

Methyl Radical Initiated Kharasch and Related Reactions

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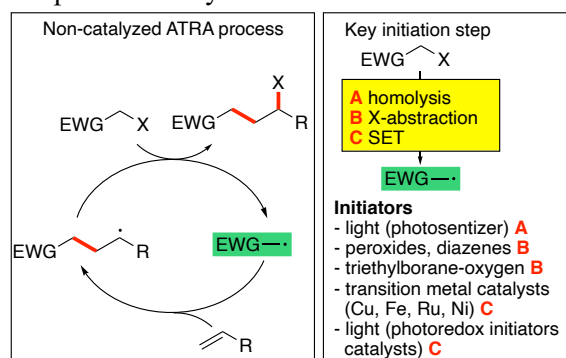
Abstract. An improved procedure to run halogen atom and related chalcogen group transfer radical additions is reported. The procedure relies on the thermal decomposition of di-*tert*-butylhyponitrite (DTBHN), a safer alternative to the explosive diacetyl peroxide, to produce highly reactive methyl radicals that can initiate the chain process. This mode of initiation generates byproducts that are either gaseous (N₂) or volatile (acetone and methyl halide) thereby facilitating greatly product purification by either flash column chromatography or distillation. In addition, remarkably simple and mild reaction conditions (refluxing EtOAc during 30 minutes under normal atmosphere) and a low excess of the radical precursor reagent (2.0 equivalents) make this protocol particularly attractive for preparative synthetic applications. This initiation procedure has been demonstrated with a broad scope since it works efficiently to add a range of electrophilic radicals generated from iodides, bromides, selenides and xanthates over a range of unactivated terminal alkenes. A diverse set of radical trap substrates exemplifies a broad functional group tolerance. Finally, di-*tert*-butyl peroxyoxalate (DTBPO) is also demonstrated as alternative source of *tert*-butoxyl radicals to initiate these reactions under identical conditions which gives gaseous byproducts (CO₂).

Keywords: radical reaction; atom transfer; radical initiation; chain reaction; carbohalogenation; haloalkylation; ATRA; alkene.

Introduction

The atom transfer radical addition (ATRA) process discovered by Kharasch in the 1940s is one of the most attractive processes to create carbon–carbon bonds under mild conditions and a theoretical perfect atom economy (Scheme 1).^[1–6] Theoretically too, such an efficient chain reaction requires only a tiny amount of a radical initiator when the process is favored by thermodynamic and polar effects. In practice, the initiation has proven to be a crucial element for the success of this reaction. Scheme 1 summarizes three commonplace strategies to initiate ATRA processes: **A** carbon–halogen bond homolysis, **B** halogen atom/chalcogen abstraction, and **C** reductive single electron transfer. Curran has thoroughly demonstrated that the more reactive halides such as α -iodocarbonyl compounds are among the best substrates to conduct ATRA reactions.^[7–10] For such derivatives, initiation using sun lamp irradiation was possible (strategy **A**). However, the generation of a small amount of iodine resulting from the homolysis of the C–I bond was found to inhibit ATRA chain propagation by regenerating the starting radical precursor iodide before the C-centered radical could add onto the alkene. Adding hexamethylditin that reacts spontaneously with elemental iodine to form Me₃SnI

effectively solved this problem but led to product contamination with tin residues.^[11] Photoinitiation in the presence of a sensitizer such *p*-anisaldehyde was found to work well with highly activated radical precursors such as bromomalonate derivatives, CCl₄, and perfluorohexyl iodide.^[12]



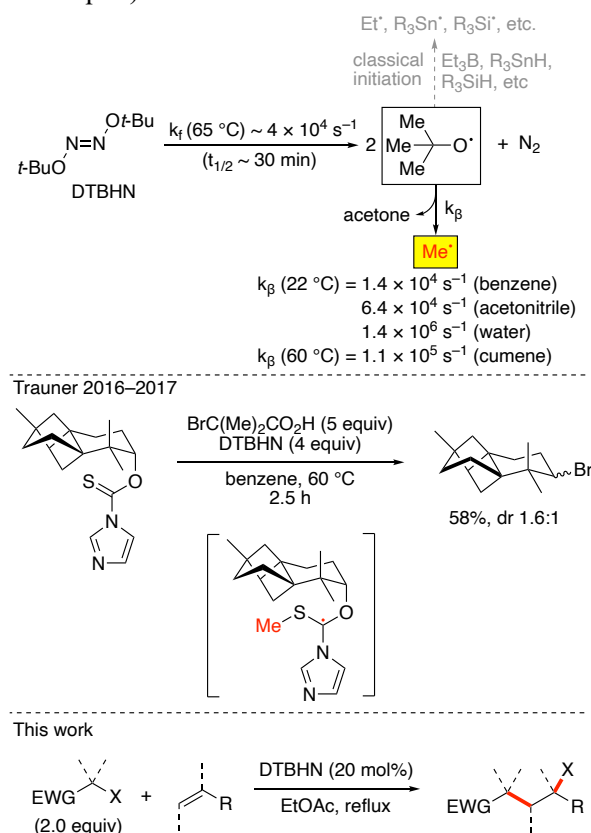
Scheme 1. Non-catalyzed ATRA process: mechanism and key approaches for the initiation step

Kharasch in his seminal work used mainly strategy **B** with diacetyl peroxide as a source of methyl radicals.^[5] However, this peroxide is explosive and shock sensitive, and has therefore been generally replaced by the more stable dilauroyl peroxide

(DLP).^[13] The DLP approach has proven to be reliable but the thermal decomposition products of DLP including lauric acid, *n*-docosane and undecyl laurate,^[14] as well as lauroyl halide from productive initiation, often contaminate the products and difficult (sometimes multiple) purifications by column chromatography are required to obtain analytically pure ATRA products. This byproduct contamination has also been observed when DLP was used to initiate the highly efficient xanthate transfer reactions developed over the last two decades by Zard and coworkers.^[15,16] One remarkably successful solution has been to initiate with triethylborane and oxygen, which works via transient ethyl radicals (strategy B).^[17–19] However the pyrophoric character of triethylborane, and inherent incompatibility with α -halo- and α -chalcoketones,^[20,21] have made this strategy less attractive. The use of transition metal catalysis (Fe, Cu, Ru, Ni for instance) is also a popular way of initiating (and often catalyzing) ATRA processes,^[22–28] this approach involves an initial inner-sphere electron transfer (strategy C) and is particularly suitable for reactions onto activated alkenes such as styrene derivatives. More recently, visible light-promoted electron transfers (strategy C) have been reported in the presence of diverse, often expensive, transition metal catalysts.^[29–37] Despite all these studies, the need of a simple and broadly applicable method to run ATRA reactions remains highly needed. Ideally, the reaction should work with a wide range of reactive—and less reactive—substrates and reagents under mild reaction conditions that avoid the use of expensive or toxic metals and the formation of byproducts which are difficult to remove.

Approaches A and C can provide very efficient continuous solutions for the ATRA reaction. However, based on their mechanism of action, they are not expected to be applicable to a broad range of radical precursors possessing different redox potentials and photochemical properties. On the other hand, method B involving classical halogen transfer processes is expected to behave in a highly predictable manner and its efficiency is governed by the difference of the C–X bond dissociation energies between the radical precursor and the halide or chalcogenide product resulting from initiation. In order to maximize the thermodynamic aspect of the initial atom transfer, the use of the least stable alkyl radical, i.e. the methyl radical, is an optimal choice insuring a fast halogen transfer step with few chain-breaking events. Besides fragmentation of diacetyl peroxide employed in Kharasch's seminal work, methyl radicals are also generated by fragmentation of *tert*-butoxyl radicals.^[38] The use of di-*tert*-butyl peroxide was not considered as an option since temperatures ≥ 120 °C are required for its homolysis.^[39,40] Interestingly, the thermal homolytic scission of di-*tert*-butyl hyponitrite (DTBHN)^[41,42] takes place facilely at moderate temperatures (40–70 °C; $t_{1/2} = 29$ min at 65 °C, neat) to result in the simultaneous formation of two *tert*-butoxyl radicals and extrusion of molecular nitrogen (Scheme 2, top). A first order rate in [DTBHN] with

constant of $k_f = 3.85\text{--}4.00 \times 10^4 \text{ s}^{-1}$ was measured for this decomposition at 65 °C in isoctane.^[41] β -Fragmentation of the *tert*-butoxyl radical to acetone and a methyl radical^[38] takes place spontaneously and quickly at ambient temperatures ($k_\beta = 1.4 \times 10^4 \text{ s}^{-1}$ in benzene at 22 °C),^[43] and is sped up with heating ($k_\beta = 1.1 \times 10^5 \text{ s}^{-1}$ in cumene at 60 °C).^[44] Even more interesting, this fragmentation is accelerated in polar ($k_\beta = 6.4 \times 10^4 \text{ s}^{-1}$ in acetonitrile at 22 °C) and protic solvents ($k_\beta = 1.4 \times 10^6 \text{ s}^{-1}$ in water at 22 °C).^[43] Up to now, most radical initiations using DTBHN involve rapid reactions of *tert*-butoxyl radicals with oxophilic species such as organoboron and ditin derivatives as well as hydrogen atom donors such as tin hydrides and silanes (Scheme 2, top, grey).^[42] However, when no such species is present in the reaction mixture, DTBHN is expected to be a source of methyl radicals and therefore a powerful system to initiate halogen / chalcogen transfer processes from a variety of radical precursors. To the best of our knowledge, the DTBHN-methyl radical mediated initiation has only been used by Trauner and coworkers for a conversion of a xanthate to a bromide (Scheme 2, middle).^[45,46] Here, we report that DTBHN is an excellent general initiator for ATRA processes under simple, mild, and clean (only volatile initiator byproducts) reaction conditions (Scheme 2, bottom). Here, only a small excess of the radical precursor reagent (2.0 equiv) relative to the substrate is employed avoiding the frequently reported and wasteful excess (typically >3.0 equiv).



Scheme 2. Thermal decomposition of DTBHN as a source of methyl radicals.

Results and discussion

Preliminary experiments with different radical precursors. The methyl radical initiation was first attempted for iodine atom transfer reactions which is a high-performing manifold for the Kharasch reaction. As polar solvents were expected to favor β -scission,^[43] we selected the environmentally benign EtOAc as a solvent that has a reflux temperature matching a short half-life of DTBHN.^[41] DTBHN is readily synthesized from *tert*-butylbromide and sodium hyponitrite, and easily crystallized from pentane in modest yields (see supplementary information).^[41,47] Initial studies were performed with 1-undecene **1a** using a short reaction time of 30 minutes. Reaction with two equivalents of ethyl iodoacetate **2a** gave ATRA product **3a** in high yields between 5–20 mol% loadings of DTBHN. Reproducibility and yields were best for DTBHN loadings over 10 mol% and had plateaued (and were very slightly eroded) by 20 mol% (Table 1, Entry 1). For the well-behaved iodine atom and xanthate group transfer reactions, 10 mol% DTBHN was generally sufficient or better (e.g. **4**, Scheme 3). Nonetheless, in order to unify the reaction conditions and maximize reproducibility over all radical precursors, the reactions were performed with 20 mol% DTBHN. The rate constants for the halogen atom transfer from the starting halide to a primary alkyl radical are also given in Table 1,^[48] to show that yields of **3** correlate well with transfer rates from **2**. The final column of Table 1 provides a point of reference for analogous reactions initiated by alkyl radical generation (examples from the literature with the same radical precursor but different terminal alkenes are given). More

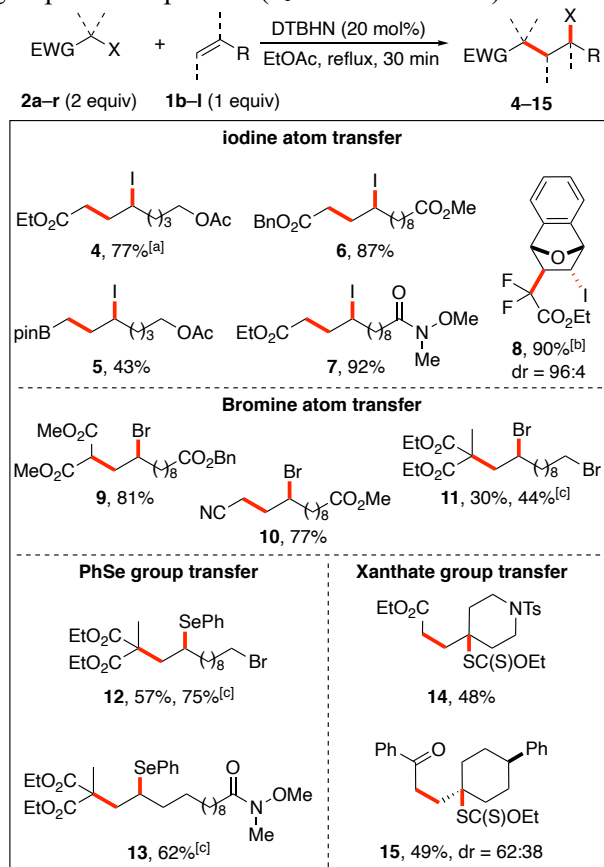
challenging radical precursors were then tested in a systematic progression (Entries 1–8). Bromine atom transfer from ethyl bromoacetate **2b**^[5,49] furnished **3b** in moderate 25% yield (Entry 2). The yield reached 33% by adding another 20 mol% of DTBHN demonstrating that the chain reaction is inefficient presumably due to the slow bromine atom transfer propagation step. Phenylseleno group transfer reaction behaved poorly for the ester precursor **2c** (entry 3) but xanthate group transfer performed well with the ester **2d** (entry 4, 90%). A similar trend was observed for the acetonitrile derivatives **2e–2h**. The iodide **2e**, a typical iodine-ATRA radical precursor, gave an anticipated good yield for iodide **3e** (entry 5, 78%), as did the bromoacetonitrile **2f** to furnish **3f** in 70% yield under our standard conditions (entry 6). Phenylselenoacetonitrile **2g** gave **3g** in low yield (entry 7) and reaction of the xanthate **2h** with **1a** delivered **3h** in excellent yield (entry 8). Less reactive iodides such as the pinacol boronic ester **2i**^[50] and the sulfone **2j**^[51–53] afforded the ATRA products in moderate to excellent yields (entries 9 and 10). The unstable heat and light sensitive 2-iodoacetophenone **2k** did not afford cleanly the iodide **3k** (entry 11). On the other hand, the corresponding bromoketone **2l**^[54,55] did provide **3l** in 50% yield (entry 12). Again, the xanthate **2m** added to **1a** in a quantitative manner (entry 13). The crude products of all reactions depicted in Table 1 were easy to purify by column chromatography, in sharp contrast to the same product mixtures prepared using DLP as an initiator that are contaminated by the aforementioned non-volatile decomposition byproducts.^[14,56–58]

Table 1. Identification of radical precursor (**2a–m**) scope with 1-undecene **1a**.^[a]

Entry ^[a]	Radical Precursor		k_T [$M^{-1} s^{-1}$]	Ref.	Product	Yield ^[b]	Literature Analogies ^[f]	
	EWG	X					Yield	Method
1	2a	CO ₂ Et I	2.6×10^7	[48]	3a	83%, 87% ^[c]	93%	DLP ^[13]
2	2b	CO ₂ Et Br	7×10^4	[48]	3b	25%, 33% ^[d]	65%	BEt ₃ /O ₂ ^[60]
3	2c	CO ₂ Et SePh	1.0×10^5	[61]	3c	<5% ^[e]		
4	2d	CO ₂ Et SC(S)OEt			3d	90%	~75%	DLP ^[62]
5	2e	CN I	1.7×10^9	[48]	3e	78%		
6	2f	CN Br	3×10^6	[63]	3f	70%		
7	2g	CN SePh	2.3×10^5	[61]	3g	13%		
8	2h	CN SC(S)OEt			3h	87%	85%	DLP ^[64]
9	2i	Bpin I			3i	51%	~60%	DLP ^[50]
10	2j	SO ₂ Ph I			3j	59%, 80% ^[d]		
11	2k	C(O)Ph I			3k	<10% ^[e]		
12	2l	C(O)Ph Br			3l	41%, 50% ^[d]		
13	2m	C(O)Ph SC(S)OEt			3m	94%	84%	DLP ^[65]

[a] All reactions were performed on 1.0 mmol of 1-undecene **1a**, 2.0 mmol of the radical precursor **2a–m**, and 0.2 mmol of DTBHN (20 mol% with respect to **1a**), and with technical grade EtOAc (3.3 mL) without any drying of solvents or reagents under air atmosphere (no inert gas). The reaction mixture was heated under reflux for 30 min and concentrated *in vacuo* for direct purification by silica-gel flash column chromatography. [b] Isolated yields. [c] 10 mol% DTBHN. [d] 2×20 mol% DTBHN, 2×30 min reaction time. [e] Not characterized. [f] Analogous reactions involving a terminal alkene and initiation via X-abstraction (Scheme 1, strategy B); only examples that employ no greater than a 3-fold excess of either radical precursor or radical trap are given.

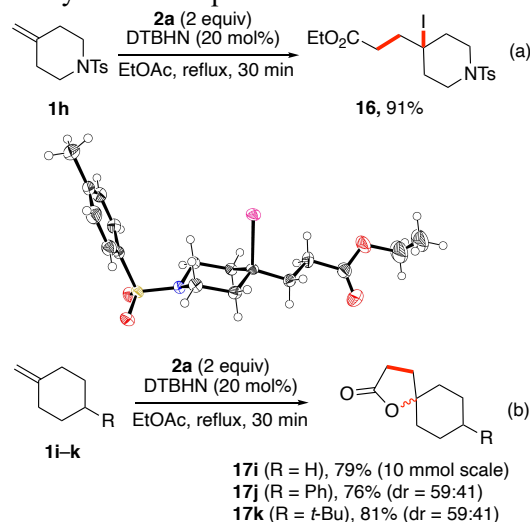
Scope of the method. Having established that a wide range of radical precursors could be added over unfunctionalized 1-substituted alkenes. More functionalized alkenes as well as different radical precursors were also tested. The wealth of examples presented in Scheme 3 demonstrates the generality of this method. Alcohols protected as esters, Weinreb amides, and 1,2-*cis*-alkenes all underwent iodine-ATRA with high yields (Scheme 3, **4–8**) except for ICH₂Bpin which furnished **5** in a modest 43% yield. Bromine-ATRA with dimethyl 2-bromomalonate **2p** and BrCH₂CN **2f** provided **9** and **10** in excellent yields. The 2-methylated bromomalonate **2q** was allowed to react with the bromide **1d** affording **11** in 30% yield along with 43% of recovered **1d**. The low yield is unlikely to be due to steric hindrance of the radical generated from **2q** since other groups have reported good results with this radical precursor.^[12] Conversion became high and yield increased to 44% with 2 × 20 mol% DTBHN. The analogous selenomalonate **2r**, reacted with **1d** and **1g** to give **12** and **13** in improved 75% and 62% yields, respectively. The efficacy of the selenophenyl group transfer reaction with **2q** relative to the monoester and nitrile derivatives **2c** and **2g** (Table 1, entries 3 and 7) is rationalized by the faster group transfer process ($k_T = 8 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$).^[61]



Scheme 3. Scope of the DTBHN initiated ATRA reactions. All reactions were performed as described in Table 1. Isolated yields are reported. [a] With 10 mol% DTBHN. [b] Yield of major diastereoisomer; the two diastereoisomers were easily separated by flash column chromatography, (see SI for details). [c] 2 × 20 mol% DTBHN, 2 × 30 min reaction time.

Finally, challenging xanthate transfer reactions involving the formation of tertiary xanthates were attempted with cyclic *exo*-methylene radical traps and α -ester and α -ketone xanthates **2d** and **2m**. The tertiary xanthates **14** and **15** were obtained in moderate 48% and 49% yields. Zard has reported a similar yield for the DLP-initiated xanthate transfer onto *N*-Boc protected 4-*exo*-methylenepiperidine.^[66]

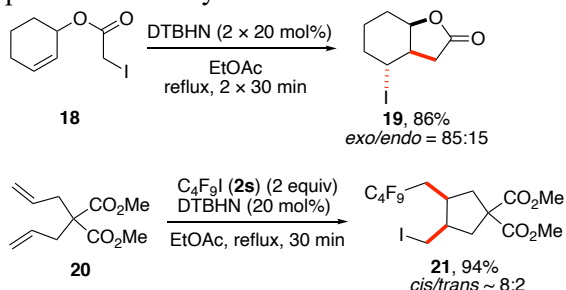
Preparation of tertiary iodides and lactones. Due to the instability of tertiary iodides under most reactions conditions reported for ATRA reactions (light, heat), iodine ATRA-reactions involving the formation of a tertiary iodides have so far only been achieved at room temperature using triethylborane^[67–69] and Mn₂(CO)₁₀^[70] initiation. Surprisingly, running the reaction between the protected 4-methylenepiperidine **1h** and ethyl 2-iodoacetate **2a** under our mild DTBHN conditions afforded the tertiary iodide **16** in an excellent 91% yield (Scheme 4, eq. a). Its structure was confirmed by single crystal X-ray crystallography. When the same reaction was performed with methylenecyclohexane derivatives **1i–k**, the intermediate tertiary iodides were spontaneously converted into the lactones **17i–k** with respectable 76–81% yields (Scheme 4, eq. b). The reaction of methylenecyclohexane **5i** with **2a** was scaled up to 10 mmol without yield depreciation for the formation of **17i** (79%) after distillation. Such lactonization processes were already observed by Kharasch in his seminal work on bromine ATRA but requires heating at $\geq 160 \text{ }^\circ\text{C}$,^[5] by Kraus and Landgrebe using iodostannylester,^[71] and by Curran with iodoesters and iodomalonate derivatives.^[7,10,72] This radical-ionic sequence has also been reported for ethyl iodoacetate^[73–75] and iodoacetic acid^[76] metal-catalyzed ATRA processes.



Scheme 4. Iodine ATRA reaction leading to tertiary iodides and lactones.

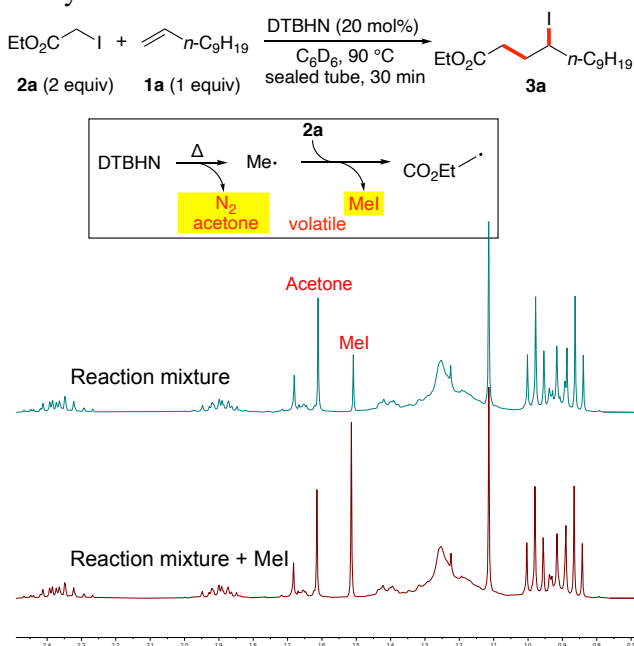
Radical cyclizations. In order to further showcase this initiation method, the iodine atom transfer cyclizations depicted in Scheme 5 were investigated. Iodoacetate **18** could be converted in good yield to the

lactone **19** in agreement with light-ditin,^[72] and DLP procedures.^[13] An intermolecular radical addition-cyclization sequence with a perfluoroalkyl iodide **2s** was employed to convert **20** to the cyclopentane **21** in 94% yield (*cis/trans* ~80:20). The observed diastereoselectivity matches expectations for such a radical process^[77] and the yield compares well with reported procedures^[77-79] including the ones requiring photoredox catalysis.^[80-82]



Scheme 5. DTBHN initiated iodine atom transfer radical cyclization (ATRC).

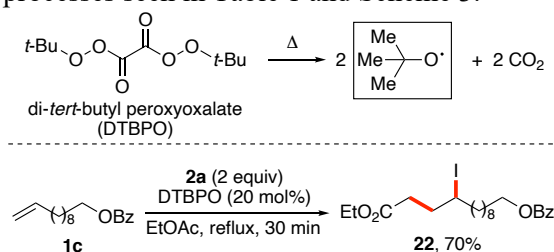
Mechanistic investigation. At the beginning of this project, we hypothesized that the initiation with DTBHN will involve the highly reactive methyl radical. In order to get insight into the mechanism and to confirm the involvement of methyl radicals, the reaction was monitored by NMR. The reaction between **2a** and **1a** was performed in a sealed tube with C₆D₆ as a solvent. NMR analysis of an aliquot revealed a ¹³C-NMR signal at -24.4 ppm corresponding to MeI (see SI). In the ¹H-NMR, a singlet at 1.51 ppm was present. Upon addition of commercial MeI to the reaction aliquot, a growth in intensity of the peak at 1.51 ppm was observed confirming the formation of methyl iodide.



Scheme 6. Mechanism of the initiation process. ¹H-NMR evidence for the formation of MeI and acetone during the reaction.

The formation of acetone resulting from the fragmentation of the intermediate *tert*-butoxyl radical could also be observed at 1.61 ppm^[83] in the ¹H-NMR spectrum of the reaction.

Initiation with di-*tert*-butyl peroxyoxalate. Since DTBHN is prepared from expensive sodium trans-hyponitrite (ca. 48 euros/g), a cheaper alternative was sought. Di-*tert*-butylperoxyoxalate (DTBPO), easily prepared from oxalyl chloride and *tert*-butyl hydroperoxide, is well-known for low temperature generation of *tert*-butoxyl radicals.^[84,85] This compound has been recently used in our group for efficient initiation of reactions involving organoborane precursors.^[86,87] Its decomposition as well as the initiation process is also expected to provide exclusively gaseous (CO₂) and volatile (MeI, acetone) byproducts (Scheme 7, top). When used in place of DTBHN for the iodine-ATRA reaction between **2a** and the unsaturated benzoate **1b**, I-ATRA product **22** was obtained in 70% yield (Scheme 7, bottom) in full accordance with the DTBHN initiated processes seen in Table 1 and Scheme 3.



Scheme 7. DTBPO initiated iodine-ATRA reaction: Another clean initiation procedure.

Conclusion

A simple, mild and generally applicable procedure for halogen ATRA and related reactions has been developed. This procedure is suitable to run non-catalyzed ATRA favored by thermodynamic and polar effects and is not intended to run challenging ATRA that require a catalyst involved in the reaction chain process to overcome kinetically or thermodynamically difficult steps.^[22-28] The use of DTBHN (or DTBPO) allows efficient initiation involving atom/group transfer processes, mediated by methyl radicals, at moderate temperature. The main advantage of this approach is the absence of product contamination caused by the initiation thus greatly facilitating product purification. Indeed, the byproducts of initiation are either gaseous (N₂ or CO₂) or volatile (acetone, methyl iodide). Under these conditions, efficient and clean radical chain reactions can occur without the assistance of either toxic or expensive metal additives. In contrast to photoinitiated processes, thermal initiation with DTBHN is easily scalable as demonstrated by running the reaction on 10 mmol scale without the need to modify the reaction conditions. Finally, we have shown that DTBPO functions as a cheaper and otherwise entirely equivalent alternative, although stricter safety

precautions are necessary. We believe that the simplicity of this method will make it attractive for application of ATRA reactions in a broad of organic synthesis such as the synthesis of natural and biologically active products, preparation of novel material, and even construction of all kinds of molecular devices. In all these types of applications, purification is often a major problem for the delivery of high-quality material.

Experimental Section

Precautions: The preparation and manipulation of DTBHN^[42] and DTBPO^[88] must be conducted behind a blast shield. DTBHN has been reported to be insensitive to scratching and is considered as handleable.^[41] DTBPO is sensitive to scratching and shock.^[89] Ear defenders, face shield, and thick leather gloves should be mandatory, in addition to standard PPE, as well as restrictions in quantities. Once in solution peroxides are safer: during this work no explosions occurred. For more information on working with peroxides consult the appropriate literature.^[90]

See the SI for full experimental details. A representative procedure is given below.

Preparation of 3a. Under air atmosphere (no inert gas protection required), 1-undecene **1a** (0.21 mL, 1.0 mmol), ethyl 2-iodoacetate **2a** (0.24 mL, 2.0 mmol), and EtOAc (technical grade, 3.3 mL, 0.3 M) were loaded into a 10 mL, 1-neck, round bottom flask equipped with a cold finger. DTBHN (35 mg, 20 mol%) was added in one portion to the flask which was then plunged into a 90 °C pre-heated oil bath. The reaction was heated under reflux for 30 min. After concentration *in vacuo*, to the crude residue was purified by flash column chromatography to afford **3a** as a clear oil (306 mg, 0.831 mmol, 83%). $R_f = 0.45$ (8% EtOAc/heptanes). ¹H NMR (300 MHz, CDCl₃): δ 4.14 (q, $J = 7.1$ Hz, 2H), 2.74–2.33 (m, 2H), 2.19–2.00 (m, 2H), 1.98–1.79 (m, 1H), 1.71 (ddt, $J = 14.5, 10.2, 5.1$ Hz, 1H), 1.55–1.46 (m, 1H), 1.46–1.36 (m, 1H), 1.36–1.20 (m, 15H), 0.91–0.85 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 172.7 (C=O), 60.5 (CH₂), 40.8 (CH₂), 38.4 (CH), 35.5 (CH₂), 34.4 (CH₂), 31.9 (CH₂), 29.52 (CH₂), 29.48 (CH₂), 29.45 (CH₂), 29.3 (CH₂), 28.8 (CH₂), 22.7 (CH₂), 14.2 (CH₃), 14.1 (CH₃). IR (thin film): $\nu_{\max} = 1733$ (s) cm⁻¹. Only the characteristic carbonyl stretch of the acyclic ester is reported. HRMS (ESI): Calculated for C₁₅H₃₀O₂I [M+H]⁺: 369.1285. Found: 369.1284.

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