JOC The Journal of Organic Chemistry

Article

Cite This: J. Org. Chem. 2019, 84, 11068−11079

pubs.acs.org/joc

Light-Mediated Dual Phosphine-/Copper-Catalyzed Atom Transfer Radical Addition Reaction

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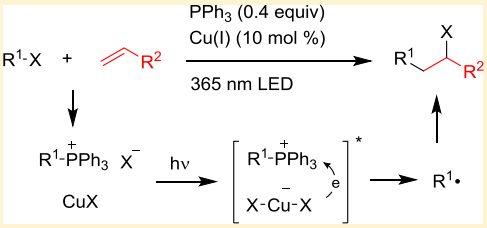
Supporting Information

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 was performed in regular glassware. The proposed mechanism involves the formation of quaternary phosphonium salt, which undergoes single electron reduction by copper(I) salt via photo-induced 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.

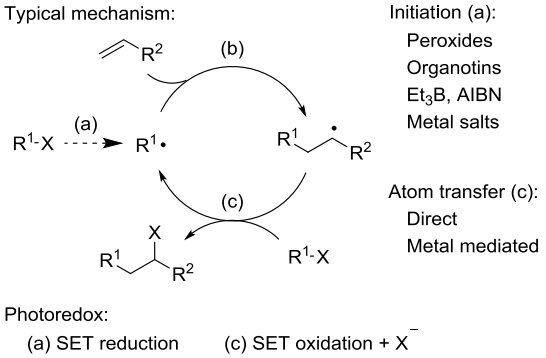


INTRODUCTION

Since the original report in 1945,[1] the interaction of halocarbons with alkenes known as atom transfer radical addition (ATRA, Kharasch 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, the 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 azobisisobutyronitrile,[7] which trigger generation of free radicals by abstraction of the 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 the metal to the carbon-centered radical.[10]

Scheme 1. ATRA Process



Another step forward was achieved because of 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 mechanisms involving single electron oxidation of the radical to carbocation followed by trapping by the 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]

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

Received: June 20, 2019
Published: August 14, 2019

DOI: 10.1021/acs.joc.9b01649
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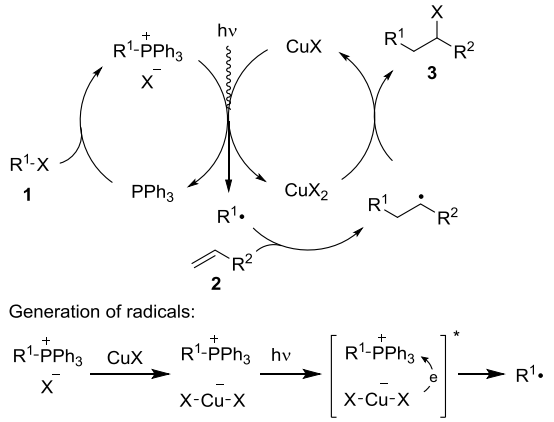
Scheme 2. Dual Phosphine-/Copper-Catalyzed Reaction



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 the 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 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 a 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 an oxidative addition/reductive elimination sequence.[18]

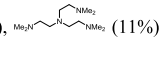
The ability of phosphonium salts to undergo fission of the C−P bond has previously been described. In the absence of the photocatalyst, this process requires harsh UV light (<300 nm) as evidenced by photolysis of benzyl and benzhydryl phosphonium salts.[19] For reactions with visible light, a photocatalyst 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 phosphine, whereas in our approach, phosphine may be used as the catalyst. Examples of using phosphines and phosphates as catalysts or mediators have been reported, with P-centered radicals being proposed as reactive intermediates.[23]

For successful realization of the process catalytic in phosphine, several criteria should be satisfied. First, phosphine must interact with substrate **1** much faster than with product **3**. This, in fact, is easy to achieve because 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 electron-withdrawing 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 (DCM) by irradiation using a 365 nm light emitting diode,

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.

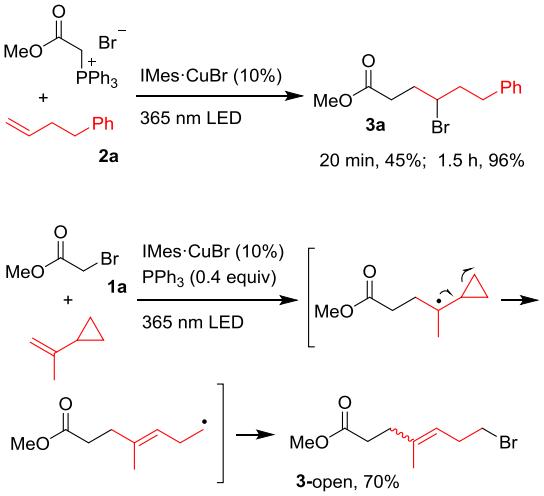
and the temperature was maintained around 20 °C. In the presence of 0.4 equiv of triphenylphosphine and 10 mol % of copper(I) bromide, the expected product **3a** was formed in 53% yield after 15 h (entry 2). Addition of ligands led to notable improvement, with the highest efficiency achieved with a 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 h. Decrease of the 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). The effect of the solvent was briefly evaluated. Ethereal solvents were less efficient, apparently, because of their ability to serve as sources of the hydrogen atom, which is transferred onto intermediate radical species. DCM wasoptimal 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 the 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).

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 ACN under

DOI: 10.1021/acs.joc.9b01649
J. Org. Chem. 2019, 84, 11068−11079

standard conditions (Scheme 3, upper equation). Thus, a quite fast reaction was observed, with the meaningful yields of

Scheme 3. Mechanistic Experiments



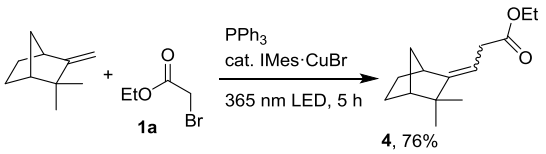
product **3a** achieved even in 20 min. To support the radical character of the process, a radical clock experiment was carried out using isopropenylcyclopropane as the alkene counterpart, and only the ring-opened product (**3**-open) was formed (Scheme 3, bottom equation). Though this experiment favors the radical mechanism, the light-absorbing species remains unclear. Indeed, the intermediate phosphonium salt, the copper catalyst, phosphine, as well as their mixtures do not absorb light at wavelengths greater than 320 nm (see the Supporting Information for the absorption spectra). This phenomenon is similar to that observed in our previous work.[17]

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 h, 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 an addition product in good yield (entries 17 and 18). Bromoacetonitrile was also successfully used, though for good conversion, a slightly increased amount of bromide (1.6 equiv) was employed (entries 20−23).

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).

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*-

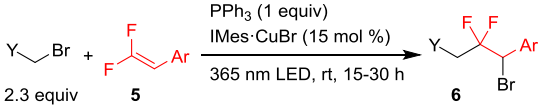
Scheme 4. Formation of the Alkene Product



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 a 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 the 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.

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. ACN was distilled from CaH_2 and stored over MS 4 Å. Dimethylformamide was distilled under vacuum from P_2O_5 and stored over MS 4 Å. DCM was distilled from CaH_2 prior to use. Column chromatography was carried out employing silica gel (230−

DOI: 10.1021/acs.joc.9b01649
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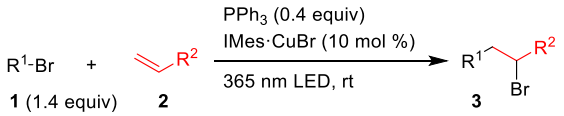
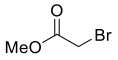
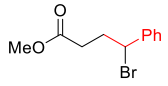
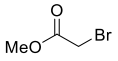
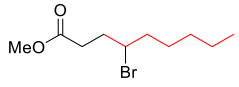
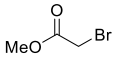
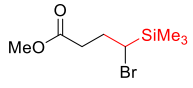
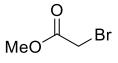
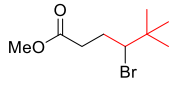
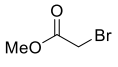
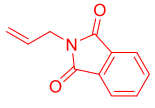
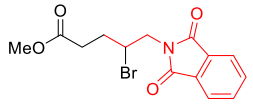
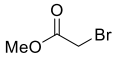
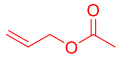
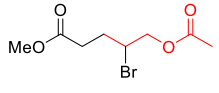
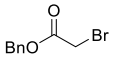
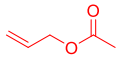
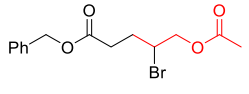
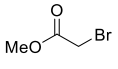
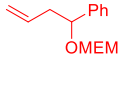
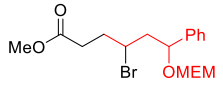
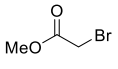
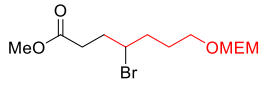
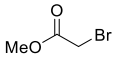
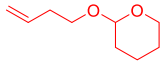
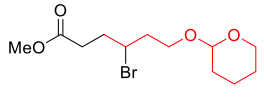
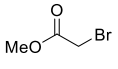
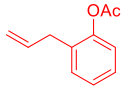
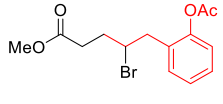
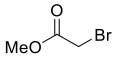
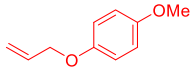
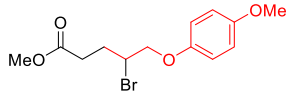
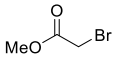
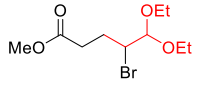
Table 2. Reactions of Alkenes



#	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

DOI: 10.1021/acs.joc.9b01649
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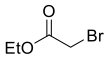
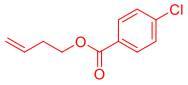
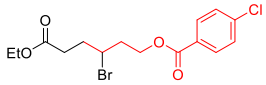
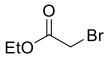
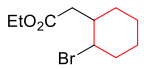
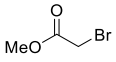
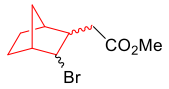
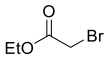
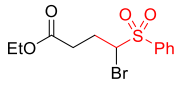
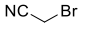
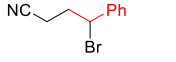
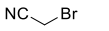
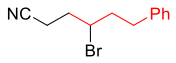
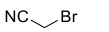
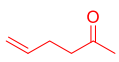
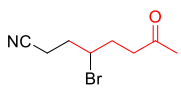
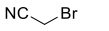
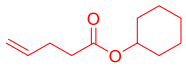
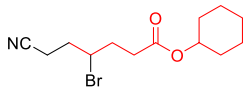
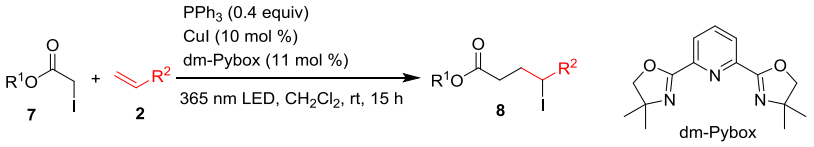
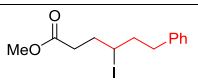
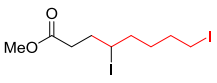
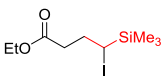
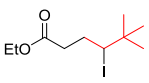
Table 2. continued

#	Solv.	Time, h	Bromide	Alkene	Product		Yield, %[a]
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 the internal standard. [c]Mixture of isomers, ratio 1:1. [d]As the 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 the catalyst, a combination of CuBr (15%) and bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (16%). [i]As the catalyst, a combination of CuBr (10%) and bis(3,5-diphenyl-1*H*-pyrazol-1-yl)methane (11%) was used.

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 %).

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 mass analyzer (Bruker micrOTOF II). For preparative high-performance liquid chromatography (HPLC), reversed-phase column (C18-kromasil, 5 μm, 21.2 × 250 mm) and

DOI: 10.1021/acs.joc.9b01649
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UV-HPLC grade ACN/water as a mobile phase were used. All photochemical reactions were performed in regular borosilicate glassware. As a light source, 100 W LED chip (BLD-HP100UV2-E45 operated at 32 V, 2.2 A) was used, the distance from the light source to the reaction vessel was 5 mm. For the reaction setup, see the Supporting Information. 1,3-Bis(2,4,6-trimethylphenyl)imidazolium carbene-copper(I) bromide complex (IMes·CuBr),[32] dm-Pybox,[33] (2,2-difluorovinyl)benzene (**5a**),[34] 1-(2,2-difluorovinyl)-4-methoxybenzene (**5b**),[30] isopropenylcyclopropane.[35]

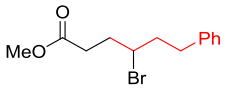
{1-[(2-Methoxyethoxy)methoxy]but-3-en-1-yl}benzene (2i).[36] MEMCl (934 mg, 7.5 mmol, 1.5 equiv) was added portionwise to a solution of 1-phenyl-3-buten-1-ol (741 mg, 5 mmol, 1 equiv) and EtN(*i*-Pr)$_2$ (840 mg, 6.5 mmol, 1.3 equiv) in DCM (8 mL). The reaction was stirred at room temperature for 2.5 h, 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). It is obtained in 1.02 g yield (87%) and as 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 DCM (5 mL), the reaction was stirred at room temperature for 2.5 h, 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 by distillation using the Hickman distillation head (40 mbar, bath temperature 110−125 °C). It is obtained in 644 mg yield (74%) and as 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.

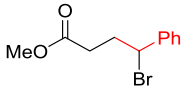
General Procedure 1 (Synthesis of Compounds 3a−j, l, m, o−s, u−w, 4). A 25 mL vial equipped with a magnetic stirrer and a screw cap with septum was charged with triphenylphosphine (210 mg, 0.8 mmol, 0.4 equiv), and a copper(I) catalyst [for **3a−i**, **l**, **m**, **o−r**, **u**, **v**, **4**, IMes·CuBr (44 mg, 0.2 mmol, 0.1 equiv); for **3j**, CuBr (29 mg, 0.2 mmol, 0.1 equiv) and bis(3,5-dimethyl-1*H*-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-1*H*-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-1*H*-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**, ACN; for **3g−i**, **l**, **m**, **o**, **r**, **t−w**, **4**, DCM) was added by a gas-tight 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 using a gas-tight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with a transparent bottom (Figure S2d) and was irradiated with 365 nm LED until full conversion of the starting alkene [verified by gas chromatography (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 DCM (or ACN for **3k**) was added by using a gas-tight 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 using a gas-tight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with a transparent bottom (Figure S2d), 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**.

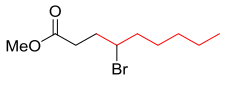
General Procedure 3 (Synthesis of Compounds 8a−d). A 25 mL vial equipped with a magnetic stirrer and a screw cap with septum was charged with triphenylphosphine (PPh_3, 210 mg, 0.8 mmol, 0.4 equiv), CuI (38 mg, 0.2 mmol, 0.1 equiv), and dm-Pybox (60 mg, 0.44 mmol, 0.11 equiv). The vial was evacuated and filled with argon, and DCM (2.5 mL) was added by using a gas-tight 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 the reaction mixture by using a gas-tight syringe. The reaction vessel was put into water-filled beaker (water temperature 20 °C) with a transparent bottom (Figure S2d) 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 h, 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 ACN, and irradiated for 3.5 h. It is obtained in 517 mg yield (91%) and as 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 ACN, and irradiated for 2 h. It is obtained in 415 mg yield (81%) and as 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 ACN, and irradiated for 6 h. It is obtained in 426 mg yield (85%) and as 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,

DOI: 10.1021/acs.joc.9b01649
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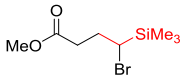
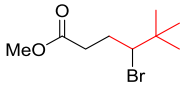
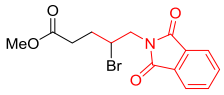
273.0455; calcd for $C_{10}H_{19}{}^{81}BrNaO_2$ (M + Na), 275.0440; found, 275.0432.



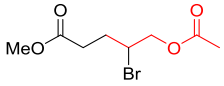
Methyl 4-Bromo-4-(trimethylsilyl)butanoate (3d). Following the general procedure **1**, the reaction was carried out in ACN, and irradiated for 3.5 h. It is obtained in 399 mg yield (79%) and as colorless oil. R_f 0.35 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.23 (dd, J = 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.



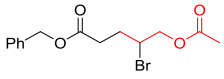
Methyl 4-Bromo-5,5-dimethylhexanoate (3e). Following the general procedure **1**, the reaction was carried out in ACN, and irradiated for 6 h. It is obtained in 410 mg yield (87%) and as colorless oil. R_f 0.33 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (dd, J = 11.7, 1.8 Hz, 1H), 3.62 (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.



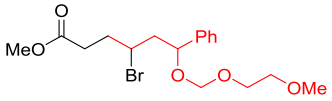
Methyl 4-Bromo-5-(1,3-dioxoisoindolin-2-yl)pentanoate (3f). Following the general procedure **1**, the reaction was carried out in ACN, and irradiated for 15 h. It is obtained in 549 mg yield (81%) and as white crystals. mp 97−99 °C. R_f 0.12 (hexane/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (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.



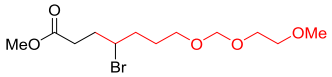
Methyl 5-Acetoxy-4-bromopentanoate (3g). Following the general procedure **1**, the reaction was carried out in DCM, and irradiated for 15 h. It is obtained in 424 mg yield (84%). R_f 0.25 (hexane/EtOAc, 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.38−4.00 (m, 3H), 3.59 (s, J = 15.7 Hz, 3H), 2.63−2.32 (m, 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{^{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 $C_8H_{14}{}^{79}BrO_4$ (M + H), 253.0070; found, 253.0060; calcd for $C_8H_{14}{}^{81}BrO_4$ (M + H), 255.0050; found, 255.0038.



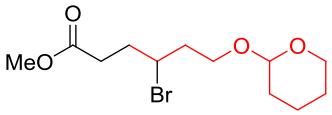
Benzyl 5-Acetoxy-4-bromopentanoate (3h). Following the general procedure **1**, the reaction was carried out in DCM, and irradiated for 15 h. It is obtained in 578 mg yield (88%) and as colorless oil. R_f 0.12 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.28 (m, 5H), 5.14 (s, 2H), 4.42−4.22 (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{^{1}H} 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.



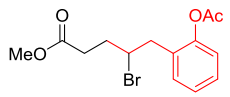
Methyl 4-Bromo-6-[(2-methoxyethoxy)methoxy]-6-phenylhexanoate (3i). Following the general procedure **1**, the reaction was carried out in DCM, and irradiated for 15 h. It is obtained in 560 mg yield (72%) and as colorless oil. Mixture of diastereoisomers, ratio 1:1. R_f 0.23 (hexane/EtOAc, 4/1). ^{1}H 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 ACN 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, 0.22 mmol, 0.11 equiv) and irradiated for 15 h. It is obtained in 463 mg yield (71%) and as colorless oil. R_f 0.35 (hexane/EtOAc, 3/1). Further purification was performed via preparative HPLC (flow rate 12 mL·min^{-1}, mobile phase: isocratic, 10% water in ACN, 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-2*H*-pyran-2-yl)oxy]-hexanoate (3k). Following the general procedure **2**, the reaction was carried out in ACN, and irradiated for 15 h. It is obtained in 475 mg yield (77%) and as 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 DCM and irradiated for 15 h. It is obtained in 473 mg yield (72%) and as 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),

DOI: 10.1021/acs.joc.9b01649
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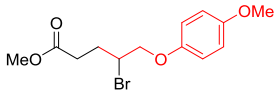
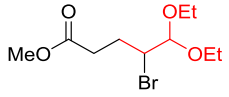
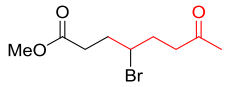
2.35 (s, 3H), 2.21 (tdd, J = 10.8, 7.8, 3.2 Hz, 1H), 2.10−1.89 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 21.1, 32.2, 33.5, 40.7, 51.8, 54.5, 122.7, 126.2, 128.4, 130.1, 131.4, 149.2, 169.3, 173.1. HRMS (ESI): calcd for $C_{14}H_{18}{}^{79}BrO_4$ (M + H), 329.0383; found, 329.0384; calcd for $C_{14}H_{18}{}^{81}BrO_4$ (M + H), 331.0363; found, 331.0366.



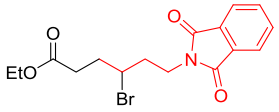
Methyl 4-Bromo-5-(4-methoxyphenoxy)pentanoate (3m). Following the general procedure **1**, the reaction was carried out in DCM using 1.6 equiv of methyl bromoacetate and irradiated for 20 h. It is obtained in 518 mg yield (83%) and as colorless oil. R_f 0.21 (hexane/EtOAc, 8/1). ^1H NMR (300 MHz, $CDCl_3$): 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). $^{13}C\{^1H\}$ 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.



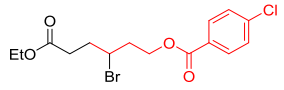
Methyl 4-Bromo-5,5-diethoxypentanoate (3n). Following the general procedure **2**, the reaction was carried out in DCM using 1.6 equiv of methyl bromoacetate, and irradiated for 20 h. It is obtained in 344 mg yield (61%) and as colorless oil. R_f 0.28 (hexane/EtOAc, 9/1). ^1H NMR (300 MHz, $CDCl_3$): 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). $^{13}C\{^1H\}$ 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.



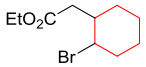
Methyl 4-Bromo-7-oxooctanoate (3o). Following the general procedure **1**, the reaction was carried out in DCM and irradiated for 5 h. It is obtained in 443 mg yield (87%) and as colorless oil. R_f 0.23 (hexane/EtOAc, 5/1). ^1H NMR (300 MHz, $CDCl_3$): δ 4.03 (tt, J = 9.4, 3.8 Hz, 1H), 3.64 (s, 3H), 2.76−2.60 (m, 2H), 2.60−2.39 (m, 2H), 2.23−1.84 (m, 4H), 2.13 (s, 3H). $^{13}C\{^1H\}$ 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.



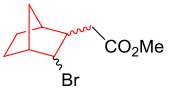
Ethyl 4-Bromo-6-(1,3-dioxoisoindolin-2-yl)hexanoate (3p). Following the general procedure **1**, the reaction was carried out in ACN, and irradiated for 15 h. It is obtained in 490 mg yield (67%) and as white crystals. mp 45−46 °C. R_f 0.11 (hexane/EtOAc, 4/1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (dd, 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.



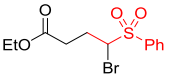
3-Bromo-6-ethoxy-6-oxohexyl 4-Chlorobenzoate (3q). Following the general procedure **1**, the reaction was carried out in DCM, and irradiated for 15 h. It is obtained in 605 mg yield (80%) and as colorless oil. R_f 0.27 (hexane/EtOAc, 8/1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (dm, J = 8.6 Hz, 2H), 7.35 (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.



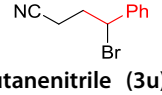
Ethyl 2-(2-Bromocyclohexyl)acetate (3r). Following the general procedure **1**, the reaction was carried out in DCM, and irradiated for 15 h. It is obtained in 174 mg yield (35%) and as colorless oil. Mixture of diastereoisomers, ratio 3:2. R_f 0.11 (hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (dd, 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 ACN with 15 mol % CuBr (43 mg, 0.3 mmol, 0.15 equiv) and 16 mol % bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (66 mg, 0.32 mmol, 0.16 equiv) and irradiated for 6 h. It is obtained in 427 mg yield (87%) and as colorless oil. Mixture of diastereoisomers, ratio 3:2. R_f 0.26 (hexane/EtOAc, 10/1). ^1H 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). $^{13}C\{^1H\}$ 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 DCM, and irradiated for 15 h. It is obtained in 391 mg yield (59%) and as colorless oil. R_f 0.28 (hexane/EtOAc, 2/1). ^1H 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). $^{13}C\{^1H\}$ 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 DCM using 1.6 equiv of

DOI: 10.1021/acs.joc.9b01649
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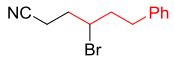
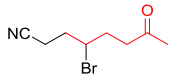
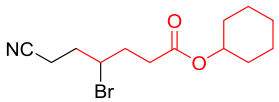
bromoacetonitrile and irradiated for 30 h. It is obtained in 220 mg yield (49%) and as colorless oil. R_f 0.30 (hexane/EtOAc, 5/1). Further purification was performed via preparative HPLC (flow rate 12 mL·min^{-1}, mobile phase: isocratic, 25% water in ACN, retention time 19.3 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.28 (m, 5H), 5.04 (m, 1H), 2.66−2.33 (m, 4H). $^{13}C\{^1H\}$ 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.



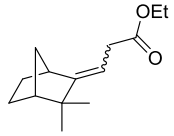
4-Bromo-6-phenylhexanenitrile (3v). Following the general procedure **1**, the reaction was carried out in DCM using 1.6 equiv of bromoacetonitrile, and irradiated for 15 h. It is obtained in 487 mg yield (97%) and as colorless oil. R_f 0.25 (hexane/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.31 (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). $^{13}C\{^1H\}$ 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.



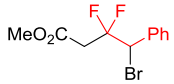
4-Bromo-7-oxooctanenitrile (3w). Following the general procedure **1**, reaction was carried out in DCM with 10 mol % CuBr (29 mg, 0.2 mmol, 0.1 equiv), 11 mol % bis(3,5-diphenyl-1*H*-pyrazol-1-yl)methane (99 mg, 0.22 mmol, 0.11 equiv), bromoacetonitrile (384 mg, 3.2 mmol, 1.6 equiv), and irradiated for 15 h. It is obtained in 266 mg yield (61%) and as 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). $^{13}C\{^1H\}$ 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.



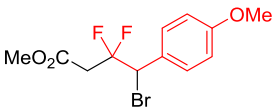
Cyclohexyl 4-Bromo-6-cyanohexanoate (3x). Following the general procedure **2**, the reaction was carried out in DCM and irradiated for 30 h. After column chromatography (R_f 0.35, hexane/EtOAc, 3/1), further purification was performed by preparative HPLC (flow rate 12 mL·min^{-1}, mobile phase: isocratic, 10% water in ACN, retention time 8.1 min). It is obtained in 436 mg yield (72%) and as 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). $^{13}C\{^1H\}$ 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.



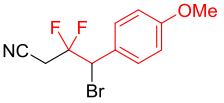
Ethyl 3-(3,3-Dimethylbicyclo[2.2.1]heptan-2-ylidene)-propanoate (4). Following the general procedure **1**, the reaction was carried out in DCM and irradiated for 5 h. It is obtained in 316 mg yield (76%) and as colorless oil. R_f 0.64 (hexane/EtOAc, 10/1). Mixture of isomers, ratio ~11.5:1. ^{1}H NMR (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). $^{13}C\{^1H\}$ 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.



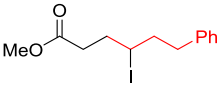
Methyl 4-Bromo-3,3-difluoro-4-phenylbutanoate (6a). Following the general procedure **2**, the reaction was carried out in DCM and irradiated for 30 h. It is obtained in 478 mg yield (82%) and as colorless oil. R_f 0.30 (hexane/EtOAc, 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58−7.46 (m, 2H), 7.42−7.31 (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). $^{13}C\{^1H\}$ 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 DCM and irradiated for 15 h. It is obtained in 560 mg yield (87%) and as 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). $^{13}C\{^1H\}$ 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 h. It is obtained in 121 mg yield (21%) and as 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). $^{13}C\{^1H\}$ 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**, it is obtained in 484 mg yield (73%) and as 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,

DOI: 10.1021/acs.joc.9b01649
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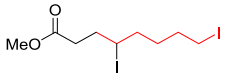
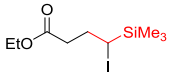
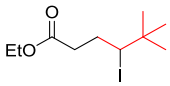
1H), 2.37−1.97 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 34.1, 35.5, 37.1, 42.3, 51.7, 126.2, 128.5, 140.6, 172.9. HRMS (ESI): calcd for $C_{13}H_{17}INaO_2$ (M + Na), 355.0165; found, 355.0158.



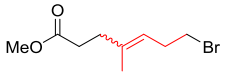
Methyl 4,8-Diiodooctanoate (8b). Following the general procedure **3**, it is obtained in 678 mg yield (83%) and as colorless oil. R_f 0.14 (hexane/EtOAc, 25/1). ^1H NMR (300 MHz, $CDCl_3$): δ 4.05 (ddd, J = 13.2, 8.4, 4.9 Hz, 1H), 3.62 (s, 3H), 3.14 (t, J = 6.9 Hz, 2H), 2.61−2.32 (m, 2H), 2.09−1.92 (m, 2H), 1.92−1.36 (m, 6H). $^{13}C\{^1H\}$ 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**, it is obtained in 546 mg yield (87%) and as colorless oil. R_f 0.12 (hexane/EtOAc, 25/1). ^1H 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). $^{13}C\{^1H\}$ 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 h. It is obtained in 429 mg yield (72%) and as colorless oil. R_f 0.14 (hexane/EtOAc, 25/1). ^1H 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). $^{13}C\{^1H\}$ 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 ACN and irradiated for 3.5 h. The desired product was obtained as colorless oil (329 mg, 70%). R_f = 0.33 (hexane/EtOAc, 10/1). Mixture of isomers 2:1. ^1H 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). $^{13}C\{^1H\}$ 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01649.

Reaction setup and copies of NMR spectra for all the compounds (PDF)

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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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

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