]



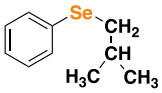
17, 99%[b,f], 66%[d]



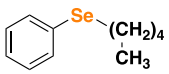
from L-selenocystine

18, 90%[g], 61%[h]

*from **alkyl** iodides and Ph-Se-Se-Ph:*

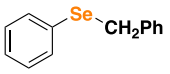


19, 73%[b], 56%[i]

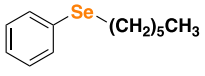


20, 90%[b], 71%[i]

*from **alkyl** bromides and Ph-Se-Se-Ph:*



21, 98%[b], 86%[i]



22, 93%[b], 70%[i]

[a]*Conditions 1* but 2-h reaction; [b]*Conditions 2*; [c]*Conditions 2* but employing C_6F_{13}–Br as R_F source; [d]Isolated yields under *conditions 1*; [e]*Conditions 1* but employing C_6F_{13}–Br as R_F source; [f]*Conditions 1*; [g]*Conditions 1* but 24-h reaction; [h]Isolated yield under *conditions 1* but 24-h reaction; [i]Isolated yields under *conditions 2*.

Encouraged by the excellent results obtained for the synthesis of perfluoroalkyl selenoethers (from alkyl/aryl diselenides) under both *conditions 1* and *2* we attempted the alkylation reactions of diaryldiselenides with alkyl iodides and alkyl bromides in order to obtain alkyl–aryl selenoethers with our new methodologies. Indeed, when diphenyldiselenide was made to react with diisobutyl iodide and *n*-pentyl iodide, products **19** and **20** were obtained in 73% and 90% yields, respectively, under *conditions 2*. Diphenyldiselenide failed to react with the alkyl iodides under *conditions 1*.

In view of the excellent outcomes achieved for the alkylation of diphenyldiselenide, PhSeSePh, with alkyl iodides under *conditions 2*, we next examined alkyl bromides as potential alkylating agents for the synthesis of alkyl aryl selenoethers. When

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PhSeSePh was made to react with benzyl bromide, product **21** was obtained in 99% yield under *conditions 2*. In the same manner, PhSeSePh reacted with *n*-hexyl bromide to render product **22** in 93% yield, under *conditions 2* (Table 2). Under conditions 1, PhSeSePh did not react with alkyl bromides.

When employing C_6F_{13}–Br as the fluoroalkylating reagent and diphenyldiselenide as substrate, product **1** was obtained in 99% yield under *conditions 2* (Table 2, entry c), whereas under *conditions 1*, the reaction failed to yield the desired product (Table 2, entry e). Notably, *conditions 2* broaden the range of perfluoroalkyl radical precursors, enabling the use of perfluoroalkyl bromides (entry c, Table 2) and alkyl bromides (products 21 and 22, Table 2) as effective reagents in this transformation.

Both methods are excellent choices for the synthesis of perfluoroalkyl selenoethers from diselenides and represent simplified methodological procedures with respect to the published ones.[41,44,46,48] On the other hand, only *conditions 2* are suitable for the alkylation of diaryldiselenides.

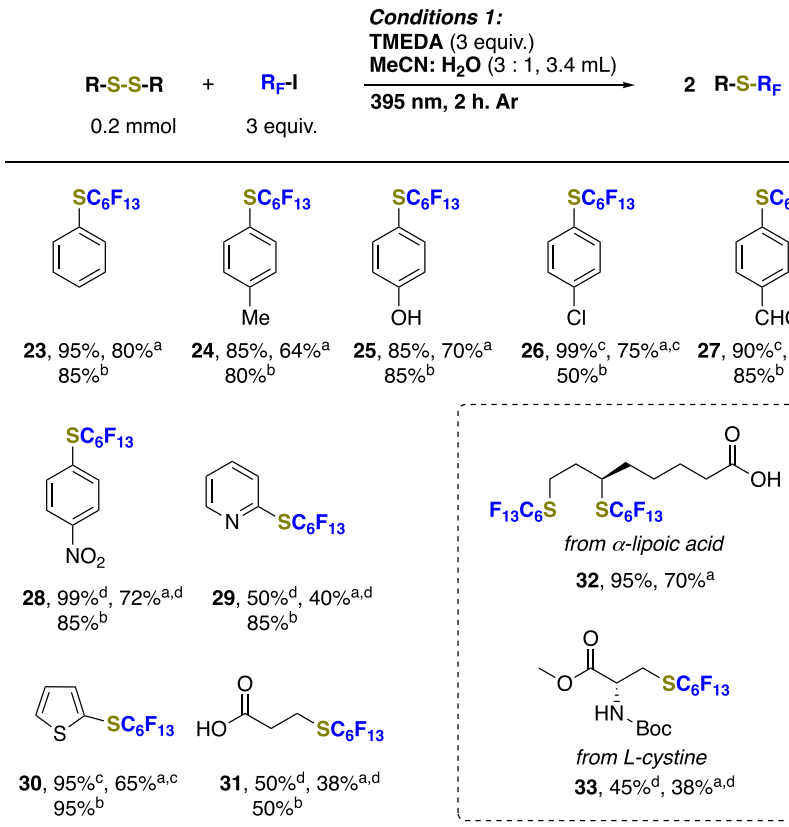
To further demonstrate the scope of the photoinduced methodology, the biologically relevant *L*-selenocystine derivative dimethyl 3,3′-diselanediyl(2*R*,2′*R*)-bis(2-((*tert*-butoxycarbonyl)amino)propanoate) (see Supporting Information for details) was subjected to reaction under *conditions 1*, affording product **18** (Table 2) in 90% yield.

We then investigated whether these methodologies could also be applied to disulfides. Given the higher bond dissociation energy (BDE) of the S—S bond in diphenyl disulfide (PhS–SPh) compared to the Se—Se bond in diselenides (BDE: Se—Se = 192 kJ mol^{-11} < S—S = 266 kJ mol^{-11}),[57] we anticipated that the 395 nm light-induced reaction of disulfides with C_6F_{13}–I would be less efficient than the analogous transformation with diselenides. Furthermore, the residual absorbance of PhS–SPh at 395 nm is minimal (see Figure S3, Supporting Information), suggesting that direct photolytic cleavage of the S—S bond under these conditions is more challenging than that of the Se—Se bond. The scope of disulfide reactivity under visible-light irradiation is presented in **Table 3**.

As observed from Table 3, direct irradiation (395 nm) of di(hetero)aryl- and dialkyl-disulfides in the presence of C_6F_{13}–I, TMEDA in MeCN: H_2O water mixture provided the perfluorohexyl alkyl/aryl thioethers in good to excellent yields as well. Diphenyldisulfide afforded product **23** in 95% yield upon 2 h-irradiation. Electron-rich di(hetero)aryl disulfides such as 1,2-di-*p*-tolyldisulfane, 4,4′-disulfanediyldiphenol, and 1,2-di(thiophen-2-yl)disulfane afforded products **24**, **25**, and **30** in 85%, 85%, and 95% yields, respectively (2 h-reactions).

Electron-poor diaryldisulfides demanded longer irradiation times, with 1,2-bis(4-chlorophenyl)disulfane and 4,4′-disulfanediyldibenzaldehyde affording products **26** and **27** in 99% and 90%

Table 3. Scope of the perfluoroalkylation of organodisulfides under photochemical conditions. % Yields from ^{1}H-NMR integration or otherwise noted.



[a]Isolated yields; [b]Yields obtained by Eosin Y-photocatalysis: Ref. [41]; [c]6 h reaction; [d]24 h-reaction.

yields after 6 h, while 1,2-bis(4-nitrophenyl)disulfane and 1,2-di(pyridin-2-yl)disulfane furnished products **28** and **29** in 99% and 50% yields after 24 h. Aliphatic disulfide 3,3′-disulfanediyldipropionic acid afforded products **31** in 50% yield after 24 h-irradiation.

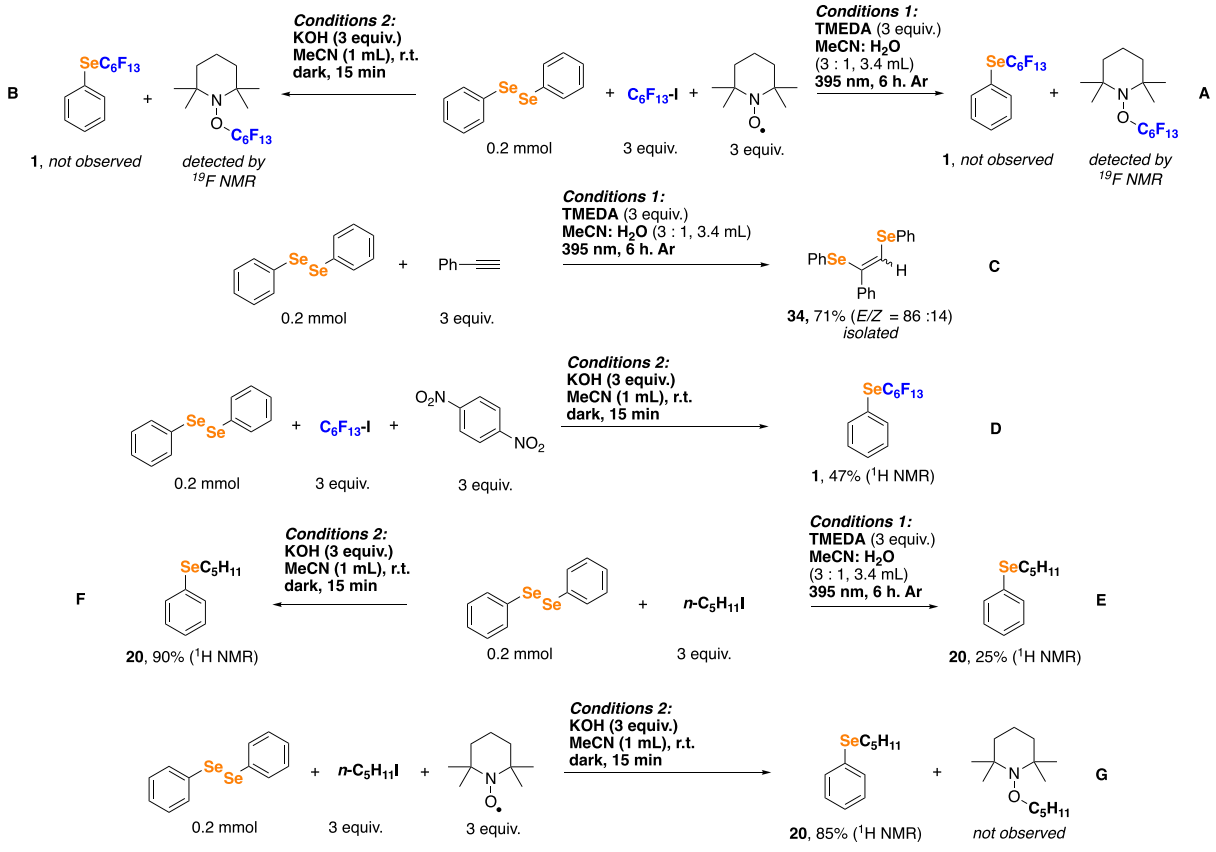
The versatility of the direct photoinduced methodology using disulfides is showcased with the reactions of two biologically relevant substrates: α-lipoic acid, which delivered product **32** in 95% yield after only 2 h-reaction, and the *L*-cystine derivative dimethyl 3,3′-disulfanediyl-(*2R,2′R*)-bis(2-((*tert*-butoxycarbonyl)amino) propanoate), who afforded compound **33** in 45% yield after 24 h-reaction.

However, the dark reaction of diphenyldisulfide with C_6F_{13}–I in the presence of KOH in pure MeCN as solvent (under *conditions 2*) provided product **23** in only 3% yield.

The mechanism of the reaction of diselenides toward the formation of perfluoroalkyl selenoethers was investigated, either for the photoinduced process at 395 nm (*conditions 1*), and for the dark reaction with KOH (*conditions 2*). Mechanistic probe experiments for the perfluorohexylation of diphenyl diselenides under *conditions 1* and *2* are shown in **Scheme 3**.

As mentioned above, the absence of light (under *conditions 1*) precluded product formation (entry 4, Table 1). In the photoinduced reaction, absence of TMEDA did not provide product whatsoever (entry 5, Table 1). The halogen atom bonding complex between R_F–I and TMEDA, which debilitates the C—I bond in $R_F'F_2C$—I, is photoactive at 395 nm, playing a role in the formation of R_F radicals, that can initiate the radical change process (Figure S2, Supporting Information; however under our reaction conditions practically all light is absorbed by diphenyldiselinde. At 395 nm, diaryldiselenides show a tail of absorption (Figure S1, Supporting Information) that triggers homolysis of Se—Se bond through irradiation, generating selenyl radicals. In the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), under both *conditions 1* and *2*, no product **1** is formed, and the adduct TEMPO-C_6F_{13} is detected by ^{19}F-NMR (Scheme 3A, B), indicating the presence of radicals both under illumination and dark conditions. In order to trap the phenyl selenyl radical intermediate with a suitable radical acceptor, C_6F_{13}–I was replaced by phenyl acetylene in the photoreaction under *conditions 1*. In this way, product **34**[58] was obtained in 71% isolated yield (*E/Z* = 86: 14, Scheme 3C). The quantum yield of the reaction of PhSeSePh in the presence of C_6F_{13}—I / TMEDA (*conditions 1*) was measured at 395 nm wavelength with calibrated diodes (see Supporting Information), and resulted to be 5.1 +/– 0.2. This value indicates the presence of a moderate radical chain reaction in the mechanism.

The presence of 1,4-dinitrobenzene (radical anion scavenger) partially halts the reaction (Scheme 3D). This latter experiment probes the presence of radical anion species, congruent with a $S_{RN}1$ mechanism.[59] The reaction of PhSeSePh with 1-iodopentane C_5H_{11}–I produced 90% isolated yield under *conditions 2*



Scheme 3. Probe experiments for the perfluorohexylation of diphenyl diselenides under *conditions 1* and *2*.

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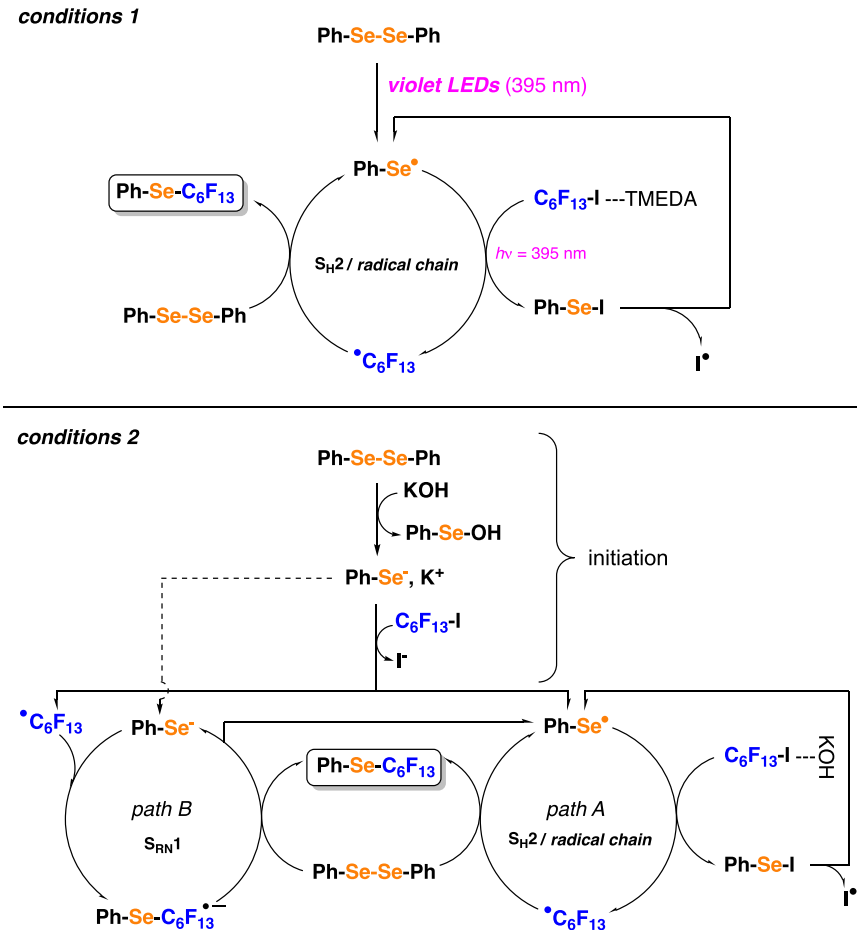
(calculated assuming a 1:1 stoichiometric ratio between substrate and product) of pentyl phenyl selenide ether **20** (Scheme 3F), while the presence of TEMPO did not affect product **20** yield (Scheme 3G) under these conditions. This latter being a typical S_N2 displacement reaction of pentyl iodide by selenide anion, an intermediate formed from reaction of PhSeSePh with KOH. These results indicated that the reaction under *conditions 2* initiates as a standard $S_{RN}1$ reaction.

Proposals for mechanisms under 1- and 2- reaction conditions are illustrated in **Scheme 4**.

Under *reaction conditions 1*, direct irradiation of PhSeSePh produces phenylselenyl radicals PhSe• by direct homolysis of the Se—Se bond,[60] which abstract iodine from the complex C_6F_{13}—I···TMEDA (where the C—I bond in $F(CF_2)_5F_2C$—I is debilitated) to produce PhSeI[61] and •C_6F_{13} radicals. •C_6F_{13} radicals substitute PhSeSePh to furnish the final product PhSeC_6F_{13} and more PhSe• radicals, which can either dimerize or enter the radical chain. PhSe—I can undergo facile Se—I bond homolysis to further produce PhSe• radicals (and iodine radicals), also reentering the cycle. Another plausible route involves ET from the photoexcited C_6F_{13}—I···.TMEDA complex to form •C_6F_{13};[52,53] however, diphenyldiselenide primarily absorbs the incident light in our system, limiting the participation in the photoactivation of the EDA complex.

The presence of a radical chain propagating step was confirmed by the quantum yield of the global reaction ($\phi = 5.1$], see Section 3.2.-, Supporting Information). Utilization of C_6F_{13}–Br as a precursor of perfluorohexyl radicals under photoinduced *conditions 1* did not afford any detectable product (Table 2, entry e). This outcome can be attributed to the higher C—Br BDE—and less polarization—C_6F_{13}–Br relative to the C—I BDE (i.e., and polarization) in C_6F_{13}–I, resulting into a more negative reduction potential for C_6F_{13}–Br compared to C_6F_{13}–I (peak potentials in 0.1 M Bu_4NPF_6/MeCN at a glassy carbon electrode: –2.11 V vs. –1.60 V, vs. SCE, for C_6F_{13}–Br and C_6F_{13}–I, respectively[54]).

Under *reaction condition 2*, KOH promotes heterolytic cleavage of the Se—Se bond, generating PhSeK,[62] similar to the effect of reducing agents such as $NaBH_4$ and other hydrides or reductants which furnish the selenide anion.[63,64] Selenide anion PhSeK readily effects an ET to C_6F_{13}–I, providing PhSe• and •C_6F_{13} radicals (and iodide anion) in an initiation event. Recombination of $PhSe^-$ and •C_6F_{13} radicals affords the radical anion of the substitution product PhSeC_6F_{13}•$^-$ (*path B*, Scheme 4), which transfers its odd electron to PhSeSePh, as a typical $S_{RN}1$ reaction,[59,65] affording the thermoneutral product PhSeC_6F_{13} and furnishing PhSeSePh•$^{-1}$ which fragments (mesolysis) to $PhSe^-$ and PhSe• radicals. The $PhSe^{-1}$ re-enters the $S_{RN}1$ propagation cycle (*path*



Scheme 4. Proposed reaction mechanism under *conditions 1* and *conditions 2*.

B, Scheme 4), whereas PhSe• enters the radical chain described as *path A* (Scheme 4). In an alternative *pathway (not shown)*, recombination of $PhSe^-$ and $\bullet C_6F_{13}$ radicals could afford the radical anion of the substitution product $PhSeC_6F_{13}\bullet^{-1}$, which transfers its odd electron to C_6F_{13}–I, generating more $\bullet C_6F_{13}$ radicals and thermoneutral product $PhSeC_6F_{13}$.

Interestingly, there is an effective EDA complex informed between KOH and C_6F_{13}–I,[66] that could further debilitate the C—I bond in $F(CF_2)_5F_2C$—I. Although under dark conditions this complex was not reported to produce R_F• radicals, the C—I bond weakening would further facilitate the abstraction of iodine from C_6F_{13}–I by PhSe• radicals. This facile iodine atom abstraction from C_6F_{13}—I···OHK complex renders $\bullet C_6F_{13}$ radicals and PhSe—I; this latter undergoes prompt homolysis of the PhSe—I bond to produce more phenylselenyl radicals PhSe• (and iodine radical), that reenter the propagation cycle (*path A*, Scheme 4) in a fashion similar to that proposed under *reaction conditions 1*. $\bullet C_6F_{13}$ radicals perform a homolytic substitution on PhSeSePh to furnish the final product $PhSeC_6F_{13}$ and more PhSe• radicals, reinforcing the radical chain process (*path A*, Scheme 4). The short reaction times observed under *conditions 2* relate to the efficient ET processes occurring at the initiation level.

Regarding the reaction of disulfides through direct irradiation (*conditions 1*), the homolysis of PhS—SPh bond at 395 nm would produce phenylthiyl PhS• radicals in a manner similar to the production of PhSe• radicals from 395 nm-irradiation of PhSe–SePh, albeit less efficiently as the S—S BDE of ArS-SAr is $\approx$24 Kcal mol^{-1} higher than that of PhSe–SePh ($BDE_{PhS\text{-}SPh}$ = 50 Kcal mol^{-1},[67] $BDE_{Se\text{-}Se}$ = 25.9 Kcal mol^{-1}[60,61]); however, yields of perfluoroalkyl thioethers are fairly good compared with perfluoroalkyl selenoethers.

3. Conclusions

We herein report two complementary, operationally simple routes to build Se—R_F bonds from organodiselenides and perfluoroalkyl iodides. Direct 395 nm irradiation of organodichalcogenides and R_F—I in aqueous MeCN (*conditions 1*) delivers perfluoroalkyl selenoethers and uniquely thioethers, while a dark KOH/MeCN variant (*conditions 2*) furnishes selenoethers in high yields without the need for polar hydride-based reducing agents. Both protocols proceed under mild, metal- and photocatalyst-free conditions with excellent chemoselectivity and functional group tolerance and are applicable to late-stage modification of selenocysteine/cysteine derivatives; scalability is demonstrated by gram-scale synthesis. In the case of the direct irradiation approach (*conditions 1*), the use of photoreactive organic compounds is the optimal strategy to harness visible photons as ideal reagents. Notably, the thermal approach (*conditions 2*) delivers perfluoroalkyl selenolated products in just 15 min. Compared with established photocatalytic or thermal methods, these orthogonal conditions offer greater versatility and operational simplicity.[68,69]

4. Experimental Section

All reactions were carried out under argon atmosphere unless otherwise indicated. Water was purified with a Millipore system. Chromatography and extraction solvents, such as ethyl acetate, acetonitrile (MeCN), dichloromethane (DCM), and *n*-hexane, were of chromatographic quality and used without further purification. 1-Iodotridecafluorohexane (perfluorohexyl iodide) and 1-Iodononafluorobutane (perfluorobutyl iodide) were commercial reagents and used without further purification. *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was 99% pure and used as received from the supplier. Trifluoroiodomethane (10% in dimethyl sulfoxide) was commercially acquired and used as received.

Organic substrates 1,2-bis(2-methoxyphenyl)diselane, 1,2-di-*o*-tolyldiselane, 1,2-bis(4-methoxyphenyl)diselane, 1,2-bis(2,6-dimethylphenyl)diselane, 1,2-bis(2-fluorophenyl)diselane, 4,4′-diselanediyldibenzaldehyde, 1,2-bis(2-nitrophenyl)diselane, 1,2-di(pyridin-3-yl)diselane, 1,2-di([1,1′-biphenyl]-4-yl)diselane, 1,2-di(thiophen-3-yl) diselane, and 1,2-dihexyldiselane were synthesized and purified according to literature procedures.[41] Diphenyl diselenide was commercially available from Sigma Aldrich and used as received from the supplier. Diphenyldisulfide, 1,2-di-*p*-tolyldisulfane, 4,4′-disulfanediyldiphenol,1,2-bis(4-chlorophenyl)disulfane, 1,2-bis(4-nitrophenyl)disulfane, 1,2-di (pyridin-2-yl)disulfane, 1,2-di(thiophen-2-yl)disulfane, and (*S*)-3-(1,2-dithiolan-3-yl)propanoic acid (lipoic acid) were commercially available (TCI) and used without further purification. 4,4′-disulfanediyldibenzaldehyde, 3,3′-disulfanediyl-(*2R,2′R*)-bis(2-((*tert*-butoxycarbonyl) amino)propanoate), and dimethyl 3,3′-diselanediyl(*2R,2′R*)-bis (2-((*tert*-butoxycarbonyl)amino)propanoate) were synthesized as described in the Supporting Information. TEMPO was an ultrapure-grade reagent. 1,4-dinitrobenzene, phenylacetylene, and 1-iodopentane were commercially available from Sigma Aldrich and used as received from the supplier.

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm, Merck). TLC plates were visualized with ultraviolet light or by treatment with ceric ammonium molybdate (CAM) solution followed by heating. Purification of the reaction products was carried out by column chromatography using ultra-pure silica gel (230–400 mesh), standard silica gel for column chromatography (60 mesh), or silica gel for thin-layer preparative chromatography with fluorescent indicator (rhodamine).

The light sources were commercially available high-power LEDs (3 W): violet light, LED of $\lambda_{max} = 395 \pm 2$ nm, ET = 10 mW.

General Procedure for the Syntheses of Perfluoroalkyl Selenoethers by Direct Irradiation at 395 nm

In a 4 mL glass reaction vial equipped with a screw-cap septum and a magnetic micro stir bar, the substrate (0.2 mmol, 1 equiv.), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 0.6 mmol, 3 equiv., 0.0697 g, 89 μL), and 3.4 mL of a 3:1 MeCN/H_2O solvent mixture were added. The solution was purged with a stream of argon for 10 min or otherwise indicated. Then, the liquid fluorinated reagents (0.6 mmol, 3 equiv) were introduced using a microliter syringe. The sealed vial was placed on a magnetic stir plate above a heat dissipator (as shown in Figure S1, Supporting Information) and stirred vigorously for 6 h at 22 °C under continuous irradiation with high-power violet LEDs (3 W; $\lambda_{max} = 395 \pm 2$ nm).

Following the irradiation period, the reaction mixture was extracted three times with ethyl acetate and water. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60 mesh), using eluents corresponding to the TLC conditions (see Supporting Information). Final compounds were characterized using ^1H, ^{13}C, and ^{19}F NMR

spectroscopy, as well as mass spectrometry (MS) or high-resolution mass spectrometry (HRMS).

*General Procedure for the Syntheses of Perfluoroalkyl Selenoethers by Thermal KOH-Induced Methods

In a screw-cap Wheaton vial equipped with a micro stir bar, the substrate (0.2 mmol, 1 equiv), potassium hydroxide (KOH, 0.6 mmol, 3 equiv., 34 mg), and 1 mL of MeCN were combined. Liquid fluorinated reagents (0.6 mmol, 3 equiv.) were added using a microliter syringe. The sealed vial was placed on a magnetic stirrer and stirred vigorously for 15 min at 22 °C in the dark. Upon completion, the reaction mixture was extracted three times with ethyl acetate and water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

Detailed experimental procedures, syntheses of the starting materials, and complete characterization data are provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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