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Arona Fall, Guillaume Tintori, Marion Rollet, Yuxi Zhao, Amandine Avenel, et al.. α -Trifluoromethylated Quinolines as Safe and Storable PET-Donor for Radical Polymerizations.. *Macromolecular Rapid Communications*, 2024, 10.1002/marc.202400710 . hal-04807831

HAL Id: hal-04807831

<https://amu.hal.science/hal-04807831v1>

Submitted on 27 Nov 2024

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α -Trifluoromethylated Quinolines as Safe and Storable PET-Donor for Radical Polymerizations.

Arona Fall, Guillaume Tintori, Marion Rollet, Yuxi Zhao, Amandine Avenel, Laurence Charles, David Bergé-Lefranc, Jean Louis Clément, Sébastien Redon, Didier Gignes, Miquel Huix-Rotllant,* Patrice Vanelle, and Julie Broggi*

In the quest for powerful, safe, and storable photoinduced-electron transfer (PET) donors, the attention is turned to the α -trihalomethylated amine moiety that is not studied in the context of PET-reductants. The thermal and photophysical properties of α -trifluoromethylated quinolines are thus studied and their reducing abilities evaluated as initiators of polymerization reactions. Polymers of high molecular weights are obtained through a radical polymerization process and the PET-donor can be stored within the monomer for several months without losing its efficiency. Mechanistic investigations, combining spectroscopic analysis and theoretical calculations, confirm the mode of activation of these electron donors and the generation of radical intermediates through single electron transfer.

in synthetically important cyclization and addition reactions.^[5–9] Hence, air-stable tertiary aliphatic amines serve as mild and scope-limited photo-reductants,^[10,11] while more powerful but oxygen-unstable super enamine donors reduce numerous substrates with low reduction potentials (<2.5 V),^[12–15] including monomers in efficient polymerization processes.^[16,17] In our quest for powerful electron transfer donors,^[18,19] we became interested in the α -trihalomethylated amine moiety. Amines bearing a trihalomethylated group at the α -position of the nitrogen are important patterns, appreciated for their

electron-withdrawing and lipophilic nature in pharmaceuticals or agrochemicals applications.^[20,21] Nevertheless, to the best of our knowledge, the α -trihalomethylated amine moiety has not been studied in the context of a PET-reductant.

Hence in this work, α -trifluoromethylated quinoline derivatives were developed as new photoinduced-electron transfer donors (**Scheme 1**). The thermal and photophysical properties of these α -trifluoromethylated amines were studied and their reducing abilities evaluated as PET-initiators of polymerization reactions or as PET-reductants in organic synthesis. Extensively used in industry to initiate radical polymerization, type-I photoinitiators are activated by homolytic cleavage into radical fragments, while bimolecular type-II systems use a photosensitizer (oxidant like an aromatic ketone) to abstract an electron and a proton from a donor (synergist).^[4,22–25] More recently, new photo-initiated organocatalytic systems with unique properties, including high initiation efficiency, have been reported.^[26,27] They usually rely on multicomponent systems combining a catalyst and a sacrificial electron donor. To favor visible-light activation, complex and highly conjugated polyaromatic structures are necessary. The goal with our α -trifluoromethylated quinolines was thus to have both the photosensitizer and the ET-donor in one simple metal-free molecule that could directly reduce the monomer (oxidant), without resorting to a second initiating component. Moreover, the PET-donor had to be a safe and stable component that can be stored for several months in the monomer mixture without losing its efficiency. Our evaluation and mechanistic investigations, combining spectroscopic analysis and theoretical calculations, confirmed the properties and mode of activation of these trifluoromethylated PET-donors and the generation of radical intermediates through single electron transfer.

1. Introduction

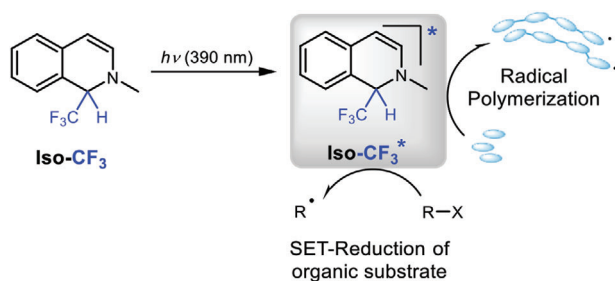
Thanks to their relatively low oxidative potentials, amines have been extensively employed as organic electron donors in single electron-transfer (SET) promoted reactions, and especially in photochemically induced electron transfer (PET) reactions.^[1–4] Direct photoexcitation of amines can trigger the reduction of an acceptor to generate radical anion intermediates, further engaged

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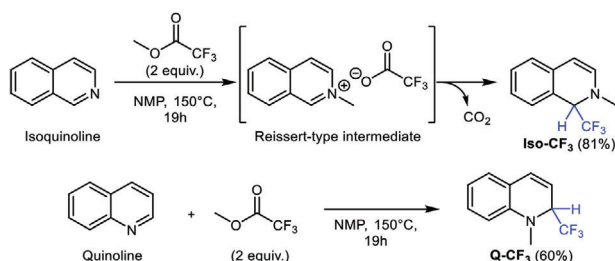
 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/marc.202400710>

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DOI: 10.1002/marc.202400710



Scheme 1. Photoactivation of an α -trifluoromethylated isoquinoline to promote SET-reduction of monomers and organic substrates.



Scheme 2. Synthesis of α -trifluoromethylated quinoline derivatives (NMP = *N*-Methyl-2-pyrrolidinone).

2. Synthesis of the PET-Reductants

The α -trifluoromethylated isoquinoline Iso-CF₃ and quinoline Q-CF₃ were synthesized in good yields (81 and 60%, respectively) following a reported one-step procedure.^[28] The latter consisted of the methylation of the imine with methyl trifluoroacetate and subsequent trifluoromethylation of a Reissert-type intermediate (**Scheme 2**).

Thermogravimetric analysis (TGA) of a solid sample of Iso-CF₃ indicated a decomposition peak above 90 °C corresponding to \approx 80% of weight loss (**Figure 1**).^[29] In our case,^[30] the theoretical % weight loss of fluoroform (CHF₃, 33%) could not be specifically distinguished from the thermolysis profile. UV-vis spectroscopy displayed an absorption band between 252 and 365 nm with a maximum wavelength $\lambda_{\text{max}} = 330$ nm (**Figure 2**). Theoretical simulations show that the spectrum can be decomposed from three excited states of $\pi \rightarrow \pi^*$ type.^[29] Cyclic voltammetry of Iso-CF₃ at its ground state showed a single irreversible ox-

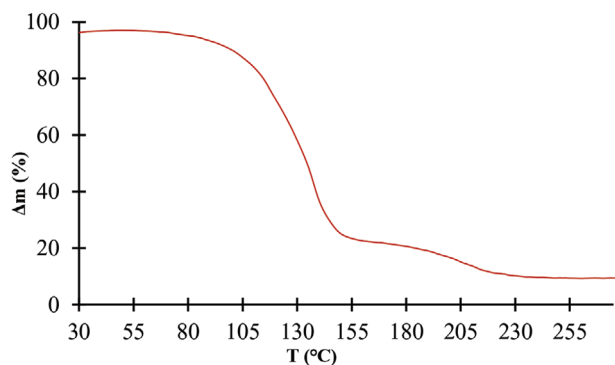


Figure 1. Thermogravimetric analysis of Iso-CF₃.

idation wave at $E_{\text{pa}} = +0.99$ V versus SCE in MeCN (calibrated using Fc/Fc⁺).^[29] Differential scanning calorimetry (DSC) analysis confirmed the stability to the storage of Iso-CF₃.^[29] DSC analysis of Iso-CF₃ indicated good stability up to 90 °C, even subjected to a premature aging cycle, and slow endothermic decomposition above 90 °C. Risks of thermal runaway or explosion are therefore unlikely during its storage. For comparison, we attempted the synthesis of the non-trifluoromethylated 1,2-dihydroisoquinoline. However, this form was extremely sensitive to atmospheric oxygen, making its isolation and manipulation difficult. It highlighted the stabilizing role of the trifluoromethyl group by strong inductive withdrawing effect. Finally, Iso-CF₃ did not display cytotoxic effects on HepG2 human cell lines ($\text{CC}_{50} = 122 \mu\text{M} \pm 3.9$, Doxorubicine was used as cytotoxic reference-drug: $\text{CC}_{50} = 0.2 \mu\text{M} \pm 0.1$).^[31]

3. Application as Polymerization Initiator

3.1. Optimization and Scope

The initiating ability of Iso-CF₃ was first assessed in the polymerization of the ethyl methacrylate monomer EMA under UV-light irradiations (365 ± 5 nm)^[33] and neat conditions (**Table 1**). Partial polymerization into the expected poly(ethyl methacrylate) PEMA was obtained using 2 or 5 mol% of Iso-CF₃ (Entries 1–2). The decrease in conversion rates and molar masses observed when the quantity of radical initiator increases was consistent with a higher number of propagating radical chains and a higher rate of chain-transfer termination reactions. However, full conversions and high weight-average molar masses (M_w) were obtained when the amount of Iso-CF₃ was decreased below 1 mol% (Entries 3–5). At 0.2 mol%, time optimization indicated full conversion (91%) in 7 h, with $M_n = 176.2 \text{ kg mol}^{-1}$ and $D = 3.77$ (Entry 6). Photoexcitation of Iso-CF₃ was then examined with different irradiation sources. Irradiation of Iso-CF₃ with a less energetic light at the edge of the visible light spectra (390 ± 20 nm) still allowed full conversion (97%) in 9 h,

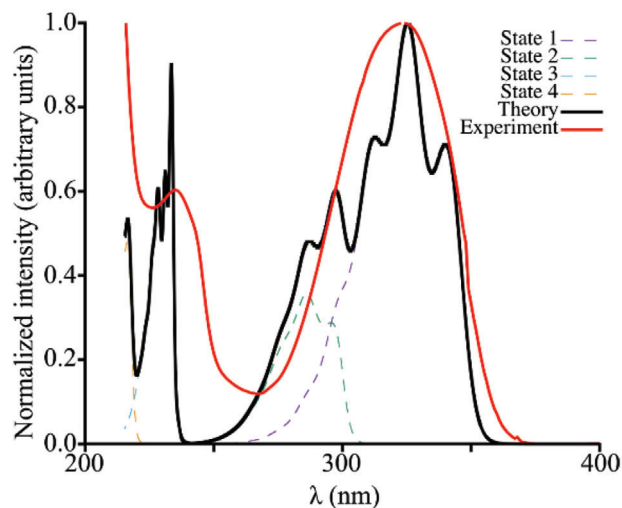


Figure 2. UV-absorption of Iso-CF₃ (red curve). The total vibrationally resolved theoretical spectrum (black solid curve) is decomposed in the contribution for each electronic excited state (dashed lines).^[32]

Table 1. Optimization of the polymerization of EMA initiated by Iso-CF₃.

Entry ^{a)}	Iso-CF ₃ [mol%]	LED [nm] ^{b)}	Conv. [%] ^{c)}	M _n [g mol ⁻¹]	M _w [g mol ⁻¹]	Đ
1	5	365	42	6900	13 400	1.95
2	2	365	70	35 300	205 200	5.81
3	1	365	94	79 200	402 100 ^{d)}	5.08
4	0.5	365	93	155 400	707 600	4.55
5	0.2	365	93	181 700	830 800	4.57
6	0.2	365	91 ^{e)}	176 200	664 600	3.77
7	0.2	390	97 ^{f)}	145 900	770 800 ^{d)}	5.28
8	0.2	440	60 ^{f)}	nd	nd	Nd
9	0.2	525	0	–	–	–
10	0.2 ^{g)}	390	93 ^{f)}	75 900	326 600 ^{d)}	4.30
11	–	390	6	–	–	–
12	0.2	390	>99 ^{h)}	46 600	165 600	3.60
13	0.2 ⁱ⁾	390	29	–	–	–
14	0.2 ^{j)}	390	33	–	–	–

^{a)} Reaction conditions: EMA (1.6 mmol, 1 equiv.), Iso-CF₃ (0.5–10 mol%), neat, 25 °C, Ar, 24 h; ^{b)} LED-Light source: UV (365 ± 5 nm, 2 cm), UV (390 ± 20 nm, <0.5 cm), Blue (440 ± 30 nm, <0.5 cm), Green (525 ± 40 nm, <0.5 cm); ^{c)} Conversions determined by ¹H NMR spectroscopy. M_n and M_w values were determined by SEC analysis (eluent: THF, molar masses in PMMA-equivalent (g mol⁻¹)); ^{d)} Molar masses are underestimated; ^{e)} 7 h; ^{f)} 9 h; ^{g)} Q-CF₃ (0.2 mol%); ^{h)} 9 h of irradiations after 7 months of storage of an Iso-CF₃/EMA mixture at 42 °C; ⁱ⁾ TPO (0.2 mol%), 24 h; ^{j)} BAPO (0.2 mol%), 24 h.

with M_n = 145.9 kg mol⁻¹ and Đ = 5.28 (Entry 7). Note that, in the applied chromatographic conditions, high-molar mass chains (>1000 kg mol⁻¹) were eluted at the limit of exclusion of the column. Therefore, the molar masses of this PEMA were underestimated, and the molar mass distribution is not fully representative of the sample.^[29] With a blue-light LED (440 ± 30 nm), partial polymerization (60%, entry 8) obtained upon excitation of Iso-CF₃ was certainly triggered by the low wavelength portion (≈410–420 nm) of the lamp. Green-light excitation (525 ± 40 nm) did not allow the polymerization of EMA (Entry 9). The quinoline counterpart Q-CF₃ also initiated polymerization of equivalent effectiveness albeit molar masses were lower (Entry 10). Moreover, Q-CF₃ seemed more sensitive to autoxidation than Iso-CF₃. Interestingly, in the absence of light, Iso-CF₃ (0.2 mol%) could be stored in EMA at 42 °C for 7 months without any sign of polymerization. After this long period of storage, irradiation (390 nm) of the mixture allowed full conversion into PEMA, with an M_n value of 46 kg mol⁻¹ and Đ = 3.6 (Entry 12). Under the same conditions, 0.2 mol% of the classical photoinitiators TPO and BAPO (Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide and Phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide) only allowed 30% of polymerization of EMA after 24 h (compared to 97% in 9 h for Iso-CF₃) (Entries 13–14).

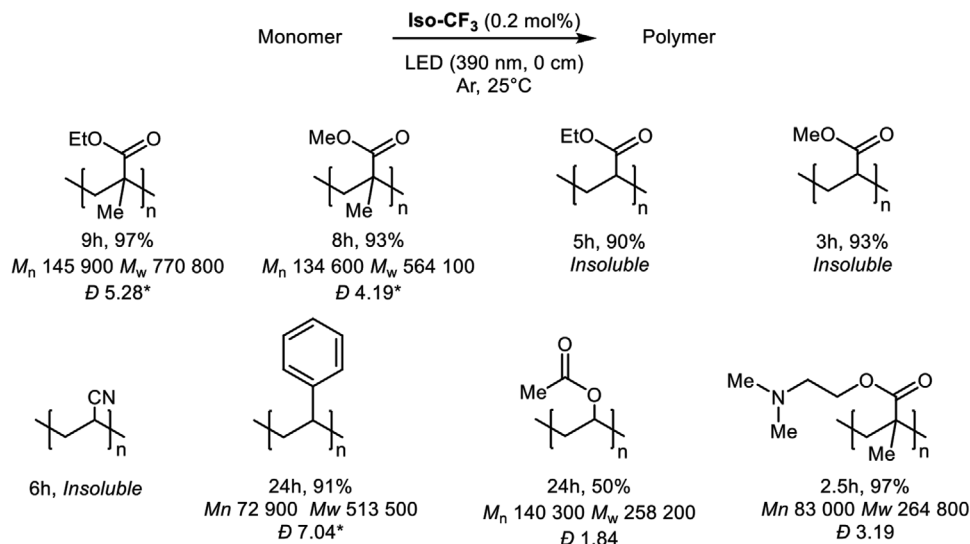
The reactivity of Iso-CF₃ was then extended to the polymerization of diverse monomers (Scheme 3). Upon photoexcitation at 390 nm, 0.2 mol% of Iso-CF₃ could efficiently initiate the polymerization of other acrylate derivatives, like methyl acrylate, 2-(dimethylamino)ethyl methacrylate and acrylonitrile. As well, styrene could be totally polymerized giving a polystyrene with an M_n value of 73 kg mol⁻¹ and Đ = 7.04. Like for PEMA, the average molecular weights of these polymers were particularly high, with elution peaks at the limit of exclusion of the column. As a matter of fact, the poly(alkyl acrylate) (PMA, PEA) and polyacrylonitrile (PAN) chains were so long that they could not be solubilized for SEC analysis (insoluble in THF, DMSO, CHCl₃ (only for PAN) and DMF).^[29,34] The solubility of PMA, PEA, and PAN polymers with lower molar masses, prepared this time with 1 mol% of Iso-CF₃, confirmed the involvement of high-molar mass chains rather than a reticulation phenomenon. A less activated monomer such as vinyl acetate could also be polymerized with a high M_n of 140.3 kg mol⁻¹ and Đ = 1.84, albeit with a lower conversion rate of 50%. As expected, the ring opening anionic polymerization of *D, L*-lactide did not proceed, pointing toward a radical process with Iso-CF₃.

3.2. Mechanistic Investigations

Several mechanistic experiments were then conducted to confirm the initiation mode and identify the reactive species at work.

The kinetic study of the polymerization of EMA with Iso-CF₃ showed an immediate initiation with a clear auto-acceleration of the propagation rate from 30% of conversion (4 h), along with a sharp increase in the M_n value (Figure 3). This gel effect (Trommsdorff effect) was typical of bulk radical polymerizations. Inhibition of the polymerization with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) further confirmed this radical process while polymerization in a protic solvent like methanol excluded the occurrence of an anionic propagation (See Table S3, Supporting Information).

To identify this radical species, polymer end-group analysis was performed. Overlaying both refractive index RI and UV signals obtained in SEC of the Iso-CF₃-primed PEMA evidenced the presence of chromophoric groups absorbing at 254 nm while no UV-absorption was detected for an AIBN-primed PEMA (See Supporting Information, Figure S7, Supporting Information). As well, the solid-state ¹³C NMR spectrum of the Iso-CF₃-primed PEMA revealed the presence of aromatic carbons from the phenyl ring between 113.7 and 144.5 ppm and a large peak for the C_{sp3}-F bonds at 128.9 ppm (See Supporting Information, Figure S10, Supporting Information). Finally, high resolution mass spectrometry performed after positive mode electrospray ionization (ESI-MS) of the Iso-CF₃-primed PEMA sample exhibited three distributions with the same 114.0681 Da EMA repeating unit (Figure 4). MS data analysis and accurate mass measurements (Figure S8, Table S4, Supporting Information) allowed structures to be proposed for the end-groups of the dominant polymer A (in red, with *n* = 0–18) as well as for the two minor polymeric species named B (in blue, with *n* = 3–25) and C (in green, with *n* = 1–8). These structural assumptions were further supported by tandem mass spectrometry (MS/MS) experiments. The α-trifluoromethyl-isoquinoline moiety was found at both ends of



Scheme 3. Scope of the polymerization reaction. *Molar masses are underestimated.

polymer C (Figure S9c, Supporting Information) as well as the ω end-group of polymer A which has H as the α termination (Figure S9a, Supporting Information), whereas polymer B was H,H-terminated (Figure S9b, Supporting Information). Of note, initiation of the polymerization by a trifluoromethyl radical^[35–37] was not observed in our case, confirming the robustness of the C–CF₃ bond.

Based on this information, the mechanism depicted in **Scheme 4** was inferred from the theoretical study (**Figure 5**). The DFT study excluded the possibility of a UV-promoted homolytic cleavage of a C–H or C–F bond in the CH–CF₃ moiety. The formation of carbene upon elimination of a molecule of fluoroform CHCF₃ was also ruled out. The reaction happens instead in two regimes. First, a photochemical regime, in which the two molecules undergo a large energy reorganization of the photon energy inducing an electron and a proton transfer between the two. Initially, the complex is stacked and stabilized by π – π stacking. In ≈ 0.1 picoseconds after photon absorption, Iso-CF₃ forms a charge transfer complex with EMA (2) where Iso-CF₃ in the photoexcited Iso-CF₃–EMA* complex acts as a PET-reducer and transfers one electron to the monomer. Indeed, the lowest absorption peak of the Iso-CF₃–EMA complex has a strong

contribution of $\pi_{\text{iso}} \rightarrow \pi_{\text{iso}}^*$ transition localized in the Iso-CF₃ moiety and a weak charge-transfer (CT) transition of the type $\pi_{\text{iso}} \rightarrow \pi_{\text{EMA}}^*$ in which an electron is transferred from Iso-CF₃ to EMA. From the CT complex, the complex is reoriented in ≈ 0.5 picoseconds, with the carbonyl of the as-formed radical anion EMA* pointing toward the α -CH of the aminium radical Iso-CF₃*⁺ (3). Still in the excited state, the oxygen of EMA* deprotonates the α -CH of Iso-CF₃*⁺. This process occurs in ≈ 1.2 picoseconds after photon absorption. This starts a regime of radical initiation of polymerization. Indeed, the two resulting radicals Iso-CF₃* and EMA-H* (4) can both initiate the radical polymerization through the addition on EMA monomers. Although, given the MS(/MS) analysis, Iso-CF₃* is a poor initiator leading to minor polymeric species C (Figure 4) and EMA-H* mainly propagates the polymerization of EMA. Termination of the polymerization upon radical coupling of the propagating radical chain (EMA)_n* with the stabilized carbon-centered α -amino captodative radical Iso-CF₃* affords the major polymer A, identified by MS(/MS) analysis. The calculated energy barriers for this termination reaction (Iso-CF₃* + (EMA)_n* \rightarrow Iso-CF₃–(EMA)_n) determined that it is a highly exothermic reaction, barrierless and spontaneous at standard conditions and at a temperature of

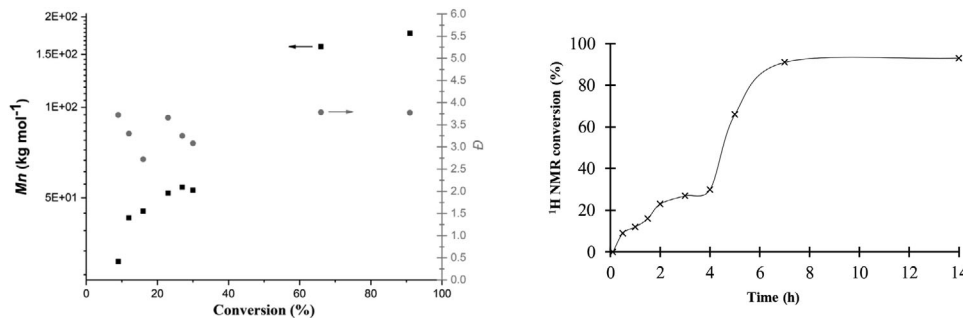


Figure 3. Kinetic of EMA polymerization with Iso-CF₃ (0.2 mol%).

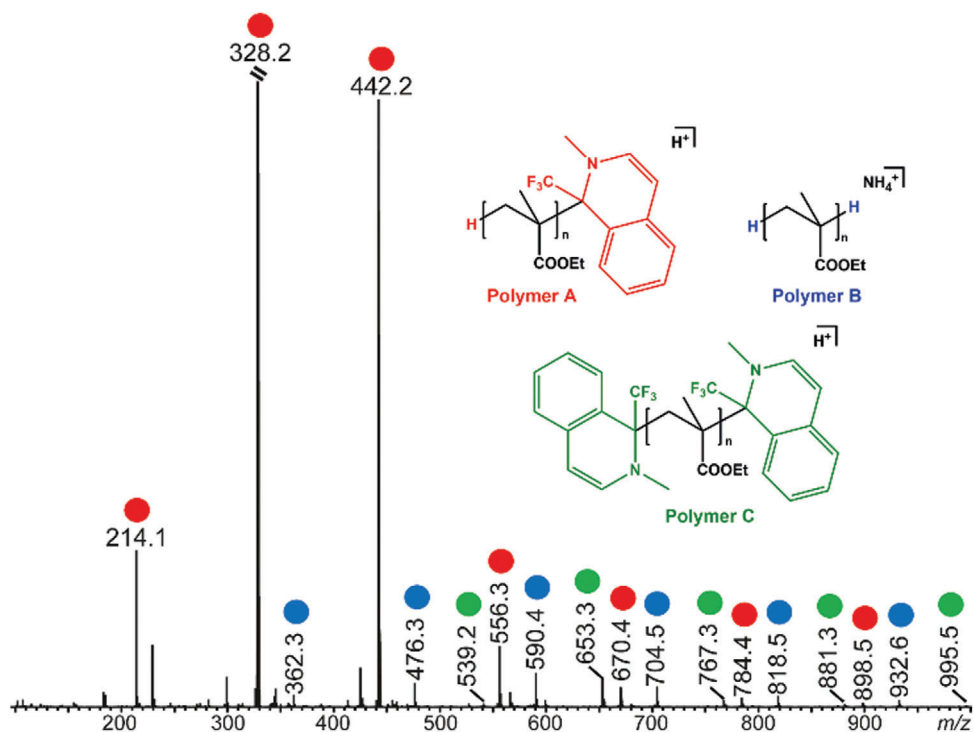
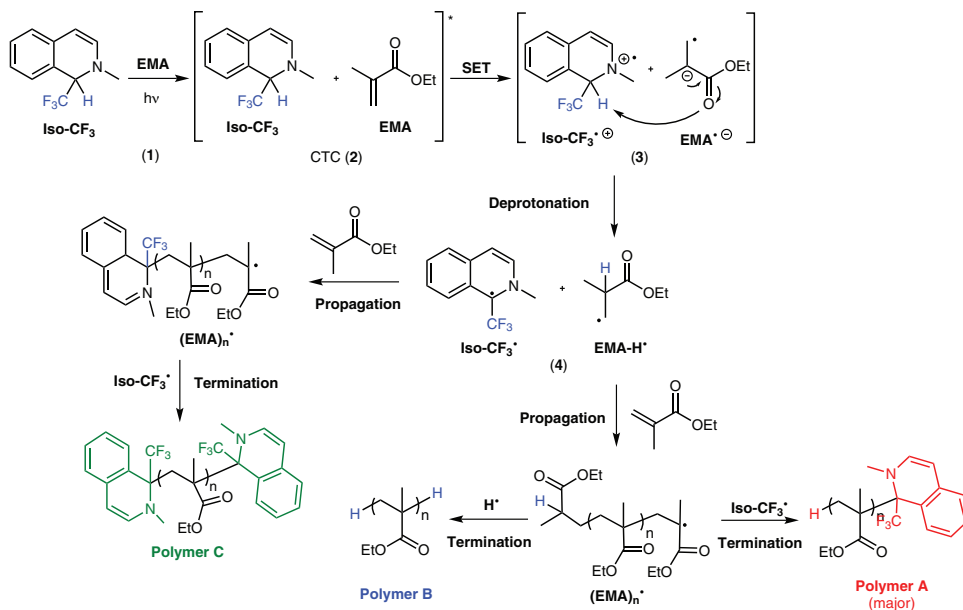


Figure 4. Expanded (x2) ESI(+)-mass spectrum of PEMA in a methanolic solution of ammonium acetate (3 mM).

298 K. Same kind of termination affords the minor polymer C while some hydrogen-atom termination (HAT) affords minor polymer B.

A radical species was indeed detected by electron paramagnetic resonance upon UV-irradiations (365 nm) of an air-exposed solution of Iso-CF₃. The spectra could correspond to the formation

of Iso-CF₃[•] upon photo-assisted oxidation of Iso-CF₃ (Scheme 5). This carbon-centered α -amino captodative radical is probably stabilized by the inductive electron-withdrawing effects of CF₃. A 1:3:3:1 quadruplet with a measured coupling constant of 2.4 mT and the fine structure observed were compatible with the formation of a radical species with the free electron in α -position of



Scheme 4. The suggested mechanism for the Iso-CF₃-initiated polymerization of EMA.

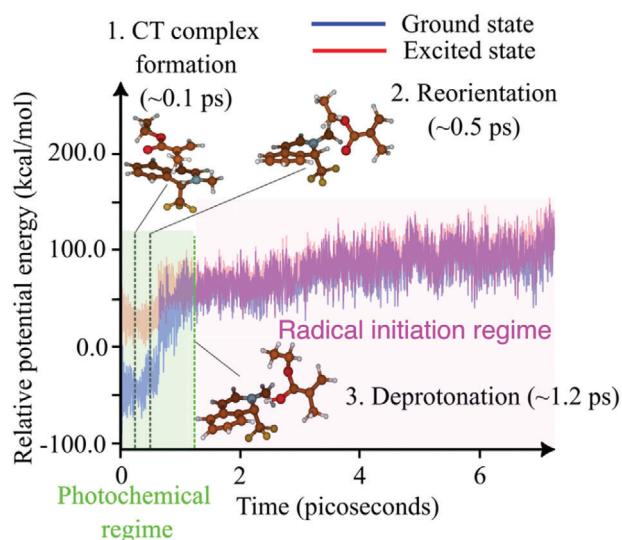
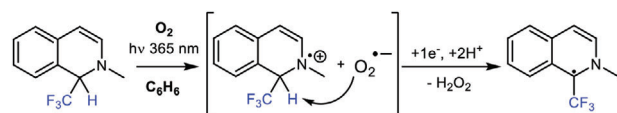


Figure 5. Time-evolution (in picoseconds) of the potential energy (in kcal mol⁻¹) during a reactive non-adiabatic dynamics trajectory explaining the photochemical mechanism of the complex Iso-CF₃ + EMA → Iso-CF₃[•] + EMA-H[•]. The key steps of the reaction are summarized, and the snapshots are shown in an offset (The time evolution is available in the video in the Supporting Information). Two regimes are shown, the photochemical regime, in which the proton is not yet transferred between the two species, and the radical initiation regime in which the radicals are formed.

a CF₃ group and agree with the structure of the radical species Iso-CF₃[•] (See Supporting Information).^[29]

Hence, Photoexcitation of the reducer/monomer complex was mandatory to generate the propagating species EMA-H[•]. We wondered if the termination reaction could be reversible and if the Iso-CF₃-(EMA)_n polymer A could dissociate to reactivate a dormant chain. First, an ON-OFF experiment was conducted to evaluate the influence of the UV-light irradiations on the propagation process (Figure 6). During the polymerization of EMA, the UV irradiations were iteratively switched on for 1 h then switched off for 2 to 96 h. While polymerization proceeded under light-irradiations (an increase of 10 to 30% of the conversion at each ON phase), the chain growth was stopped in darkness (<5% over a period of 96 h). Compared to a continuously photo-irradiated PEMA (Table 1, Entry 6: M_n = 176.2 kg mol⁻¹, M_w = 664.6 kg mol⁻¹ and Đ = 3.77), the PEMA of the ON-OFF cycles presented similar molar masses and polydispersity values (M_n = 176.5 kg mol⁻¹, M_w = 706.3 kg mol⁻¹ and Đ = 4.00). To test if a reversible-deactivation radical polymerization mechanism was involved, we subjected isolated and air-stored Iso-CF₃-PMMA or Iso-CF₃-PEMA polymers to a new reaction where it was mixed with fresh EMA monomer under UV-light irradiations.^[29] Interestingly, both polymerization reactions pro-



Scheme 5. The suggested mechanism for the photo-assisted autoxidation of Iso-CF₃.

ceeded to full completion. However, SEC analysis indicated that a new PEMA homopolymer was formed in a mixture with the first PMMA or PEMA rather than an extension of the existing polymer chains. Dynamic theoretical studies also confirmed that the termination reaction of the Iso-CF₃-EMA[•] polymer (radical coupling between (EMA)_n[•] and Iso-CF₃[•]) is not reversible. Further studies are now underway to understand the origin of this ON-OFF propagation. Under photoirradiations, the Iso-CF₃-PEMA could play the role of macroinitiator through the formation of a charge-transfer complex between a monomer and the Iso-CF₃ end chain.

4. Application as a Reducing Agent in Organic Synthesis

The mechanistic study of our polymerization reaction evidenced the role of Iso-CF₃ as a PET-donor agent. To investigate further its abilities, we then subjected Iso-CF₃ as a reducing agent for the reduction of halogenated compounds. Complete reduction of the 2-(bromomethyl) naphthalene 1 was achieved with one equivalent of Iso-CF₃ under UV-irradiations, leading to the major formation of the binaphthyl dimer 2 in DMF (Scheme 6). The same reaction in THF (favoring Hydrogen Atom Transfer) led to the major formation of the reduced 2-methylnaphthalene 2'. Reduction of iodoarene 3 and 5 required harsher conditions, leading to the corresponding dehalogenated products 4 and 6 in 80 and 75% of conversion, respectively. Hence, the α-trifluoromethylated isoquinoline Iso-CF₃ could also be used as an organic PET-reducer in organic synthesis, notably for the reduction of carbon-halogen bonds.

As Iso-CF₃ could theoretically transfer two electrons (one from photoexcited Iso-CF₃[•] and one from the carbon-centered α-amino radical Iso-CF₃[•]),^[38] we wondered if the reduction of these halogenated compounds generated radical or anionic intermediates. Indeed, the formation of dimer 2 could arise from the reductive homocoupling of two naphthylmethyl radicals^[39] or from the nucleophilic substitution of naphthylmethyl bromide with a naphthylmethyl anion. The non-reduction of 1 in the presence of oxygen or a competitive oxidant (1,4-dinitrobenzene

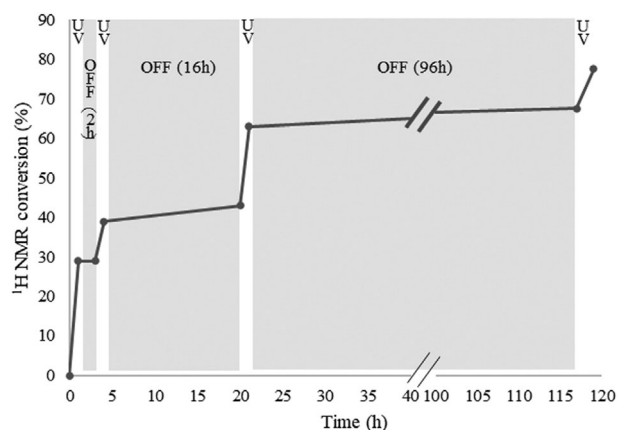
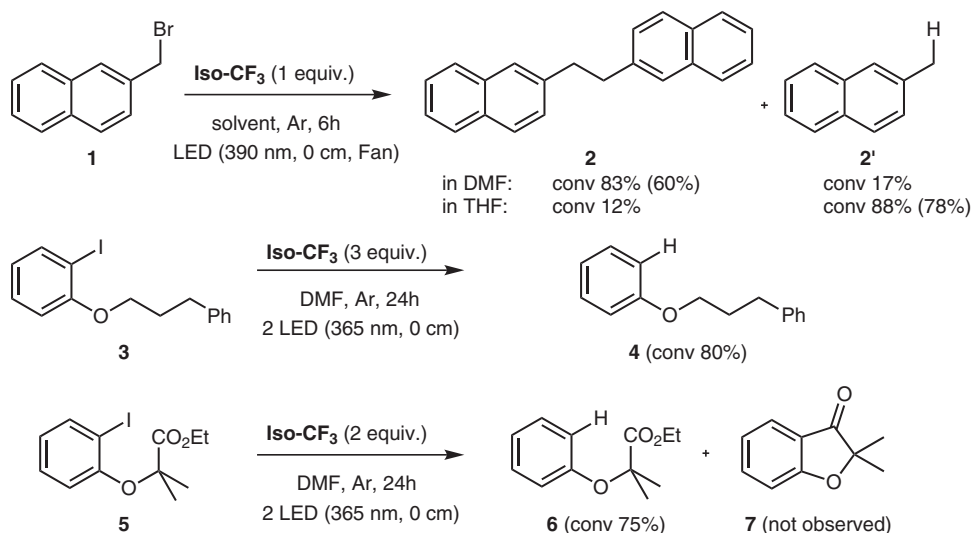


Figure 6. Kinetic of the polymerization of EMA with Iso-CF₃ under ON-OFF cycles of UV-light irradiations.



Scheme 6. Reduction of benzyl and aryl halides by Iso-CF₃.

(*p*-DNB)) confirmed the electron transfer mechanism (Table 2, entries 1 and 2). Then, the major formation of the coupling product 8 (58%)^[40] in the presence of the radical scavenger TEMPO leaned toward the generation of a naphthylmethyl radical intermediate upon SET from excited Iso-CF₃* (entry 3). Delocalization of the radical over the naphthyl moiety favors the stability of the naphthylmethyl radical and the homocoupling reaction. The absence of the cyclized product 7 (arising from the double electron-transfer reduction of 5 and subsequent cyclization of the aryl anion intermediate)^[41] reinforced the hypothesis of a radical process.

5. Conclusion

In conclusion, we demonstrated that α -trifluoromethylated quinoline derivatives are a new class of safe and storable photoinduced-electron transfer donors that can be conveniently and efficiently used for the initiation of radical polymerizations or the reduction of halide derivatives. Contrary to the classical Norrish type II initiator, Iso-CF₃ operates both as the photosensitizer and the ET-donor, directly reducing the monomer without resort-

ing to a second initiating component. Moreover, Iso-CF₃ gives very long chain polymers and could be stored in the monomer solution for several months at 42 °C without losing its efficiency. Polymers bearing Iso-CF₃ at their chain end are now under study as possible macroinitiators.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The Agence Nationale de la Recherche is gratefully acknowledged for the JCJC ANR grant "iPOD" (17-CE07-00010). Aix Marseille Université (AMU) and the Centre National de la Recherche Scientifique (CNRS) are acknowledged for financial support. G.T. thanks the Ministère de l'Enseignement Supérieur et de la Recherche for his Ph.D. grant. Y.Z. is grateful for Ph.D. fellowships from the China Scholarship Council (CSC). The authors thank Dr Vincent Remusat for NMR analyses and the Spectropole (Fédération des Sciences Chimiques de Marseille) for spectroscopic analyses. Dr Marion Casanova, Sébastien Hutter, and Prof. Nadine Azas are also acknowledged for the cytotoxic test on HepG2 human cell lines.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

A.F., G.T., and M.R. contributed equally to this work. The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Data Availability Statement

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

Table 2. Mechanistic investigations on the electron-transfer properties of Iso-CF₃.

Entry	Additive	Product
1	Air (1 atm)	-
2	<i>p</i> -DNB (1 equiv.)	-
3	TEMPO (1 equiv.)	8 (conv. 58%)

Keywords

α -Trihalomethylated amine, photoinduced-electron transfer, PET donor, radical polymerizations, reduction

Received: September 9, 2024

Revised: October 22, 2024

Published online:

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