Photochemical Perfluoroalkylation Hot Paper

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Metal-Free Photochemical Aromatic Perfluoroalkylation of α-Cyano Arylacetates**

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Abstract: *We report here an operationally simple protocol for the direct aromatic perfluoroalkylation and trifluoromethylation of α-cyano arylacetates. This metal-free approach, which occurs at ambient temperature and under visible-light irradiation, is driven by the photochemical activity of electron donor–acceptor (EDA) complexes, formed in situ by the interaction of transiently generated enolates and perfluoroalkyl iodides. Preliminary mechanistic studies are reported.*

Introducing fluorine-containing functional groups into the molecular scaffold of organic compounds greatly alters their intrinsic properties. This strategy is often exploited in medicinal chemistry to enhance the biological activity of a drug candidate,[1] justifying the profuse efforts made by the synthetic community to develop effective methodologies for incorporating perfluoroalkyl groups into aromatic compounds. Cross-coupling technologies, promoted by stoichiometric amounts of transition metals, traditionally served to accomplish this target.[2] Recently, copper- or palladium-based catalytic variants have been developed, increasing the overall efficiency of the technology.[3] These strategies can effectively install the fluorinated fragments in place of halides or boronic acid derivatives. The direct functionalization of simple arenes provides a more straightforward path. A large proportion of direct perfluoroalkylation methods developed so far[4] have been conceived by capitalizing on the strongly electrophilic nature of the perfluoroalkyl radicals,[5] which are eager to react with arenes through the classical homolytic aromatic substitution (HAS) pathway.[6] The generation of such radicals generally requires harsh reaction conditions, including high reaction temperatures,[7a,b] the use of stoichiometric radical initiators and/or metals,[7c–h] and potentially explosive oxidants.[7i–k] Recently, metal-based photoredox catalysis driven by visible light has been identified as a suitable approach for generating perfluoroalkyl radical intermediates under very mild reaction conditions.[8]

Herein, we report a photochemical strategy for generating open-shell reactive species from perfluoroalkyl iodides, which does not rely upon any metal- or organic-based photoredox catalysts. The reaction, which occurs at ambient temperature and requires irradiation by a household 23 W compact fluorescent light (CFL) bulb in order to proceed, accounts for the direct aromatic perfluoroalkylation and trifluoromethylation of α-cyano arylacetates.

Our initial investigations were motivated by the desire to photogenerate radical species under mild reaction conditions. We recently discovered that the photochemical activity of in situ formed electron donor–acceptor (EDA) complexes, molecular aggregations that occur in the ground state[9] upon interaction of organic substrates, can serve this purpose. Specifically, we developed a photochemical intermolecular α alkylation of aldehydes.[10] The success of this asymmetric, metal-free process relied upon the formation of photon-absorbing EDA complexes, which arose from the association of a transiently generated chiral electron-rich enamine **I** with alkyl bromides with a high electron affinity (Figure 1). Visible-light irradiation of the colored EDA complex induced an electron transfer, thus allowing easy access to radical species.

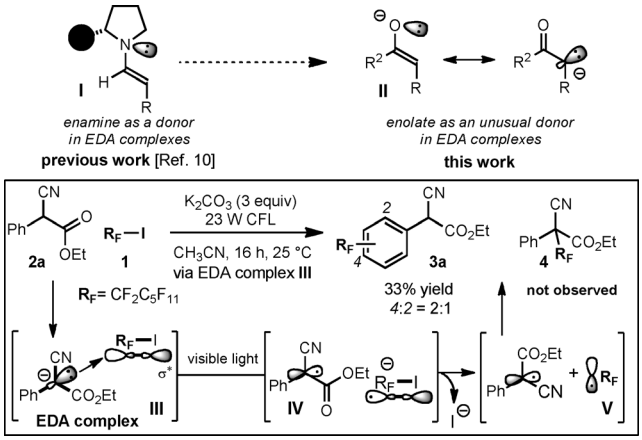

Figure 1. Visible-light-induced perfluoroalkylation of α-cyano arylacetates.

Expanding upon this precedent, we wondered if the EDA-based strategy could be used to conceive other synthetically appealing photochemical transformations. Specifically, we envisioned the possibility of using donor substrates other than enamines **I** to form photoactive EDA complexes. Given the

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electronic similarities with **I**, in situ generated enolates of type **II** were considered as suitable donors.[11] Perfluoroalkyl iodides **1** were selected as electron-accepting substrates, because sparse literature precedents[12] qualify them as potential acceptors for facilitating associations of EDA complexes. The feasibility of our plan was tested by reacting ethyl α-cyano phenylacetate (**2a**) with perfluorohexyl iodide **1a** under irradiation by a 23 W CFL bulb (R_F indicates the perfluoroalkyl fragment). The reaction was conducted in MeCN and in the presence of K_2CO_3 (3 equiv, Figure 1) so as to favor the formation of the corresponding enolate. Immediately after mixing with the iodide **1a**, the solution developed a marked yellow-orange color, while its optical absorption spectrum showed a bathochromic displacement in the visible spectral region, diagnostic of an EDA complex (Figure 2).

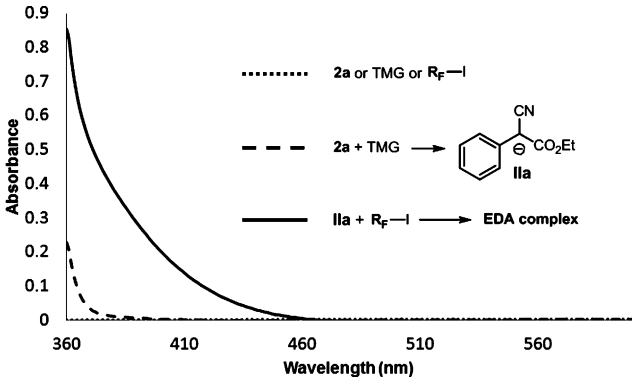
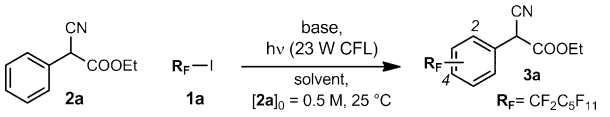


Figure 2. Optical absorption spectra recorded in MeCN in quartz cuvettes (1 cm path) using a Shimadzu 2401PC UV-visible spectrophotometer. [**2a**] = 0.01 M, [**1a**] = 0.03 M; [TMG] = 0.02 M. While the substrates **1a** and **2a** are transparent to light, the resulting enolate **IIa** showed a weak absorption at about 360 nm (dashed line): its combination with perfluorohexyl iodide **1a** leads to a strong bathochromic shift (black line).

We recognized the formation of the EDA complex as critical to reaction development, as visible-light irradiation might induce an electron transfer, giving the anionic contact radical pair **IV**. The presence of iodine as a suitable leaving group within the radical anion partner may induce a rapid fragmentation event, productively rendering the iodide anion along with the desired open-shell species, including the perfluoroalkyl radical **V**. In analogy to our alkylation of aldehydes,[10] we anticipated the formation of the α-carbonyl perfluoroalkylated adduct **4** to be favored, by means of a radical–radical combination or a radical trap by the enolate. The arene perfluoroalkylation product **3a** (*para*/*ortho* formed in a 2:1 ratio) was generated instead, suggesting an HAS pathway to be highly preferred under these reaction conditions. A control experiment, carried out by performing the reaction in the dark, did not provide any reactivity, thus testifying to the photochemical nature of the transformation.

The unanticipated reactivity prompted us toward further explorative studies to optimize the reaction conditions (Table 1). All the experiments, conducted in MeCN using a 23 W CFL bulb, provided both the *para*- and *ortho*-functionalized products **3a** in a roughly constant 2:1 ratio,

Table 1: Optimization of the perfluoroalkylation reaction.[a]



Entry	Base	Solvent	*t* [h]	Yield [%][b]	Distribution [%] 4[c]	2[c]	2,4[c]
1	none	MeCN	16	0	–	–	–
2	Cs_2CO_3	MeCN	16	70	60	33	7
3	TMG	MeCN	16	62	60	31	9
4	Cs_2CO_3	DMF	16	45	65	32	3
5	Cs_2CO_3	AcOEt	16	22	66	31	3
6	Cs_2CO_3	MeCN/Hex_F	16	73	55	31	14
7	TMG	MeCN/Hex_F	5	83	58	32	10
8[d]	TMG	MeCN/Hex_F	2	61	63	31	6
9[e,f,g]	TMG	MeCN/Hex_F	24	0	–	–	–

[a] Reactions were performed on a 0.1 mmol scale using 3 equiv of **1a** and 2 equiv of base, [**2a**]$_0$ = 0.5 M, and a 23 W CFL bulb to illuminate the reaction vessel. [b] Total yield determined by ^{1}H and ^{19}F NMR analysis using 1-fluoro-2-nitrobenzene as the internal standard. [c] Percent distribution of the *para*- (*4*), *ortho*- (*2*), and *ortho*,*para*-functionalized *(2,4)* products. [d] Reaction performed using a 300 W xenon bulb, equipped with a cut-off filter at 385 nm. [e] Reaction in the dark. [f] Reaction in air. [g] Reaction performed in the presence of 2 equiv of TEMPO. TMG = 1,1,3,3-tetramethylguanidine, Hex_F = tetradecafluorohexane.

with a minor amount of the *ortho*,*para*-bifunctionalized adduct (less than 10%). We initially confirmed that the photochemical activity of the enolate, formed in situ upon deprotonation of **2a**, was essential for reactivity, as in the absence of a base the starting substrates were completely recovered (entry 1). Further optimization of the standard reaction parameters showed that the nature of the base and the reaction medium were the crucial factors for an efficient system. When a solution of the substrates and Cs_2CO_3 (3 equiv) in acetonitrile was irradiated for 16 h, the perfluoroalkylated product **3a** was isolated in 70% yield (entry 2). The starting substrate **2a** (24%) was recovered even after prolonged irradiation. The inability of the reaction to progress to completion was rationalized on the basis of control experiments, which showed how the product **3a** inhibited the process (the enolate of **3a** has a strong absorption in the visible region, details are reported in Section D of the Supporting Information). To address this issue, we added tetradecafluorohexane[13] to the reaction mixture (in a 1:5 ratio to MeCN) to collect the generated perfluorinated product **3a** in a different phase. The use of the biphasic system, 1,1,3,3-tetramethyl guanidine (TMG, 2.5 equiv), and a high stirring speed improved the overall yield while shortening the reaction time (entry 7, 81% total yield of isolated products, 5 h).

Further experiments showed how the careful exclusion of light completely suppressed the process. In addition, the use of a 300 W xenon bulb, equipped with a cut-off filter at 385 nm, did not significantly alter the reaction efficiency (entry 8), indicating that the visible-light-induced photoactivity of the EDA complex is responsible for the reaction that occurs.[14] The inhibition of the reactivity observed under aerobic atmosphere was consistent with a radical mechanism.

This was further corroborated by the experiment that was conducted in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 2 equiv), as the product **3a** was not detected after prolonged exposure to light (entry 9).

We then evaluated the synthetic potential of the photochemical perfluoroalkylation strategy by reacting differently substituted α-cyano arylacetates with perfluorohexyl iodide (**1a**). A variety of electron-donating substituents were well tolerated, independently of their position on the aromatic ring (Figure 3b). *Para*-substituted arylacetates were selectively perfluoroalkylated at the *ortho* position, providing the corresponding adducts **3b–d** in high chemical yield. In accordance with the classic HAS reactivity, electron-withdrawing groups greatly reduced the efficiency of the reaction because of the reduced electron density on the arene (product **3e**). An *ortho*- or *meta*-substitution pattern resulted in perfluoroalkylation with moderate regioselectivity, with the *para* isomers being preferentially formed (products **3f–i**). Notably, the different positional isomers could be easily isolated by column chromatography on silica gel, thus increasing the synthetic utility of the approach. The substrate that bears a naphthyl substituent selectively reacted at the α position (product **3j**). High regioselectivity was also obtained with disubstituted substrates (products **3k** and **3l**). Remarkably, a *meta*-bromo substituent was tolerated and the product **3l** was isolated in 60% yield. The perfluoroalkylation method was also extended to heteroaromatic derivatives, including indole and thiophene substrates (products **3m** and **3n**, respectively, in Figure 3b).

The system is amenable to the use of other perfluoroalkyl iodides (Figure 3c). A shorter perfluorinated chain was installed in **2a** in a fairly good yield (product **5a**), while a longer chain resulted in less reactivity than observed in the model reaction, even at a longer reaction time (product **5b**). Notably, the trifluoromethyl moiety could be easily installed on the phenyl ring of α-cyano phenylacetate derivatives starting from CF_3I. The reaction favored the formation of the *ortho* adduct **6a**, in sharp contrast to the perfluoroalkylation with **1a**, a regiochemical divergence that likely arose from the different steric impediments of the two radical fragments. We demonstrated that our metal-free photochemical strategy can be used for the aromatic trifluoromethylation of a variety of substrates (Figure 3d).

Finally, we evaluated the importance of the two electron-withdrawing groups (EWG) at the benzylic position of substrates **2**. Replacement of the cyano group with other substituents, including NO_2, CO_2Et, or a keto moiety, resulted in the complete loss of reactivity (results not shown). In

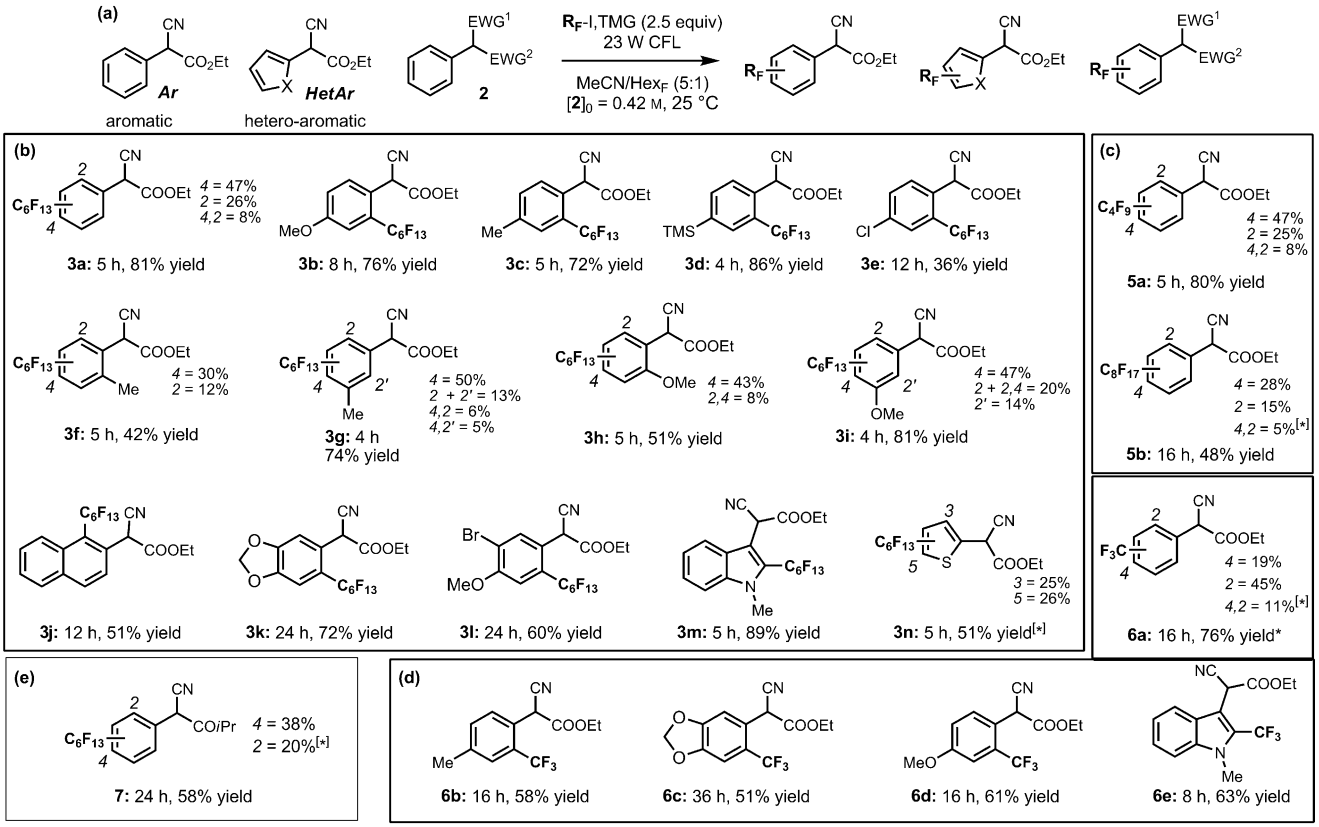


Figure 3. Metal-free photochemical aromatic perfluoroalkylation of α-cyano arylacetates. The overall yields refer to the sum of the yields of isolated regioisomeric compounds; as most of the regioisomers could be isolated by chromatography, individual yields for the isomers are also given. [*] Yields determined by ^{19}F NMR spectroscopy. a) General conditions: reactions performed on a 0.2 mmol scale using 3 equiv of perfluoroalkyl iodides **1**, 2.5 equiv of TMG, 0.4 mL of MeCN, 80 μL of perfluorohexane, and a 23 W CFL bulb; an acidic work-up (HCl 1 N) is required to isolate the products. b) Scope of the perfluoroalkylation with **1a**. c) Scope of the perfluoroalkylating agents. d) Trifluoromethylation of α-cyano arylacetates. e) Extending the reactivity to α-cyano phenylketone.

contrast, the presence of a ketone along with the CN group preserved a good level of activity (product **7**, Figure 3e). Collectively, these results indicate that the electronic properties of the EWGs at the benzylic position of **2** play a crucial role: their polar effect should be strong enough to allow the easy formation of the enolate under basic conditions, but without affecting the ensuing C–C bond formation by depleting the electronic availability on the aromatic ring. During our studies, we could not detect the formation of *meta*-substituted adducts. This result is in contrast with the very low regioselectivity generally observed in the HAS of substituted arenes with perfluoroalkyl radicals.[6a,15] It seems that, under our reaction conditions, the reactivity is mainly governed by the mesomeric effects of the anionic benzylic substituent, which channels the reaction exclusively toward the *para* and *ortho* alkylation pathways. To corroborate our interpretation that the enolate derived from **2a** (**IIa** in Figures 2 and 4) acts as a powerful electron-releasing group, we ran the model reaction in the presence of five equivalents of anisole. This competitive experiment provided adduct **3a** exclusively and only traces of the perfluoroalkylated anisole derivative. In addition, using the ^{19}F NMR spectroscopic method defined by Taft,[16] we determined a reactivity resonance parameter (σ_R) for the enolate-type anion **IIa** of −0.40 (for comparison, an *N*,*N*-dimethyl amino substituent has a $\sigma_R = -0.56$[16b]).

A series of experiments were performed to gain insight into the mechanism of the model reaction. A quantum yield (Φ) of 3.8 was determined ($\lambda = 400$ nm), suggesting a radical chain mechanism as the main reaction pathway. To further corroborate this scenario, we conducted the model reaction under exclusion of light in order to completely suppress a mechanism initiated by the excitation of an EDA complex, but adding Et_3B and O_2 to generate the R_F radical (R_F·) from iodine **1a**. The formation of the arene perfluoroalkylated product **3a** (11% yield, 8 h, 47% of R_F-H formed) was indicative of a radical chain mechanism occurring.[17] On this basis, we propose a HAS mechanism (Figure 4) which is initiated by the photochemical activity of the EDA complex of type **III**, formed upon aggregation of the enolate-type compound **IIa** with **1a**. A visible-light-driven electron transfer leads to the formation of R_F·, which then reacts with the arene within the deprotonated **2a** (compound **IIa**)[17] to form the new C–C bond. The mesomeric effect of the anionic substituent in **IIa** facilitates the C–C bond formation leading to the cyclohexadienyl radical **VI**. Two pathways are feasible for the propagation step: 1) **VI** is oxidized by R_FI through a single-electron-transfer (SET) mechanism to give the cyclohexadienyl intermediate **VII** along with R_F· and the iodide anion (**VII** would be eventually deprotonated to form the final arene product **3a**); or 2) **VI** abstracts an iodine atom from **1**, thus generating the intermediate **VIII** and the chain propagating R_F·. The endothermic I-transfer step would be followed by the fast rearomatization of **VIII** through HI elimination. Because the reactivity of the model reaction, when performed in the presence of a redox trap such as 2,4-dinitrobenzene (0.2 equiv), was strongly inhibited (14% yield, 5 h), we consider the SET as the more likely propagation pathway. Finally, performing the model reaction with equivalent amounts of **2a** and [D_5]-**2a** showed a kinetic isotope effect (KIE) of 0.97 ± 0.01 after 41% conversion, which excludes the aromatization being the rate-limiting event.

In summary, we have developed a direct and effective method to install perfluoroalkyl and trifluoromethyl groups within the aromatic ring of α-cyano arylacetates. The reaction protocol is operationally simple, conducted at ambient temperature with readily available substrates and reagents, and uses household CFL bulbs as the light source. The reaction is driven by the photochemical activity of in situ generated EDA complexes, formed by the aggregation of enolates and perfluoroalkyl iodides. This study establishes the possibility for enolates to work as suitable donors in the formation of EDA complexes.

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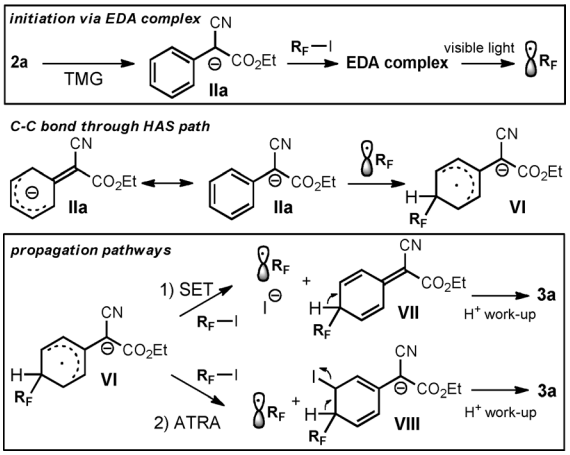

Figure 4. The proposed mechanism. ATRA = atom-transfer radical addition.

[1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.
[2] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475.
[3] For a review, see: a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; for selected examples, see: b) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909; c) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; d) O. A. Tomashenko, E. C. Escudero-Adán, M. M. Belmonte, V. V. Grushin, *Angew. Chem.* **2011**, *123*, 7797; *Angew. Chem. Int. Ed.* **2011**, *50*, 7655; e) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 551; *Angew. Chem. Int. Ed.* **2012**, *51*, 536; f) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034.
[4] Another direct strategy involves metal-catalyzed C–H activation, which requires the presence of a directing group on the arene: a) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648; b) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948.

[5] W. R. Dolbier, Jr., *Chem. Rev.* **1996**, *96*, 1557.
[6] A. Studer, *Angew. Chem.* **2012**, *124*, 9082; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950.
[7] a) G. V. D. Tiers, *J. Am. Chem. Soc.* **1960**, *82*, 5513; b) A. B. Cowell, C. Tamborski, *J. Fluorine Chem.* **1981**, *17*, 345; c) D. Naumann, B. Wilkes, J. Kischkewitz, *J. Fluorine Chem.* **1985**, *30*, 73; d) Y. Tanabe, N. Matsuo, N. Ohno, *J. Org. Chem.* **1988**, *53*, 4582; e) C. W. Lai, T. E. Mallouk, *J. Chem. Soc. Chem. Commun.* **1993**, 1359; f) N. Kamigata, T. Fukushima, M. Yoshida, *Chem. Lett.* **1990**, 649; g) Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464; h) E. Mejía, A. Togni, *ACS Catal.* **2012**, *2*, 521; i) H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.* **1990**, *46*, 423; j) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525; k) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411.
[8] a) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; for a related approach, see: b) L. Cui, Y. Matusaki, N. Tada, T. Miura, B. Uno, A. Itoha, *Adv. Synth. Catal.* **2013**, *355*, 2203; See also: c) N. Iqbal, S. Choi, E. Ko, E. J. Cho, *Tetrahedron Lett.* **2012**, *53*, 2005.
[9] a) R. S. Mulliken, *J. Phys. Chem.* **1952**, *56*, 801; b) R. Foster, *J. Phys. Chem.* **1980**, *84*, 2135; c) S. V. Rosokha, J. K. Kochi, *Acc. Chem. Res.* **2008**, *41*, 641.
[10] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750.
[11] For precedents describing the participation of enolates in the formation of EDA complexes, see: a) M. A. Fox, J. Younathan, G. E. Fryxell, *J. Org. Chem.* **1983**, *48*, 3109; b) J. E. Argüello, A. B. Peñeñory, R. A. Rossi, *J. Org. Chem.* **2000**, *65*, 7175.
[12] a) R. N. Haszeldine, *J. Chem. Soc.* **1953**, 2622; b) D. Cantacuzène, C. Wakeselman, R. Dorme, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1365; c) S. Barata-Vallejo, M. Martin, B. Lantaño, J. E. Argüello, A. B. Peñeñory, A. Postigo, *Eur. J. Org. Chem.* **2013**, 998; formation of EDA complexes was postulated as a key step of the perfluoroalkylation of silylketene acetals, see reference [16] in: d) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119.
[13] D. P. Curran, *Angew. Chem.* **1998**, *110*, 1230; *Angew. Chem. Int. Ed.* **1998**, *37*, 1174.
[14] Under these conditions ($\lambda > 385$ nm), the EDA complex of type **III** is the only species that can absorb light, as the enolate **IIa** formed by deprotonation of **2a** has an absorption residue at 360 nm (see Figure 2). This leaves the visible-light-induced photoactivity of the EDA complex as the only plausible means to access radical reactivity, as homolytic cleavage of the C–I bond is not feasible at $\lambda > 385$ nm.
[15] A. Bravo, H.-R. Bjørsvik, F. Fontana, L. Liguori, A. Mele, F. Minisci, *J. Org. Chem.* **1997**, *62*, 7128.
[16] a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, G. T. Davis, *J. Am. Chem. Soc.* **1963**, *85*, 3146; b) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165.
[17] The same experiment, when conducted in the dark and in the absence of TMG as the base, did not provide product **3a**, thus indicating that the enolate **IIa**, and not the precursor **2a**, is the active species of the HAS pathway.

