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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 14 Aug 2019

Light mediated dual phosphine/copper catalyzed atom transfer radical addition reaction

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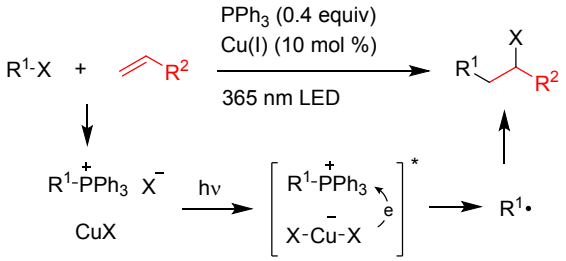


KEYWORDS Atom Transfer, Copper Catalysis, Photocatalysis, Radical Addition

ABSTRACT The atom transfer radical addition reaction catalyzed by triphenylphosphine and copper(I) halide is described. The reaction proceeds under irradiation with 365 nm light using a light emitting diode, and performed in a regular glassware. The proposed mechanism involves the formation of quaternary phosphonium salt, which undergoes single electron reduction by the copper(I) salt via photoinduced electron transfer. The method works well for terminal alkenes and activated organic halides such as esters of bromo- and iodoacetic acid and bromoacetonitrile. *gem*-Difluorinated styrenes, for which atom transfer reactions are rare, also proved to be good substrates for this phosphine/copper catalyzed protocol.

INTRODUCTION

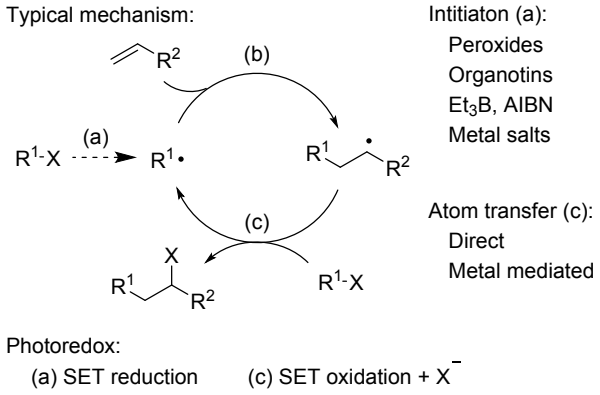
Since the original report in 1945,[1] the interaction of halocarbons with alkenes known as atom transfer radical addition (ATRA, Kharash reaction), has evolved into an attractive strategy for carbon-carbon bond formation.[2-4] Despite significant advances in this field associated with the use of transition metal catalysts, ATRA process has notable limitations, and, as a result, it still remains largely underemployed in synthetic applications.

In a typical ATRA mechanism, the radical chain process is operative (Scheme 1). The reaction efficiency depends on two major factors: the initiation event, when a free radical is generated (step a), and the atom transfer event (step c). Moreover, if the halide transfer is slow, the formation of oligomers by iterative radical addition to the alkene may dominate. Both steps (initiation and halide transfer) require cleavage of carbon-halogen bond, which may necessitate harsh conditions. Historically, ATRA reactions were conducted at elevated temperatures in the presence of radical initiators such as peroxides,[1] organotin reagents,[5] triethylborane,[6] or AIBN,[7] which trigger generation of free radicals by abstraction of halogen atom from a halocarbon substrate. Homolysis of the carbon-halogen bond by harsh UV light was also occasionally used to initiate the reaction.[8] Later, transition metal salts and complexes,[3] and, in particular, derivatives of copper,[4] were shown to be effective catalysts of ATRA reaction and related polymerization processes.[9] The metal can facilitate the generation of radicals, whereas formed metal-halide species can effect rapid transfer of the halide from metal to the carbon-centered radical.[10]

Another step forward was achieved due to the advent of photoredox catalysis,[11,12] in which the initiation event involves the single electron reduction of the substrate by the light activated catalyst. In this case, the reduction potential of the starting alkyl halide is an important factor. The atom transfer event can also proceed via different mechanism involving single electron oxidation of the radical to carbocation followed by trapping by halide anion. The latter mechanistic scenario is likely for ruthenium-based photocatalysts.[13,14] Recently, photoactive copper(I) complexes bearing diaryl-

substituted phenanthrolines as ligands have emerged as catalysts for visible light photoredox chemistry, and, in particular, for promoting ATRA reactions.[15,16]

Scheme 1. ATRA process.

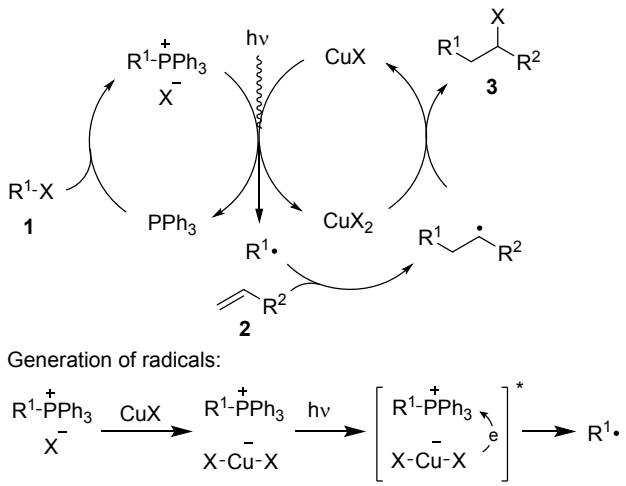


Herein we report a novel mechanistic pathway for performing light-mediated ATRA processes. Our approach is based on combined use of triphenylphosphine and copper(I) halide as catalysts (Scheme 2). The role of phosphine is to convert alkyl halide into phosphonium salt, which would serve as a source of free radicals. Thus, the phosphonium salt could interact with Cu(I) to generate ion pair consisting from phosphonium cation and cuprate anion (Scheme 2, bottom equation). Then, light mediated electron transfer leads to the generation of the radical with concomitant formation of copper(II) halide and regeneration of the phosphine. Such type of radical generation from fluorinated phosphonium salts has recently been proposed.[17] After radical addition to the double bond, copper(II) halide would rapidly convert the radical into product **3**. Back in 1983, there was a report on ATRA reaction using copper halide and stoichiometric amount of tri(*n*-butyl)phosphine by irradiation with 254 nm UV light.[18] However, based on mechanistic experiments, it was proposed that the reaction proceeds via two-electron pathway involving copper(III) intermediates and oxidative addition/reductive elimination sequence.[18]

The ability of phosphonium salts to undergo fission of the C-P bond has previously been described. In the absence of photocatalyst, this process requires harsh UV light (< 300 nm) as evidenced by photolysis of benzyl and benzhydryl phosphonium salts.[19] For reactions with visible light, a photocatalyst is needed. In particular, phosphonium salts bearing adjacent fluorine atoms[20] or a carbonyl group,[21] were activated using typical iridium photocatalysts.[22] It should be pointed out

that in these reactions, phosphonium salts were employed as stoichiometric reagents thereby wasting one equivalent of the phosphine, whereas in our approach, the phosphine may be used as catalyst. Examples of using phosphines and phosphates as catalysts or mediators have been reported, with P-centered radicals being proposed as reactive intermediates.[23]

Scheme 2. Dual phosphine/copper catalyzed reaction.



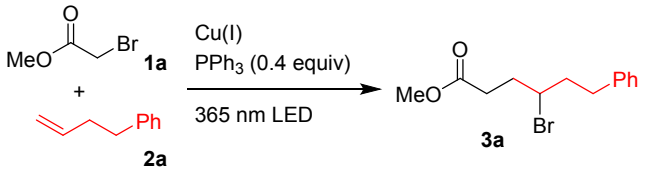
For successful realization of the process catalytic in phosphine, several criteria should be satisfied. First, the phosphine must interact with substrate **1** much faster than with product **3**. This, in fact, is easy to achieve, since formation of phosphonium salts is sensitive to steric effects, and required differentiation is realized when the substrate is a primary halide, while the product is a secondary halide. The second issue is that the intermediate phosphonium salt should be prone to undergo single electron reduction. Correspondingly, alkyl halides bearing adjacent electronwithdrawing groups should be considered.

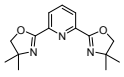
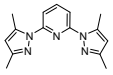
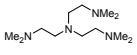
RESULTS AND DISCUSSION

For optimization studies, the interaction between methyl bromoacetate (**1a**) and 4-phenylbut-1-ene (**2a**) was evaluated (Table 1). The reaction was performed in dichloromethane by irradiation using 365 nm light emitting diode, and the temperature was maintained around 20 °C. In the presence of 0.4 equiv of triphenylphosphine and 10 mol % of copper(I) bromide, the expected product **3a** was formed in 53% yield after 15 hours (entry 2). Addition of ligands led to notable improvement, with the highest efficiency achieved with a copper salt complexed with 1,3-bis(2,4,6-

trimethylphenyl)imidazolium carbene, IMes (entry 6). With the latter catalyst the reaction time can be reduced to 3.5 hours. Decrease of amount of the copper catalyst and phosphine, as well as use of tributylphosphine instead of triphenylphosphine, led to decreased yields (entries 7, 8, 10, 11). Effect of solvent was briefly evaluated. Ethereal solvents were less efficient, apparently, because of their ability to serve as sources of hydrogen atom, which is transferred onto intermediate radical species. Dichloromethane (DCM) was the optimal from the point of view of solubility of reagents and catalysts. However, in this solvent, products bearing chloride instead of bromide were occasionally observed in minor amounts. In this cases, acetonitrile (ACN) can be successfully used as solvent. Application of light with longer wavelengths (400 or 465 nm) gave decreased yields, while in the dark, there was no product at all (entries 12-14).

Table 1. Optimization studies.



#	Solv.[a]	Time, h	Cat.	Y., %[b]
1	DCM	15	CuBr (10%)	53
2	DCM	15	CuBr (10%),  (11%)	25
3	DCM	15	CuBr (10%),  (11%)	65
4	DCM	15	CuBr (10%),  (11%)	97 (90)[c]
5	DCM	15	CuBr (10%),  (11%)	69
6	DCM	3.5	 (IMes·CuBr) (10%)	96 (89)[c]
7[d]	DCM	3.5	IMes·CuBr (10%)	22
8[e]	DCM	3.5	IMes·CuBr (10%)	6
9	ACN	3.5	IMes·CuBr (10%)	quant. (91)[c]
10[f]	ACN	3.5	IMes·CuBr (10%)	55
11	ACN	3.5	IMes·CuBr (5%)	76
12[g]	ACN	3.5	IMes·CuBr (10%)	24
13[h]	ACN	3.5	IMes·CuBr (10%)	10
14[i]	ACN	3.5	IMes·CuBr (10%)	-
15	ACN	15	-	2

[a] DCM, dichloromethane; ACN, acetonitrile

[b] Determined by GC analysis.

[c] Isolated yield.

[d] Bu_3P instead of PPh_3.

[e] No PPh_3.

[f] 0.2 equiv of PPh_3.

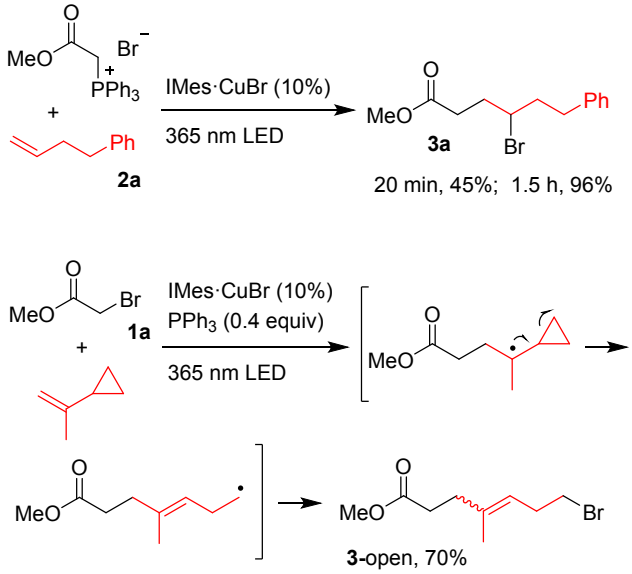
[g] 400 nm LED.

[h] 465 nm LED.

[i] In the dark.

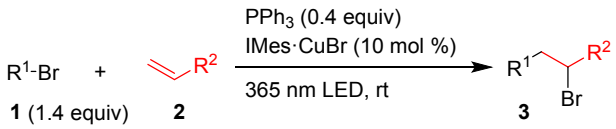
To confirm intermediacy of phosphonium salt in the reaction, the salt prepared from **1a** and triphenylphosphine was combined with 4-phenylbut-1-ene **2a** in acetonitrile under standard conditions (Scheme 3, upper equation). Thus, a quite fast reaction was observed, with the meaningful yields of product **3a** achieved even in 20 minutes. To support the radical character of the process, a radical clock experiment was carried out using isopropenylcyclopropane as alkene counterpart, and only ring-opened product (**3**-open) was formed (Scheme 3, bottom equation). Though this experiment favors radical mechanism, the light absorbing species remains unclear. Indeed, the intermediate phosphonium salt, the copper catalyst, the phosphine, as well as their mixtures, do not absorb light at wavelengths greater than 320 nm (see Supporting Information for the absorption spectra). This phenomenon is similar to that observed in our previous work.[17]

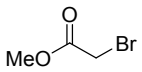
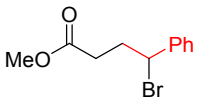
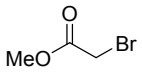
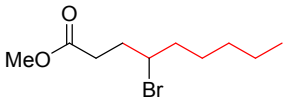
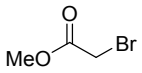
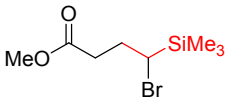
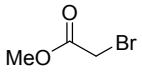
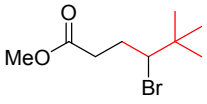
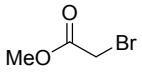
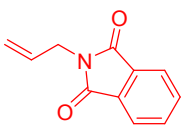
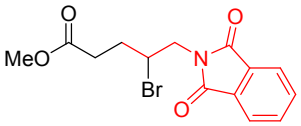
Scheme 3. Mechanistic experiments.

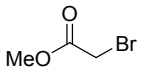
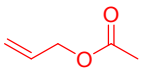
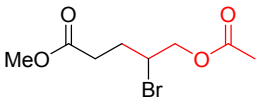
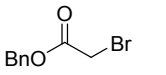
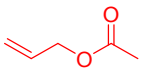
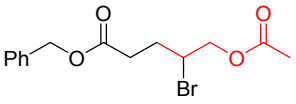
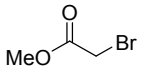
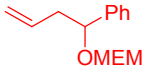
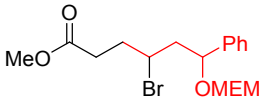
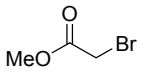
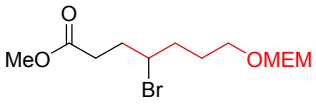
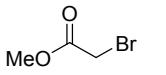
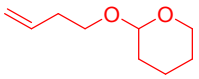
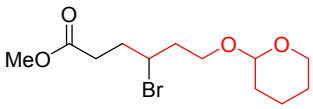
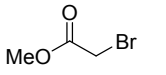
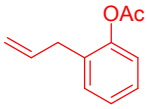
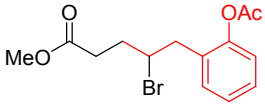
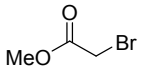
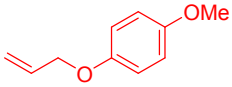
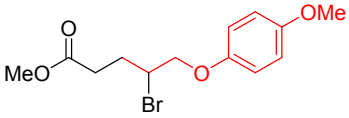
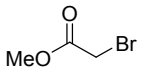
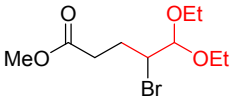
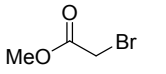
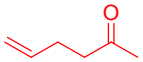
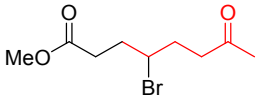
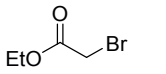
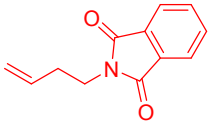
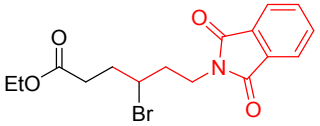
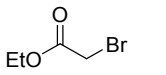
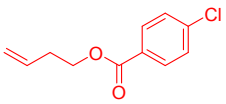
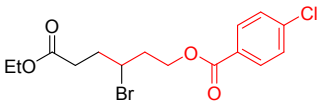
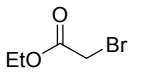
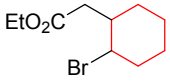
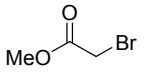
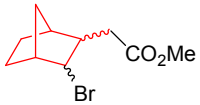
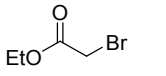


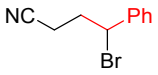
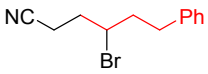
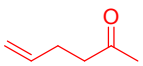
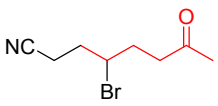
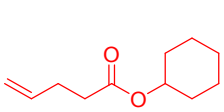
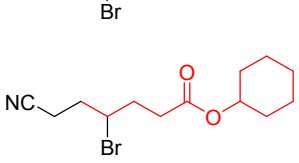
Under the optimized conditions, a series of alkenes **2** were subjected to the atom transfer reaction with bromoacetic esters (Table 2, entries 1-19). These reactions were performed on 2 mmol scale of the alkene. Though for some alkenes the process was complete within few hours, in many cases longer time was needed. The reaction between bromoacetates and terminal alkenes proceeded cleanly and with high yields. Unactivated alkyl-substituted linear and branched alkenes proved to be excellent substrates for this atom transfer reaction. Allylic and homoallylic ethers and esters were successfully employed. While cyclohexene was poorly effective, a more reactive alkene, norbornene, gave addition product in good yield (entries 17 and 18). Bromoacetonitrile was also successfully used, though for good conversion, slightly increased amount of bromide (1.6 equiv) was employed (entries 20-23).

Table 2. Reactions of alkenes.



#	Solv.	Time, h	Bromide	Alkene	Product		Yield, %[a]
1	ACN	2				**3b**	81
2	ACN	6				**3c**	85 (94[b])
3	ACN	3.5				**3d**	79 (90[b])
4	ACN	6				**3e**	87
5	ACN	15				**3f**	81

6	DCM	15				**3g**	84
7	DCM	15				**3h**	88
8	DCM	15				**3i**[c]	72
9[d]	ACN	15				**3j**	71
10[e]	ACN	15				**3k**[c]	77
11	DCM	15				**3l**	72
12[f]	DCM	20				**3m**	83
13[e]	DCM	20				**3n**	61
14	DCM	5				**3o**	87
15	ACN	15				**3p**	67
16	DCM	15				**3q**	80
17	DCM	15				**3r**[g]	35
18[h]	ACN	6				**3s**[g]	87
19[e]	DCM	15				**3t**	59

20[f]	DCM	30				**3u**	49
21[f]	DCM	15				**3v**	97
22[f,i]	DCM	15				**3w**	61
23[e]	DCM	30				**3x**	72

[a] Isolated yield

[b] Yield determined by NMR with dibromomethane as internal standard.

[c] Mixture of isomers, ratio 1:1.

[d] As catalyst, a combination of CuBr (10%) and bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (11%) was used.

[e] PPh_3 (1 equiv), R^1-Br (2.25 equiv), IMes·CuBr (15%).

[f] 1.6 equiv of R^1-Br was used.

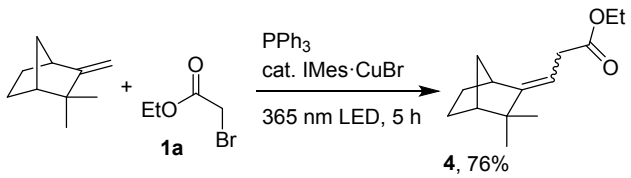
[g] Mixture of isomers, ratio 1.5:1.

[h] As catalyst, a combination of CuBr (15%) and bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (16%)

[i] As catalyst, a combination of CuBr (10%) and bis(3,5-diphenyl-1*H*-pyrazol-1-yl)methane (11%) was used.

Of special note is that in reaction of styrene we were able to isolate benzylic bromide **3b** in relatively good yield (entry 1). Indeed, benzylic halides are prone to elimination under the conditions of atom transfer, and, typically, even slightly basic medium can cause dehydrohalogenation with the formation of alkene.[24,25] This was the case with 2,2-dimethyl-3-methylenenorbornene, which afforded alkene **4** (Scheme 4).

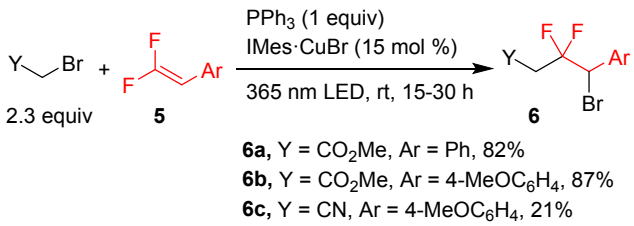
Scheme 4. Formation of alkene product.



However, the method is inapplicable to the coupling of unactivated alkyl bromide with Michael acceptors, as shown for attempted reaction of ethyl bromide with *tert*-butyl acrylate, in which the desired product was not detected. Similarly, the interaction of benzyl bromide with either *tert*-butyl acrylate or 4-phenylbut-1-ene **2a** did not furnish expected ATRA products.

Addition of carbon-centered radicals to 1,1-difluorinated alkenes is a rare process. Indeed, two fluorine atoms exert notable deactivating effect on the radical addition. While atom transfer reactions of perfluorinated alkenes with polyhalogenated hydrocarbons have been reported,[26,27] the use of 1,1-difluoroalkenes is rare.[28,29] At the same time, these alkenes can be readily prepared from carbonyl compounds by a Wittig-type process.[30] When 1,1-difluoroalkenes were subjected to our standard conditions, conversions did not exceed 70%. Higher loading of the reagents and longer times were needed to obtain good yields in reactions with ethyl bromoacetate. However, the reaction with bromoacetonitrile gave the product in moderate yield (Scheme 5).

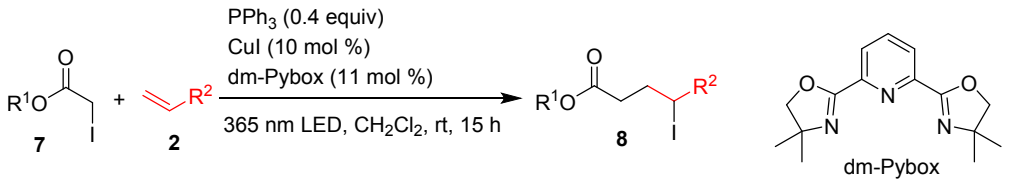
Scheme 5. Reactions of 1,1-difluoroalkenes.

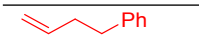
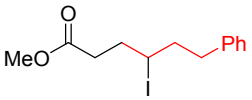
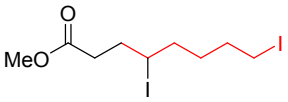
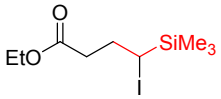
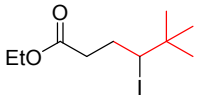


6a, Y = CO_2Me, Ar = Ph, 82%
6b, Y = CO_2Me, Ar = 4-$MeOC_6H_4$, 87%
6c, Y = CN, Ar = 4-$MeOC_6H_4$, 21%

It was also interesting to evaluate iodides in the ATRA process. Owing to higher reactivity of the C-I bond compared to the C-Br bond, the iodide products are expected to be prone to dehydrohalogenation. On the other hand, higher reactivity of iodides makes them more attractive for further transformations. In the literature, a complex between CuI and IMes ligand has not been described. Our attempts to prepare it were unsuccessful, leading to species bearing two NHC ligands at copper,[31] which were inactive in the ATRA reaction. Screening of ligands allowed to identify dm-Pybox [2,6-bis(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)pyridine], which was successfully used to promote addition of iodoacetates to alkenes (Table 3). The expected products **8** were obtained in good yields, though for *tert*-butylethylene, increased amounts of the phosphine and copper iodide were required.

Table 3. Reactions iodoacetates.



Alekene	Product		Yield, %[a]
		**8a**	73
		**8b**	83
		**8c**	87
		**8d**	72[b]

[a] Isolated yield

[b] Ethyl iodoacetate (1.6 equiv), PPh_3 (1.0 equiv), CuI (15 mol %), dm-Pybox (16 mol %).

In summary, a method for performing light mediated ATRA reaction catalyzed by the phosphine and copper(I) salt is described. The formation of quaternary phosphonium salts, which are able to undergo single electron reduction from copper(I), is believed to be the key feature of the process. The reaction is applicable for a wide variety of alkenes leading to alkyl bromides and iodides in good yields.

EXPERIMENTAL SECTION

General methods. All reactions were performed under an argon atmosphere. Acetonitrile was distilled from CaH_2 and stored over MS 4Å. DMF was distilled under vacuum from P_2O_5 and stored over MS 4Å. Dichloromethane (DCM) was distilled from CaH_2 prior to use. Column chromatography was carried out employing silica gel (230−400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq.

$KMnO_4$ solution. NMR spectra were recorded in $CDCl_3$ (distilled from CaH_2) using a Bruker AV-300 instrument. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer (Bruker MicrOTOF II). For preparative HPLC, reversed phase column (C18-kromasil, 5 μm, 21.2×250 mm) and UV-HPLC grade acetonitrile/water as a mobile phase were used. All photochemical reactions were performed in regular borosilicate glassware. As a light source, 100W LED chip (BLD-HP100UV2-E45 operated at 32 V, 2.2 A) was used, the distance from light source to the reaction vessel was 5 mm. For the reaction set-up, see Supporting Information. 1,3-Bis(2,4,6-trimethylphenyl)imidazolium carbene-copper (I) bromide complex (IMes·CuBr),[32] 2,6-bis(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)pyridine (dm-Pybox),[33] (2,2-difluorovinyl)benzene (**5a**),[34] 1-(2,2-difluorovinyl)-4-methoxybenzene (**5b**),[30] isopropenylcyclopropane.[35]

{1-[(2-Methoxyethoxy)methoxy]but-3-en-1-yl}benzene (2i).[36] MEMCl (934 mg, 7.5 mmol, 1.5 equiv) was added portionwise to a solution of 1-phenyl-3-buten-1-ol (741 mg, 5 mmol, 1 equiv) and EtN(*i*-Pr)$_2$ (840 mg, 6.5 mmol, 1.3 equiv) in dichloromethane (8 mL). The reaction was stirred at room temperature for 2.5 h, then quenched with water (5 mL) and extracted with hexane (4×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by flash chromatography. R_f 0.19 (hexane/EtOAc, 10/1). Yield 1.02 g (87%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.22 (m, 5H), 5.78 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.15–4.97 (m, 2H), 4.73–4.56 (m, 3H), 3.89–3.74 (m, 1H), 3.62–3.42 (m, 3H), 3.37 (s, 3H), 2.60 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.53–2.38 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 42.4, 59.1, 67.1, 71.9, 78.0, 93.4, 117.3, 127.1, 127.8, 128.4, 134.9, 141.7.

5-[(2-Methoxyethoxy)methoxy]pent-1-ene (2j).[37] MEMCl (934 mg, 7.5 mmol, 1.5 equiv) was added portionwise to a solution of 4-penten-1-ol (430 mg, 5 mmol, 1 equiv) and EtN(*i*-Pr)$_2$ (840 mg, 6.5 mmol, 1.3 equiv) in dichloromethane (5 mL), The reaction was stirred at room temperature for 2.5 h, then quenched with water (5 mL) and extracted with hexane (4×5 mL). The combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum. The residue was

purified distillation using the Hickman distillation head (40 mbar, bath temperature 110-125 °C). Yield: 644 mg (74%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.99–4.82 (m, 2H), 4.63 (s, 2H), 3.61 (dd, *J* = 5.7, 3.6 Hz, 2H), 3.52–3.42 (m, 4H), 3.31 (s, 3H), 2.13–1.98 (m, 2H), 1.68–1.52 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 28.9, 30.3, 58.9, 66.6, 67.1, 71.8, 95.4, 114.7, 138.0.

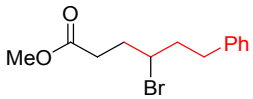
General procedure 1 (synthesis of compounds **3a-j**,**l**,**m**,**o-s**,**u-w**, **4**). A 25 ml vial equipped with a magnetic stirrer and a screw cap with septum was charged with triphenylphosphine (210 mg, 0.8 mmol, 0.4 equiv), and a copper (I) catalyst [for **3a-i,l,m,o-r,u,v**, **4,** IMes·CuBr (44 mg, 0.2 mmol, 0.1 equiv); for **3j**, CuBr (29 mg, 0.2 mmol, 0.1 equiv) and bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (45 mg, 0.22 mmol, 0.11 equiv); for **3s**, CuBr (43 mg, 0.3 mmol, 0.15 equiv) and bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (66 mg, 0.32 mmol, 0.16 equiv); for **3w**, CuBr (29 mg, 0.2 mmol, 0.1 equiv) and bis(3,5-diphenyl-1H-pyrazol-1-yl)methane (100 mg, 0.44 mmol, 0.11 equiv).] The vial was evacuated and filled with argon, and 2.5 mL of a solvent (for **3a-f,j,p,s**, acetonitrile; for **3g-i**,**l**,**m**,**o**,**r**,**t-w**, **4**, dichloromethane) was added by gastight syringe. The reaction mixture was cooled to –20 °C, and with stirring evacuated at about 12 Torr for 2 min followed by filling the vial with argon. Organic bromide **1** (for bromoacetates, RO_2CCH_2Br, 2.8 mmol, 1.4 equiv and 3.2 mmol, 1.6 equiv for **3m**; for bromoacetonitrile, $NCCH_2Br$, 3.2 mmol, 1.6 equiv) and alkene **2** (2 mmol, 1 equiv) were successively added by gastight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with transparent bottom (Figure S2, (d)), and was irradiated with 365 nm LED until full conversion of the starting alkene (verified by GC analysis of aliquots), while maintaining the reaction temperature around 20 °C (reaction time is given in Table 2). **For the workup**, water (8 mL) was added, and the mixture was extracted with pentane (4×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel.

General procedure 2 (synthesis of compounds **3k,n,t,x,6a-c**). A 25 ml vial equipped with a magnetic stirrer and a screw cap with septum was charged with triphenylphosphine (525 mg, 2

mmol, 1 equiv) and IMes·CuBr (for **3k,n,t,x,6a,b**, 66 mg, 0.3 mmol, 0.15 equiv; for **6c**, 44 mg, 0.2 mmol, 0.2 equiv). The vial was evacuated and filled with argon, and 2.5 mL of dichloromethane (or acetonitrile for **3k**) was added by gastight syringe. The reaction mixture was cooled to –20 °C, and evacuated at about 12 Torr for 2 min followed by filling the vial with argon. Organic bromide **1** (for **3k,n,t,x, 6a,b**, 4.5 mmol, 2.25 equiv; for **6c**, 3.6 mmol, 1.8 equiv) and alkene **2** (2 mmol, 1 equiv) were successively added by gastight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with transparent bottom (Figure S2, (d)), and was irradiated with 365 nm LED until full conversion of the starting alkene (verified by GC analysis of aliquots), while maintaining the reaction temperature around 20 °C (for **3k,n,t,x** reaction time is given in Table 2; for **6a,c**, reaction time 30 h; for **6b**, reaction time 15 h). The workup is the same as in **General procedure 1**.

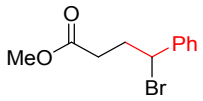
General procedure 3 (synthesis of compounds **8a-d).** A 25 ml vial equipped with a magnetic stirrer and a screw cap with septum was charged with triphenylphosphine (PPh_3, 210 mg, 0.8 mmol, 0.4 equiv), CuI (38 mg, 0.2 mmol, 0.1 equiv), and dm-Pybox (60 mg, 0.44 mmol, 0.11 equiv). The vial was evacuated and filled with argon, and dichloromethane (2.5 mL) was added by gastight syringe. The reaction mixture was cooled to –20 °C, and evacuated at about 12 Torr for 2 min followed by filling the vial with argon. Iodoacetate **7** (2.8 mmol, 1.4 equiv) and alkene **2** (2 mmol, 1 equiv) were successively added to reaction mixture by gastight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with transparent bottom (Figure S2, (d)), and was irradiated with 365 nm LED until full conversion of the starting alkene, while maintaining the reaction temperature around 20 °C. The conversion was monitored by capillary GC of aliquots, and the reaction was complete within 15 hours, unless stated otherwise. The workup is the same as in **General procedure 1**.

Methyl 4-bromo-6-phenylhexanoate (3a).



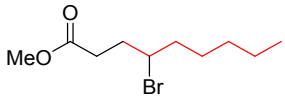
Following **General procedure 1**, the reaction was carried out in acetonitrile, and irradiated for 3.5 hours. Yield 517 mg (91%). Colorless oil. R_f 0.34 (hexane/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56–7.04 (m, 5H), 4.00 (dtd, *J* = 13.1, 8.7, 4.2 Hz, 1H), 3.67 (s, 3H), 2.91 (ddd, *J* = 14.1, 8.6, 5.7 Hz, 1H), 2.84–2.70 (m, 1H), 2.69–2.43 (m, 2H), 2.31–1.99 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 32.2, 33.8, 34.2, 40.9, 51.8, 56.2, 126.3, 128.6, 140.9, 173.3. HRMS (ESI): calcd $C_{13}H_{17}{}^{79}BrNaO_2$ (M + Na) 307.0304, found 307.0288; calcd $C_{13}H_{17}{}^{81}BrNaO_2$ (M + Na) 309.0284, found 309.0269.

Methyl 4-bromo-4-phenylbutanoate (3b).



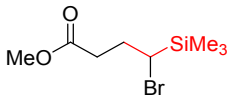
Following the **General procedure 1,** the reaction was carried out in acetonitrile, and irradiated for 2 hours. Yield 415 mg (81%). Colorless oil. R_f 0.18 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.49–7.15 (m, 5H), 5.20–4.91 (m, 1H), 3.66 (s, 3H), 2.71–2.31 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 32.4, 34.9, 51.6, 54.2, 127.1, 128.4, 128.6, 141.3, 172.5. HRMS (ESI): calcd $C_{11}H_{13}{}^{79}BrNaO_2$ (M + Na) 278.9991, found 278.9990; calcd $C_{11}H_{13}{}^{81}BrNaO_2$ (M + Na) 280.9971, found 280.9967.

Methyl 4-bromononanoate (3c).



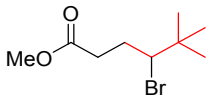
Following the **General procedure 1,** the reaction was carried out in acetonitrile, and irradiated for 6 hours. Yield 426 mg (85%). Colorless oil. R_f 0.32 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.04 (tt, *J* = 8.9, 5.2 Hz, 1H), 3.67 (s, 3H), 2.71–2.40 (m, 2H), 2.31–2.10 (m, 1H), 2.10–1.93 (m, 1H), 1.93–1.69 (m, 2H), 1.69–1.15 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 14.1, 22.6, 27.3, 31.3, 32.3, 34.1, 39.4, 51.8, 57.3, 173.4. HRMS (ESI): calcd for $C_{10}H_{19}{}^{79}BrNaO_2$ (M + Na) 273.0461, found 273.0455; calcd for $C_{10}H_{19}{}^{81}BrNaO_2$ (M + Na) 275.0440, found 275.0432.

Methyl 4-bromo-4-(trimethylsilyl)butanoate (3d).



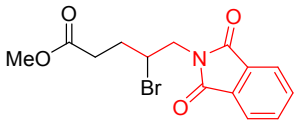
Following the **General procedure 1,** the reaction was carried out in acetonitrile, and irradiated for 3.5 hours. Yield 399 mg (79%). Colorless oil. R_f 0.35 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.67 (s, 3H), 3.23 (dd, *J* = 12.3, 2.3 Hz, 1H), 2.70 (ddd, *J* = 16.3, 8.2, 4.9 Hz, 1H), 2.60–2.38 (m, 1H), 2.19 (dt,*J* = 17.7, 7.8 Hz, 1H), 2.04–1.78 (m, 1H), 0.13 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: -3.0, 28.7, 33.8, 44.0, 51.7, 173.6. HRMS (ESI): calcd for $C_8H_{17}{}^{79}BrNaO_2Si$ (M + Na) 275.0073, found 275.0081 ; calcd for $C_8H_{17}{}^{81}BrNaO_2Si$ (M + Na) 277.0053, found 277.0055.

Methyl 4-bromo-5,5-dimethylhexanoate (3e).



Following the **General procedure 1,** the reaction was carried out in acetonitrile, and irradiated for 6 hours. Yield 410 mg (87%). Colorless oil. R_f 0.33 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.82 (dd, *J* = 11.7, 1.8 Hz, 1H), 3.62 (s, 3H), 2.64 (ddd, *J* = 16.7, 8.1, 5.1 Hz, 1H), 2.51–2.36 (m, 1H), 2.22 (dtd, *J* = 9.5, 8.0, 1.8 Hz, 1H), 1.85 (dddd, *J* = 14.7, 11.7, 8.0, 5.1 Hz, 1H), 1.02 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 27.5, 29.4, 33.3, 36.1, 51.6, 70.8, 173.4. HRMS (ESI): calcd for $C_9H_{18}{}^{79}BrO_2$ (M + H) 237.0485, found 237.0491; calcd for $C_9H_{18}{}^{81}BrO_2$ (M + H) 239.0465, found 239.0472.

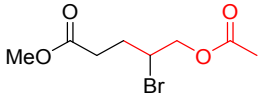
Methyl 4-bromo-5-(1,3-dioxoisoindolin-2-yl)pentanoate (3f).



Following the **General procedure 1,** the reaction was carried out in acetonitrile, and irradiated for 15 hours. Yield 549 mg (81%). White crystals. Mp 97-99 °C. R_f 0.12 (hexane/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.80 (s, 2H), 7.69 (s, 2H), 4.52–4.20 (m, 1H), 4.06 (dd, *J* = 13.8, 7.9 Hz, 1H), 3.90 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.60 (s, 3H), 2.69–2.54 (m, 1H), 2.47 (dt, *J* = 16.2, 7.4 Hz, 1H), 2.32–2.09 (m, 1H), 2.09–1.75 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 20.6, 30.2,

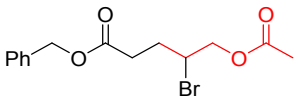
31.5, 50.1, 51.6, 67.3, 170.1, 172.7. HRMS (ESI): calcd for $C_{14}H_{14}{}^{79}BrNNaO_4$ (M + Na) 361.9998, found 361.9991; calcd for $C_{14}H_{14}{}^{81}BrNNaO_4$ (M + Na) 363.9979, found 363.9969.

Methyl 5-acetoxy-4-bromopentanoate (3g).



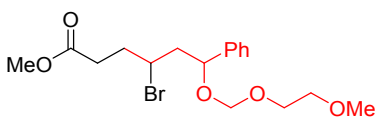
Following the **General procedure 1,** the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 424 mg (84%). R_f 0.25 (hexane/EtOAc, 6/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.38–4.00 (m, 3H), 3.59 (s, *J* = 15.7 Hz, 3H), 2.63–2.32 (m, 2H), 2.18 (dtd, *J* = 15.1, 8.1, 7.6, 3.4 Hz, 1H), 2.00 (s, 3H), 2.10–1.82 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 20.6, 30.2,31.5, 50.1, 51.6, 67.3, 170.1, 172.7. HRMS (ESI): calcd for $C_8H_{14}{}^{79}BrO_4$ (M + H) 253.0070, found 253.0060; calcd for $C_8H_{14}{}^{81}BrO_4$ (M + H) 255.0050, found 255.0038.

Benzyl 5-acetoxy-4-bromopentanoate (3h).



Following the **General procedure 1**, the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 578 mg (88%). Colorless oil. R_f 0.12 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.45–7.28 (m, 5H), 5.14 (s, 2H), 4.42–4.22 (m, 2H), 4.22–4.11 (m, 1H), 2.78–2.45 (m, 2H), 2.30 (dddd, *J* = 15.3, 8.3, 7.2, 3.5 Hz, 1H), 2.14–1.95 (m, 1H), 2.09 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 20.84, 30.36, 31.97, 50.12, 66.65, 67.59, 128.37, 128.46, 128.73, 135.84, 170.44, 172.34. HRMS (ESI): calcd for $C_{14}H_{17}{}^{79}BrNaO_4$ (M + Na) 351.0202, found 351.0210; calcd for $C_{14}H_{17}{}^{81}BrNaO_4$ (M + Na) 353.0183, found 353.0188.

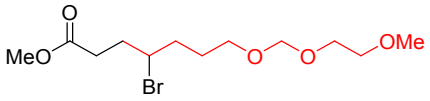
Methyl 4-bromo-6-[(2-methoxyethoxy)methoxy]-6-phenylhexanoate (3i).



Following the **General procedure 1,** the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 560 mg (72%). Colorless oil. Mixture of diastereoisomers, ratio 1:1. R_f 0.23 (hexane/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41–7.11 (m, 5H), 4.92 (dd, *J* =

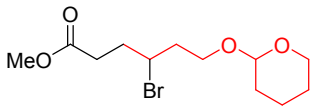
10.2, 2.6 Hz) and 4.84 (t, J = 7.0 Hz) (1H), 4.68–4.48 (m, 2H), 4.43–4.30 (m) and 3.86–3.66 (m) (1H), 3.86–3.66 (m, 1H), 3.63 (s) and 3.58 (s) (3H), 3.55–3.35 (m, 3H), 3.31 (s) and 3.31 (s) (3H), 2.68–2.30 (m) and 2.25–1.90 (m) (6H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ: 32.0, 33.7, 34.4, 46.7, 47.9, 51.6, 51.6, 52.2, 53.4, 58.9, 67.1, 67.2, 71.7, 71.7, 75.9, 76.4, 93.1, 93.3, 126.7, 127.1, 127.8, 128.1, 128.5, 128.5, 140.3, 141.4, 172.9, 173.0. HRMS (ESI): calcd for $C_{17}H_{25}{}^{79}BrNaO_5$ (M + Na) 411.0778, found 411.0772; calcd for $C_{17}H_{25}{}^{81}BrNaO_5$ (M + Na) 413.0758, found 413.0752.

Methyl 4-bromo-7-[(2-methoxyethoxy)methoxy]heptanoate (3j).



Following the **General procedure 1,** reaction was carried out in acetonitrile with 10 mol. % CuBr (29 mg, 0.2 mmol, 0.1 equiv) and 11 mol. % bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (45 mg, 0.22mmol, 0.11 equiv) and irradiated for 15 hours. Yield 463 mg (71%). Colorless oil. R_f 0.35 (hexane/EtOAc, 3/1). Further purification was performed via preparative HPLC (flow rate 12 $mL \cdot min^{-1}$, mobile phase: isocratic, 10% water in acetonitrile, retention time 9.1 min). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.65 (s, 2H), 4.03 (dddd, J = 8.9, 8.1, 4.7, 3.7 Hz, 1H), 3.69–3.58 (m, 5H), 3.57–3.46 (m, 4H), 3.34 (s, 3H), 2.64–2.38 (m, 2H), 2.30–1.57 (m, 6H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ: 27.8, 32.1, 34.1, 36.0, 51.7, 56.7, 59.0, 66.8, 66.9, 71.8, 95.5, 173.2. HRMS (ESI): calcd for $C_{12}H_{23}{}^{79}BrNaO_5$ (M + Na) 349.0621, found 349.0625; calcd for $C_{12}H_{23}{}^{81}BrNaO_5$ (M + Na) 351.0601, found 351.0606.

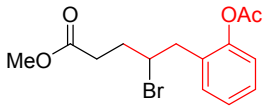
Methyl 4-bromo-6-[(tetrahydro-2H-pyran-2-yl)oxy]hexanoate (3k).



Following the **General procedure 2**, the reaction was carried out in acetonitrile, and irradiated for 15 hours. Yield 475 mg (77%). Colorless oil. Mixture of diastereoisomers, ratio 1:1. R_f 0.32 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.58–4.40 (m, 1H), 4.23–4.04 (m, 1H), 3.90–3.66 (m, 2H), 3.57 (s, 3H), 3.52–3.34 (m, 2H), 2.58–2.33 (m, 2H), 2.22–1.84 (m, 4H), 1.77–1.31 (m, 6H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ: 19.2, 19.5, 25.3, 30.5, 30.5, 32.0, 32.0, 34.0,

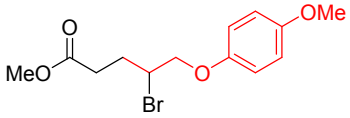
34.1, 39.0, 39.1, 51.5, 53.3, 53.5, 61.8, 62.3, 64.7, 65.1, 98.2, 99.3, 172.9. HRMS (ESI): calcd for $C_{12}H_{21}{}^{79}BrNaO_4$ (M + Na) 331.0515, found 331.0527; calcd for $C_{12}H_{21}{}^{81}BrNaO_4$ (M + Na) 333.0495, found 333.0508.

Methyl 5-(2-acetoxyphenyl)-4-bromopentanoate (3l).



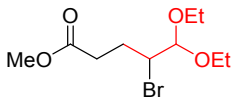
Following the **General procedure 1**, the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 473 mg (72%). Colorless oil. R_f 0.13 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.24 (m, 2H), 7.24–7.15 (m, 1H), 7.12–7.03 (m, 1H), 4.25 (ddt, *J* = 13.5, 7.2, 3.6 Hz, 2H), 3.66 (s, 3H), 3.24–3.02 (m, 2H), 2.63 (ddd, *J* = 16.7, 8.3, 5.6 Hz, 1H), 2.57–2.44 (m, 1H), 2.35 (s, 3H), 2.21 (tdd, *J* = 10.8, 7.8, 3.2 Hz, 1H), 2.10–1.89 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 21.1, 32.2, 33.5, 40.7, 51.8, 54.5, 122.7, 126.2, 128.4, 130.1, 131.4, 149.2, 169.3, 173.1. HRMS (ESI): calcd for $C_{14}H_{18}{}^{79}BrO_4$ (M + H) 329.0383, found 329.0384; calcd for $C_{14}H_{18}{}^{81}BrO_4$ (M + H) 331.0363, found 331.0366.

Methyl 4-bromo-5-(4-methoxyphenoxy)pentanoate (3m).



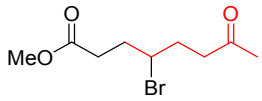
Following the **General procedure 1**, the reaction was carried out in dichloromethane using 1.6 equiv of methyl bromoacetate, and irradiated for 20 hours. Yield 518 mg (83%). Colorless oil. R_f 0.21 (hexane/EtOAc, 8/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.89–6.73 (m, 4H), 4.32–4.12 (m, 2H), 4.06 (dd, *J* = 10.0, 6.9 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 2.71–2.30 (m, 3H), 2.19–2.01 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 30.4, 31.6, 50.9, 51.6, 55.5, 72.5, 114.6, 115.8, 152.1, 154.3, 172.8. HRMS (ESI): calcd for $C_{13}H_{17}{}^{79}BrNaO_4$ (M + Na) 339.0202, found 339.0204; calcd for $C_{13}H_{17}{}^{81}BrNaO_4$ (M + Na) 341.0183, found 341.0185.

Methyl 4-bromo-5,5-diethoxypentanoate (3n).



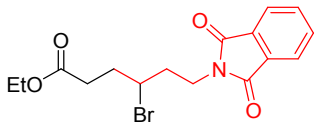
Following the **General procedure 2**, the reaction was carried out in dichloromethane using 1.6 equiv of methyl bromoacetate, and irradiated for 20 hours. Yield 344 mg (61%). Colorless oil. R_f 0.28 (hexane/EtOAc, 9/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.49 (d, J = 5.2 Hz, 1H), 3.99 (ddd, J = 10.0, 5.2, 3.2 Hz, 1H), 3.77–3.59 (m, 2H), 3.63 (s, 3H), 3.59–3.45 (m, 2H), 2.58 (ddd, J = 16.3, 8.6, 5.5 Hz, 1H),2.45 (dt, J = 16.3, 7.7 Hz, 1H), 2.31 (dddd, J = 15.5, 8.7, 7.1, 3.2 Hz, 1H), 2.06–1.88 (m, 1H), 1.18 (t, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 15.2, 28.1,31.9, 51.6, 54.4, 63.7, 63.4, 104.1, 173.2. HRMS (ESI): calcd for $C_{10}H_{19}{}^{79}BrNaO_4$ (M + Na) 305.0359, found 305.0351; calcd for $C_{10}H_{19}{}^{81}BrNaO_4$ (M + Na) 307.0339, found 307.0332.

Methyl 4-bromo-7-oxooctanoate (3o).



Following the **General procedure 1**, the reaction was carried out in dichloromethane and irradiated for 5 hours. Yield 443 mg (87%). Colorless oil. R_f 0.23 (hexane/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.03 (tt, J = 9.4, 3.8 Hz, 1H), 3.64 (s, 3H), 2.76–2.60 (m, 2H), 2.60–2.39 (m, 2H), 2.23–1.84 (m, 4H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 30.1, 32.1,32.7, 34.3, 41.4, 51.8, 56.3, 173.1, 207.3. HRMS (ESI): calcd for $C_9H_{15}{}^{79}BrNaO_3$ (M + Na) 273.0097, found 273.0094; calcd for $C_9H_{15}{}^{81}BrNaO_3$ (M + Na) 275.0077, found 275.0074.

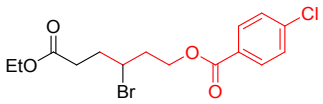
Ethyl 4-bromo-6-(1,3-dioxoisoindolin-2-yl)hexanoate (3p).



Following the **General procedure 1**, the reaction was carried out in acetonitrile, and irradiated for 15 hours. Yield 490 mg (67%). White crystals. Mp 45-46 °C. R_f 0.11 (hexane/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.80 (dd, J = 5.5, 3.1 Hz, 2H), 7.68 (dd, J = 5.5, 3.1 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 4.09–3.97 (m, 1H), 3.96–3.72 (m, 2H), 2.65–2.36 (m, 2H), 2.32–1.94 (m, 4H),

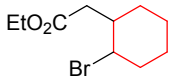
1.20 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 14.2, 32.2, 34.0, 36.4, 37.7, 52.8, 60.6, 123.3, 132.1, 134.1, 168.2, 172.5. HRMS (ESI): calcd for $C_{16}H_{18}{}^{79}BrNNaO_4$ (M + Na) 390.0311, found 390.0323; calcd for $C_{16}H_{18}{}^{81}BrNNaO_4$ (M + Na) 392.0291, found 392.0304.

3-Bromo-6-ethoxy-6-oxohexyl 4-chlorobenzoate (3q).



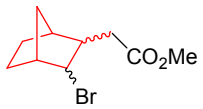
Following the **General procedure 1**, the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 605 mg (80%). Colorless oil. R_f 0.27 (hexane/EtOAc, 8/1). ^1H NMR (300 MHz, $CDCl_3$), δ: 7.91 (dm, J = 8.6 Hz, 2H), 7.35 (dm, J = 8.6 Hz, 2H),4.51 (dt, J = 11.3, 5.7 Hz, 1H), 4.42 (ddd, J = 11.3, 7.9, 5.7 Hz, 1H), 4.18 (ddd, J = 13.3, 9.2, 3.9 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.66–2.40 (m, 2H), 2.39–1.99 (m, 4H), 1.20 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 14.3, 32.3, 34.2, 38.1, 52.3, 60.7, 63.1, 128.5, 128.8, 131.1, 139.6, 165.5, 172.6. HRMS (ESI): calcd for $C_{15}H_{18}{}^{79}BrClKO_4$ (M + K) 414.9709, found 414.9699; $C_{15}H_{18}{}^{81}BrClKO_4$ (M + K) 416.9688, found 416.9674.

Ethyl 2-(2-bromocyclohexyl)acetate (3r).



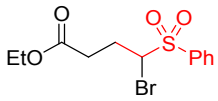
Following the **General procedure 1**, the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 174 mg (35%). Colorless oil. Mixture of diastereoisomers, ratio 3:2. (R_f 0.11 (hexane). ^1H NMR (300 MHz, $CDCl_3$), δ: 4.62 (dd, J = 3.1, 2.6 Hz, major) and 3.86 (td, J = 11.0, 4.1 Hz, minor) (1H), 4.12 (q, J = 7.1 Hz, 2H), 2.88 (dd, J = 15.0, 2.9 Hz minor), 2.51–2.03 (m, 3H), 2.02–1.80 (m, 2H), 1.79–1.63 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.59–1.01 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: Major: 14.4, 20.8, 25.3, 27.3, 35.0, 39.2, 40.4, 60.5, 61.0, 172.5; Minor: 14.4, 25.4, 27.5, 32.6, 38.7, 40.5, 43.4, 58.7, 60.4, 172.5. HRMS (ESI): calcd for $C_{10}H_{17}{}^{79}BrNaO_2$ (M + Na) 271.0304, found 271.0306; calcd for $C_{10}H_{17}{}^{81}BrNaO_2$ (M + Na) 273.0284, found 273.0287.

Methyl 2-(3-bromobicyclo[2.2.1]heptan-2-yl)acetate (3s).



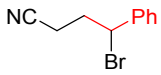
Following the **General procedure 1**, the reaction was carried out in acetonitrile with 15 mol % CuBr (43 mg, 0.3mmol, 0.15 equiv) and 16 mol % bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (66 mg, 0.32 mmol, 0.16 equiv), and irradiated for 6 hours. Yield 427 mg (87%). Colorless oil. Mixture of diastereoisomers, ratio 3:2. R_f 0.26 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.26 (dd, *J* = 7.2, 1.8 Hz, minor) and 3.86–3.77 (m, major) (1H), 3.67 (s, major) and 3.67 (s, minor) (3H), 2.70–2.47 (m, 1H), 2.47–2.15 (m, 2H), 2.30–2.16 (m, minor, 1H),2.07–1.89 (m, 2H), 1.83 (dt, *J* = 10.4, 1.7 Hz, minor, 1H), 1.73–1.11 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: Major: 23.6, 29.71, 34.8, 38.9, 40.5, 41.8, 44.6, 51.8, 59.0, 172.3. Minor: 27.4, 29.67, 33.6, 42.6, 43.8, 48.2, 50.1, 51.8, 61.4, 173.5. HRMS (ESI): calcd for $C_{10}H_{15}{}^{79}BrNaO_2$ (M + Na) 269.0148, found 269.0157; calcd for $C_{10}H_{15}{}^{81}BrNaO_2$ (M + Na) 271.0127, found 271.0136.

Ethyl 4-bromo-4-(phenylsulfonyl)butanoate (3t).



Following the **General procedure 2**, the reaction was carried out in dichloromethane, and irradiated for 15 hours. Yield 391 mg (59%). Colorless oil. R_f 0.28 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.94 (d, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 4.96 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.76–2.44 (m, 3H), 2.24–2.06 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 14.2, 27.1, 31.2, 60.9, 64.6, 129.2, 130.0,134.7, 135.2, 171.6. HRMS (ESI): calcd for $C_{12}H_{15}{}^{79}BrNaO_4S$ (M + Na) 356.9767, found 356.9770; calcd for $C_{12}H_{15}{}^{81}BrNaO_4S$ (M + Na) 358.9746, found 358.9745.

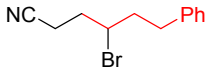
4-Bromo-4-phenylbutanenitrile (3u).



Following the **General procedure 1**, the reaction was carried out in dichloromethane using 1.6 equiv of bromoacetonitrile, and irradiated for 30 hours. Yield 220 mg (49%). Colorless oil. R_f 0.30

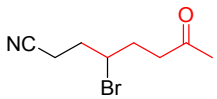
(hexane/EtOAc, 5/1). Further purification was performed via preparative HPLC (flow rate 12 mL·min^{-1}, mobile phase: isocratic, 25% water in acetonitrile, retention time 19.3 min.) ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.47–7.28 (m, 5H), 5.04 (m, 1H), 2.66–2.33 (m, 4H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ: 16.6, 35.5, 52.3, 118.4, 127.3, 129.2,140.3. HRMS (ESI): calcd for $C_{10}H_{10}{}^{79}BrNNa$ (M + Na) 245.9889, found 245.9889; calcd for $C_{10}H_{10}{}^{81}BrNNa$ (M + Na) 247.9869, found 247.9865.

4-Bromo-6-phenylhexanenitrile (3v).



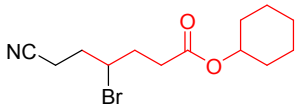
Following the **General procedure 1**, the reaction was carried out in dichloromethane using 1.6 equiv of bromoacetonitrile, and irradiated for 15 hours. Yield 487 mg (97%). Colorless oil. R_f 0.25 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41–7.31 (m, 2H), 7.30–7.20 (m, 3H), 4.05 (tt, J = 8.8, 4.2 Hz, 1H), 2.97 (ddd, J = 14.1, 8.7, 5.6 Hz, 1H), 2.89–2.74 (m, 1H), 2.72–2.48 (m, 2H), 2.34–2.02 (m, 4H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ:16.0, 33.6, 34.6, 40.5, 54.2, 118.7, 126.4, 128.5, 128.6, 140.3. HRMS (ESI): calcd for $C_{12}H_{14}{}^{79}BrNNa$ (M + Na) 274.0202, found 274.0209; calcd for $C_{12}H_{14}{}^{81}BrNNa$ (M + Na) 276.0182, found 276.0191..

4-Bromo-7-oxooctanenitrile (3w).



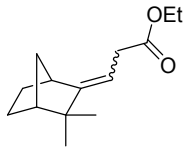
Following the **General procedure 1**, reaction was carried out in dichloromethane with 10 mol% CuBr (29 mg, 0.2 mmol, 0.1 equiv), 11 mol% bis(3,5-diphenyl-1H-pyrazol-1-yl)methane (99 mg, 0.22 mmol, 0.11 equiv), bromoacetonitrile (384 mg, 3.2 mmol, 1.6 equiv), and irradiated for 15 hours. Yield 266 mg (61%). Pale yellow oil. R_f 0.18 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.04 (tt, J = 9.7, 3.6 Hz, 1H), 2.77–2.62 (m, 2H), 2.62–2.48 (m, 2H), 2.23–1.86 (m, 4H) 2.13 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$), δ: 16.0, 30.1,32.3, 34.8, 41.2, 54.3, 118.6, 207.0. HRMS (ESI): calcd for $C_8H_{12}{}^{79}BrNNaO$ (M + Na) 239.9994, found 239.9999; calcd for $C_8H_{12}{}^{81}BrNNaO$ (M + Na) 241.9974, found 241.9978.

Cyclohexyl 4-bromo-6-cyanohexanoate (3x).



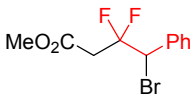
Following the **General procedure 2**, the reaction was carried out in dichloromethane and irradiated for 30 hours. After column chromatography (R_f 0.35, hexane/EtOAc, 3/1), further purification was performed by preparative HPLC (flow rate 12 mL·min^{-1}, mobile phase: isocratic, 10% water in acetonitrile, retention time 8.1 min). Yield 436 mg (72%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.70 (td, *J* = 8.6, 3.9 Hz, 1H), 4.06 (tt, *J* = 9.5, 3.6 Hz, 1H), 2.72–2.32 (m, 4H), 2.32–1.90 (m, 4H), 1.90–1.56 (m, 4H), 1.56–1.05 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 16.0, 23.6, 25.3, 31.5, 32.4, 33.8, 34.5, 53.8, 72.9, 118.5,171.6. HRMS (ESI): calcd for $C_{13}H_{21}{}^{79}BrNO_2$(M + H) 302.0750, found 302.0751; calcd for $C_{13}H_{21}{}^{81}BrNO_2$(M + H) 304.0730, found 304.0731.

Ethyl 3-(3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)propanoate (4).



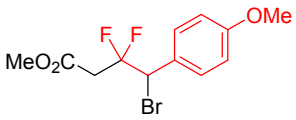
Following the **General procedure 1**, the reaction was carried out in dichloromethane, and irradiated for 5 hours. Yield 316 mg (76%). Colorless oil. R_f 0.64 (hexane/EtOAc, 10/1). Mixture of isomers, ratio ~11.5:1. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.26 (t, *J* = 7.5 Hz, minor) and 5.04 (t, *J* = 7.2 Hz, major) (1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.05 (d, *J* = 7.5 Hz, minor) and 2.99 (d, *J* = 7.2 Hz, major) (2H), 2.87 (d, *J* = 3.8 Hz, major) and 2.57 (d, J = 4.2 Hz, minor) (1H), 1.87 (d, *J* = 2.5 Hz, 1H), 1.70–1.52 (m, 3H), 1.45–1.28 (m, 1H), 1.28–1.05 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 3H), 0.98 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ, Major: 14.3, 23.8, 26.0, 28.0, 29.3, 34.9, 37.3, 41.6, 42.2, 48.1, 60.4, 107.0, 159.4, 172.7. Minor: 25.0, 27.0, 29.1, 34.1, 37.0, 48.6, 50.8, 108.7. HRMS (ESI): calcd for $C_{14}H_{22}NaO_2$ (M + Na) 245.1512, found 245.1518.

Methyl 4-bromo-3,3-difluoro-4-phenylbutanoate (6a).



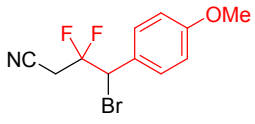
Following the **General procedure 2**, the reaction was carried out in dichloromethane, and irradiated for 30 hours. Yield 478 mg (82%). Colorless oil. R_f 0.30 (hexane/EtOAc, 10/1). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.58–7.46 (m, 2H), 7.42–7.31 (m, 3H), 5.62 (dd, *J* = 15.7, 11.7 Hz, 1H), 3.73 (s, 3H), 3.21 (td, *J* = 16.3, 10.6 Hz, 1H), 2.88 (ddd, *J* = 19.6, 16.4, 10.1 Hz, 1H). ^{19}F NMR (471 MHz, $CDCl_3$), δ: –98.4 (dtd, *J* = 251.6, 16.0, 10.1 Hz), –96.5 (ddt, *J* = 251.6, 19.6, 11.1 Hz). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ: 39.8 (t, *J* = 28.3 Hz), 51.6 (t, *J* = 26.2 Hz), 52.4, 119.1 (t, *J* = 248.3 Hz), 128.8, 129.6 (d, *J* = 1.6 Hz), 135.0 (d, *J* = 3.6 Hz), 167.0 (dd, *J* = 8.9, 6.5 Hz). HRMS (ESI): calcd for $C_{11}H_{11}{}^{79}BrF_2NaO_2$ (M + Na) 314.9803, found 314.9803; calcd for $C_{11}H_{11}{}^{81}BrF_2NaO_2$ (M + Na) 316.9783, found 316.9787.

Methyl 4-bromo-3,3-difluoro-4-(4-methoxyphenyl)butanoate (6b).



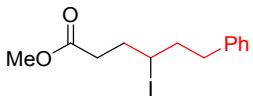
Following the **General procedure 2**, the reaction was carried out in dichloromethane and irradiated for 15 hours. Yield 560 mg (87%). Colorless oil. R_f 0.26 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.58 (dd, *J* = 16.3, 11.3 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.17 (td, *J* = 16.0, 10.6 Hz, 1H), 2.87 (ddd, *J* = 19.7, 16.3, 10.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –96.35 (ddt, *J* = 250.9, 19.7, 10.9 Hz, 1F), –98.76 (dtd, *J* = 250.9, 16.0, 10.6 Hz, 1F). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 39.8 (t, *J* = 28.4 Hz), 51.6 (t, *J* = 26.2 Hz), 52.3, 55.3, 114.2, 119.2 (t), 127.0 (d, *J* = 3.8 Hz), 130.8, 160.4, 167.0 (dd, *J* = 9.3, 5.9 Hz). HRMS (ESI): calcd for $C_{12}H_{13}{}^{79}BrF_2NaO_3$ (M + Na) 344.9908, found 344.9909; calcd for $C_{12}H_{13}{}^{81}BrF_2NaO_3$ (M + Na) 346.9888, found 346.9884.

4-Bromo-3,3-difluoro-4-(4-methoxyphenyl)butanenitrile (6c).



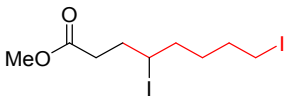
Following the **General procedure 2**, reaction was carried out with 20 mol % IMes·CuBr (176 mg, 0.4 mmol, 0.20 equiv), and bromoacetonitrile (3.6 mmol, 1.8 equiv), and irradiated for 30 hours. Yield 121 mg (21%). Colorless oil. R_f 0.16 (hexane/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 (d, *J* = 8.7 Hz, 2H), 6.91 (dm, *J* = 8.7 Hz, 2H), 5.17 (dd, *J* = 13.5, 11.9 Hz, 1H), 3.82 (s, 3H), 3.19 (ddd, *J* = 17.0, 14.3, 11.4 Hz, 1H), 2.96 (dt, *J* = 17.0, 13.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –97.71 (dq, *J* = 245.8, 12.3 Hz, 1F), –99.88 (dq, *J* = 245.8, 12.5 Hz, 1F). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 25.8 (t, *J* = 31.2 Hz), 50.8 (t, *J* = 26.1 Hz), 55.5, 112.8 (t, *J* = 6.3 Hz), 114.6, 117.0 (t, *J* = 251.7 Hz), 125.4 (d, *J* = 3.1 Hz), 130.7, 160.9. HRMS (ESI): calcd for $C_{11}H_{10}{}^{79}BrF_2NNaO$ (M + Na) 311.9806, found 311.9804; calcd for $C_{11}H_{10}{}^{81}BrF_2NNaO$ (M + Na) 313.9786, found 313.9784.

Methyl 4-iodo-6-phenylhexanoate (8a).



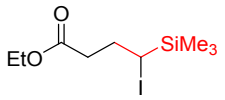
Following the **General procedure 3**. Yield 484 mg (73%). Colorless oil. R_f 0.25 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41–7.31 (m, 2H), 7.31–7.19 (m, 3H), 4.12 (tt, *J* = 8.8, 4.5 Hz, 1H), 3.72 (s, 3H), 2.96 (ddd, *J* = 13.9, 9.2, 5.1 Hz, 1H), 2.79 (dt, *J* = 13.9, 8.0 Hz, 1H), 2.72–2.59 (m, 1H), 2.52 (dt, *J* = 16.3, 7.6 Hz, 1H), 2.37–1.97 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 34.1, 35.5,37.1, 42.3, 51.7, 126.2, 128.5, 140.6, 172.9. HRMS (ESI): calcd for $C_{13}H_{17}INaO_2$(M + Na) 355.0165, found 355.0158.

Methyl 4,8-diiodooctanoate (8b).



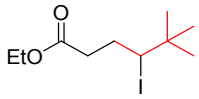
Following the **General procedure 3**. Yield 678 mg (83%). Colorless oil. R_f 0.14 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.05 (ddd, *J* = 13.2, 8.4, 4.9 Hz, 1H), 3.62 (s, 3H), 3.14 (t, *J* = 6.9 Hz, 2H), 2.61–2.32 (m, 2H), 2.09–1.92 (m, 2H), 1.92–1.36 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 6.3, 30.4, 32.5, 34.0, 35.3, 37.2, 39.5, 51.7,172.8. HRMS (ESI): calcd for $C_9H_{16}I_2NaO_2$ (M + Na) 432.9132, found 432.9128.

Ethyl 4-iodo-4-(trimethylsilyl)butanoate (8c).



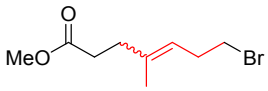
Following the **General procedure 3**. Yield (546 mg, 87%). Colorless oil R_f 0.12 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.11 (q, *J* = 7.1 Hz, 2H), 3.10 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.65 (ddd, *J* = 16.4, 8.2, 5.0 Hz, 1H), 2.50–2.33 (m, 1H), 2.06–1.69 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.14 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: –2.1, 14.3,22.5, 29.2, 36.6, 60.5, 172.9. HRMS (ESI): calcd for $C_9H_{19}INaO_2Si$ (M + Na) 337.0091, found 337.0085.

Ethyl 4-iodo-5,5-dimethylhexanoate (8d).



Following the **General procedure 3**, the reaction was carried out with 15 mol % CuI (57 mg, 0.3 mmol, 0.15 equiv), 16 mol% dm-PyBOX (87 mg, 0.32 mmol, 0.16 equiv), ethyl iodoacetate (685 mg, 3.2 mmol, 1.6 equiv), and irradiated for 20 hours. Yield 429 mg (72%). Colorless oil. R_f 0.14 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.12 (q, *J* = 7.1 Hz, 2H), 4.01 (d, *J* = 11.4 Hz, 1H), 2.67 (ddd, *J* = 16.7, 7.8, 5.3 Hz, 1H), 2.51–2.36 (m, 1H), 2.18–1.85 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 14.4, 28.6,31.3, 35.8, 36.1, 57.0, 60.5, 172.9. HRMS (ESI): calcd for $C_{10}H_{19}NaIO_2$ (M + Na) 321.0322, found 321.0324.

Radical clock experiment. Methyl 7-bromo-5-methylhept-4-enoate (**3**-open).



Following the General procedure 1 using methyl bromoacetate **1a** and isopropenylcyclopropane, the reaction was carried out in acetonitrile, and irradiated for 3.5 hours. Desired product was obtained as colorless oil (329 mg, 70%). R_f= 0.33 (hexane/EtOAc, 10/1). Mixture of isomers 2:1. ^{1}H NMR (300 MHz, $CDCl_3$), δ: Major isomer 1.62 (s, 3H), 2.23–2.45 (m, 4H), 2.46–2.62 (m, 2H), 3.31 (t, *J* = 7.3 Hz, 1H), 3.65 (s, 3H), 5.15 (t, *J* = 6.4 Hz, 1H). Minor isomer 1.69 (s, 3H), 3.32 (t, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 5.18 (d, *J* = 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: Both isomers: 16.2,

22.9, 27.3, 31.6, 32.8, 34.6, 51.5, 121.8, 136.8, 173.6. Minor isomer: 31.4, 32.5, 51.6, 123.2, 136.6, 173.5. HRMS (ESI): calcd $C_9H_{15}{}^{79}BrO_2Na$ (M + Na) 257.0148, found 257.0138; calcd $C_9H_{15}{}^{81}BrO_2Na$ (M + Na) 259.0127, found 259.0117.

ASSOCIATED CONTENT

Supporting Information. Reaction set-up and copies of NMR spectra for all compounds (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript.

ACKNOWLEDGEMENTS

This work was supported by the Russian Foundation for Basic Research (project 18-33-20015).

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