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Hydrohalogenation of Unactivated Alkenes using a Methanesulfonic Acid/Halide Salt Combination

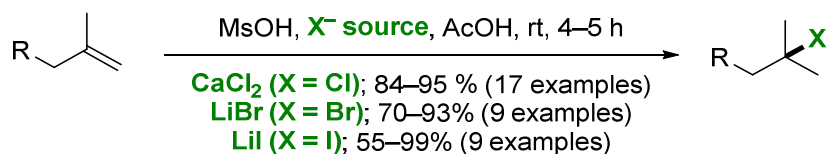
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Talence, France



- Mild conditions
- Readily available solid reagents
- No additional purification generally required

ABSTRACT

The hydrochlorination, hydrobromination and hydroiodination of unactivated alkenes using methanesulfonic acid and inorganic halide salts (CaCl₂, LiBr, LiI) in acetic acid are reported. This approach uses readily available and inexpensive reagents to provide the alkyl halides in up to 99% yield. An example of deuteriochlorination using deuterated acetic acid as the solvent is also demonstrated.

INTRODUCTION

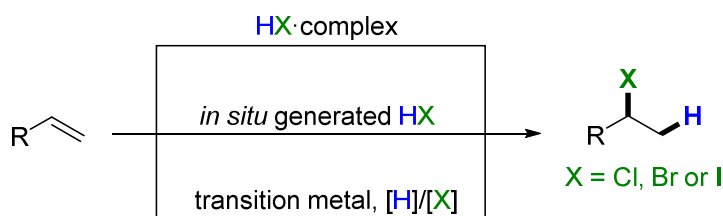
Alkyl halides are, undoubtedly, useful intermediates in organic chemistry as they can be used to perform a wide range of transformation such as substitution, elimination and cross-coupling to produce high value-added compound. Due to their great abundance, alkenes are a perfect feedstock to generate alkyl halides. The Markovnikov hydrohalogenation of alkenes is one of the most well-known reaction in organic chemistry, having been discovered more than a century ago.¹ Although one could envision to directly use gaseous HCl, HBr or HI to achieve those transformation; these reagents are highly corrosive and poses many practical problems, specially at laboratory scale. A number of alternatives approaches have been designed and can be classified into three categories (Scheme 1a). The first category, and probably the most intuitive, is the use of complexed form of the corresponding hydrogen halide.² Alternatively, the hydrogen halide can be generated *in situ*.³ This can be achieved in a number of ways, but mainly by mixing a reactive species such as an acyl or a sulfonyl halide with a protic nucleophile. Finally, the use of a transition metal allows the addition on the alkene using various sources of halogen.⁴ Interestingly, Oestreich and Chen developed a reagent, based on cyclohexadiene, that could be used as a surrogate for hydrogen halide, though this reagent was only used for the hydrohalogenation of alkynes and allenes.^{3d} Overall, considering the synthetic importance of alkyl halides the further development of conditions for the hydrohalogenation of alkenes is still highly valuable.

Recently, we reported the use of a combination of methanesulfonic acid (MsOH) and triethylamine trihydrofluoride (Et₃N·3HF) for the hydrofluorination of various methallyl

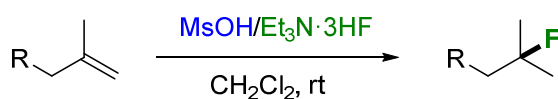
alkenes (Scheme 1b).^{5,6} Inspired by this work, we intended to adapt these conditions for the hydrochlorination, hydrobromination and hydroiodination of alkenes as a practical access to tertiary halides. Herein, we report the development of such reaction using methanesulfonic acid in the presence of an inorganic halogen salt (CaCl₂, LiBr, LiI), all widely accessible reagents (Scheme 1c).

Scheme 1. Previous work

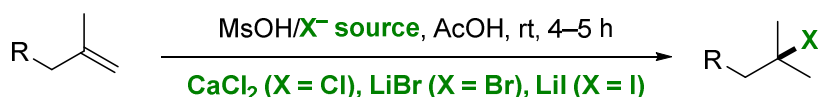
a) Classic method for the Markovnikov hydrohalogenation of alkenes



b) Previous work: Direct hydrofluorination of methallyl alkenes



c) Hydrohalogenation of alkenes without the use of HX

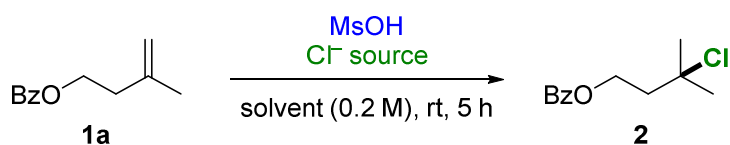


RESULTS AND DISCUSSION

We started the optimization in dichloromethane by screening a series of chloride sources while using methanesulfonic acid (MsOH) as the proton source (Table 1, entries 1-6). The use of hand-ground calcium chloride prove critical as a 40% increase in yield was obtain compared to the beads. Surprisingly, after testing other polar aprotic solvents (Table 1, entries 6-9), it was found that the use of acetic acid, a protic solvent, afforded the desired

product in 90% yield (Table 1, entry 10). Variations on the number of equivalents of MsOH and/or CaCl₂ showed no improvement on the yield (Table 1, entries 11-14). Finally, a control experiment revealed the need for the use of MsOH as an acid as a low yield of **2a** (9%) was observed without it (Table 1, entry 15). We therefore selected the conditions from entry 10 as optimal and use them for the rest of the study.

Table 1. Selected optimization results for the hydrochlorination of alkene **1a^a**



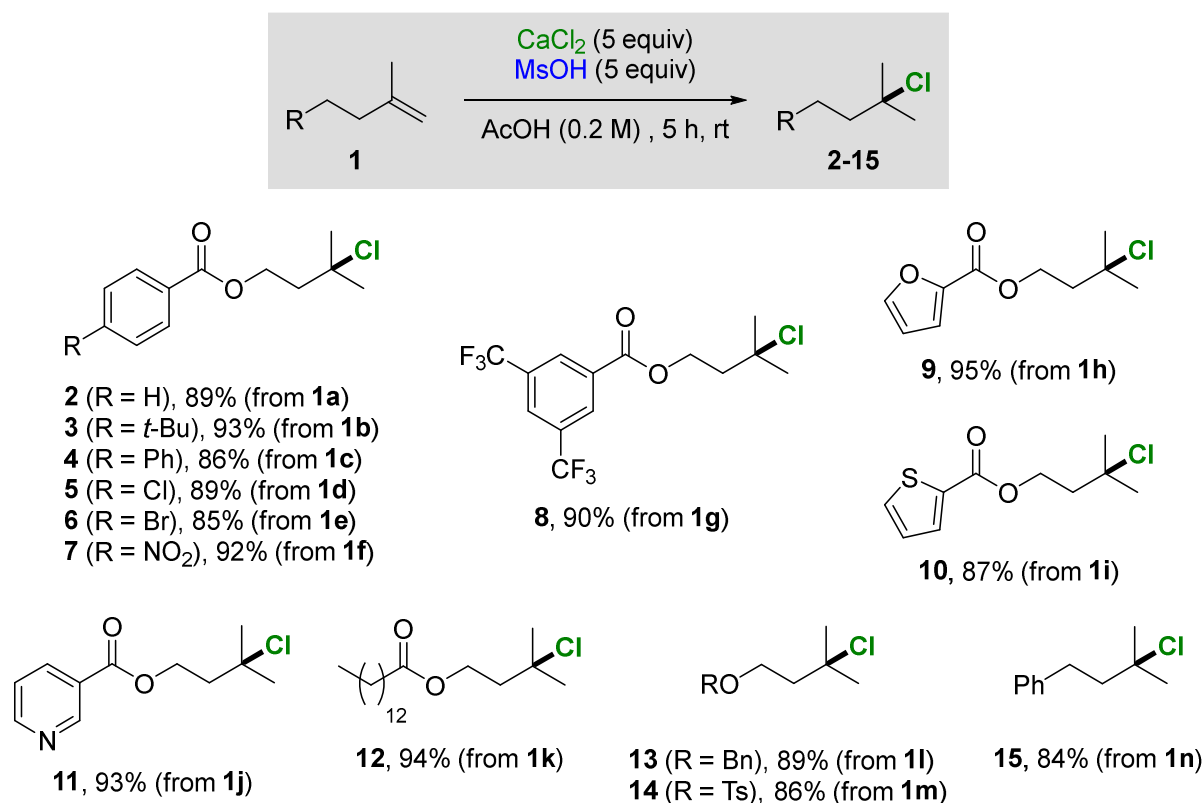
entry	chloride source (equiv.)	MsOH (equiv.)	solvent	yield (%) ^b
1	LiCl (5)	5	CH ₂ Cl ₂	1
2	NaCl (5)	5	CH ₂ Cl ₂	5
3	NH ₄ Cl (5)	5	CH ₂ Cl ₂	21
4	<i>n</i> -Bu ₄ NCl (5)	5	CH ₂ Cl ₂	9
5	CaCl ₂ (5) ^c	5	CH ₂ Cl ₂	21
6	CaCl ₂ (5) ^d	5	CH ₂ Cl ₂	61
7	CaCl ₂ (5) ^d	5	Et ₂ O	5
8	CaCl ₂ (5) ^d	5	DMF	6
9	CaCl ₂ (5) ^d	5	1,2-DCE	64
10	CaCl ₂ (5) ^d	5	AcOH	90
11	CaCl ₂ (1) ^d	1	AcOH	40
12	CaCl ₂ (10) ^d	10	AcOH	85

13	CaCl ₂ (3) ^d	3	AcOH	82
14	CaCl ₂ (5) ^d	1	AcOH	82
15	CaCl ₂ (5) ^d	0	AcOH	9

^a See the Experimental Section for the detailed experimental procedures. ^bYield estimated by ¹H NMR using 1,4-dimethoxybenzene as the internal standard. ^cBeads. ^d Hand-grounded.

We then explored the scope of the reaction on various methallyl alkenes and the results are shown in Scheme 2. It is worth noting that all the products were obtained pure after work-up without the need for further purification. Various aromatic esters derived from 3-methylbut-3-en-1-ol could be used as substrates (**1a-j**), and the corresponding products (**2-11**) were obtained in good to excellent yield (85-95%). An aliphatic ester could also be used (**1k**) and provide the corresponding product **12** in 94% yield. Benzyl and tosyl derivatives (**1l-m**) were converted easily and with excellent yield to the corresponding chlorides (**13-14**). While all the substrates tested so far contained with an ester or an ether functionality, it was shown that such group was not required (c.f. **15**).

Scheme 2. Hydrochlorination of methallyl alkenes using a MsOH/CaCl₂ combination^a

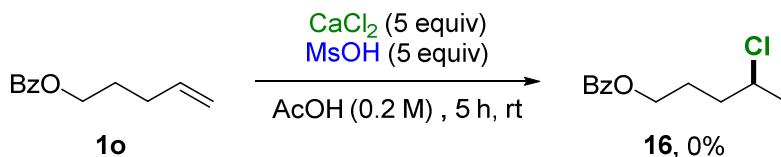


^aSee the Experimental Section for the detailed experimental procedures. All the reactions were performed on a 0.2 mmol scale. Isolated yield of the chloride after work-up.

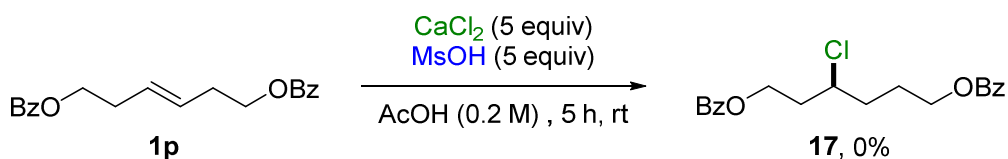
We tested different patterns of alkene substitutions as presented in Scheme 3. For monosubstituted and 1,2-disubstituted alkenes (**1o-p**), no conversion was observed. However, an exocyclic alkene (**1q**) was converted to the chloride (**18**) in excellent yield (94%, *dr* = 6:1). Trisubstituted alkenes such as citronellol (**1r**) or its benzoyl ester (**1s**) were also compatible with the reaction conditions, though in the former case, the product (**19**) is isolated as the acetate.

Scheme 3. Hydrochlorination of other alkenes using a MsOH/CaCl₂ combination^a

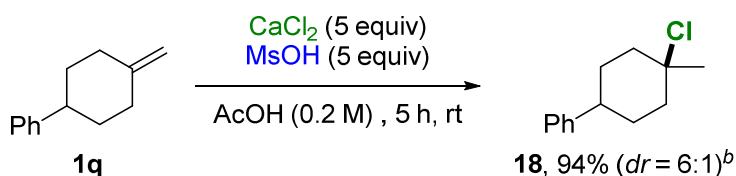
Terminal alkene



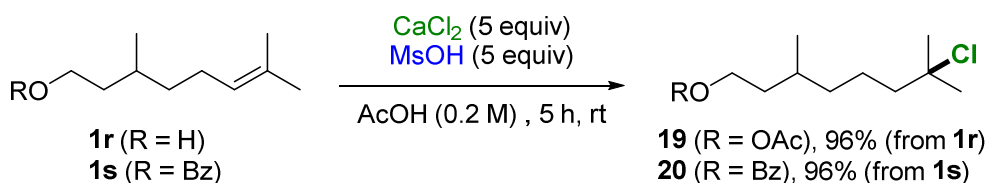
1,2-Disubstituted alkene



1,1-Disubstituted alkene



Trisubstituted alkene



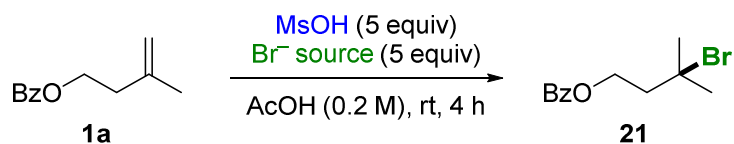
^aSee the Experimental Section for the detailed experimental procedures. All the reactions were performed on a 0.2 mmol scale. Isolated yield of the chloride after work-up.

^bDetermined by ¹H NMR analysis.

We then turned our attention to the hydrobromination and -iodination. Using the same general conditions, we screened various bromide and iodide sources. The results are presented in Table 2 (Hydrobromination) and Table 3 (Hydroiodination). The calcium salts gave good yields, but somewhat lower than the chloride analogue. The best yields were

obtained when lithium bromide and lithium iodide were used. Based on these yields, we chose the lithium salts for both reactions. Other salts didn't perform as well.

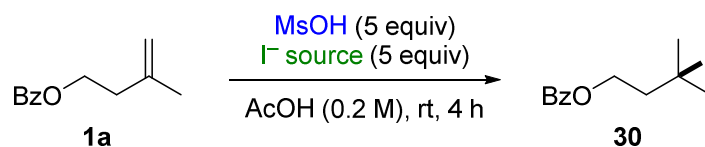
Table 2. Selected optimization results for the hydrobromination of alkene 1a^a



entry	Bromide source	yield (%) ^b
1	CaBr ₂	69
2	CaBr ₂ · xH ₂ O	74
3	MgBr ₂	74
4	LiBr	89
5	NaBr	56
6	KBr	68
7	CsBr	64
8	Et ₄ NBr	68

^a See the Experimental Section for the detailed experimental procedures. ^b Yield estimated by ¹H NMR using 1,4-dimethoxybenzene as the internal standard.

Table 3. Selected optimization results for the hydroiodination of alkene 1a^a



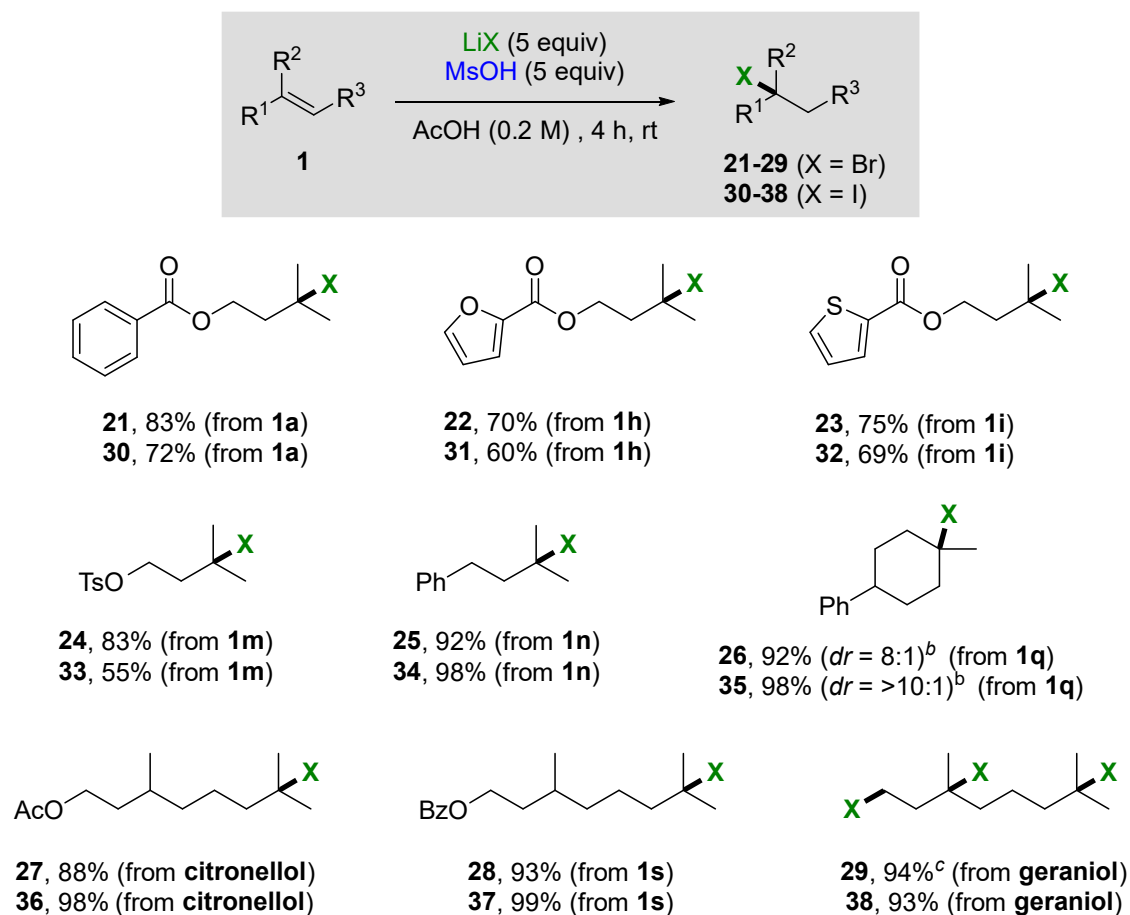
entry	iodide source	yield (%) ^b
1	CaI ₂	51
2	LiI	76
3	NaI	67
4	KI	54
5	CsI	41
6	Me ₄ NI	23
7	Et ₄ NI	42
8	<i>n</i> -Bu ₄ NI	19

^a See the Experimental Section for the detailed experimental procedures. ^b Yield estimated by ¹H NMR using 1,4-dimethoxybenzene as the internal standard.

The scope for the hydrobromination and hydroiodination reactions are presented in Scheme 4. The esters derivatives of 3-methyl-3-buten-1-ol (**21-23**, **30-32**) showed somewhat lower yields than their chlorides analogues. This could be explained by the need for purification of these compounds. We found out these substrates produce a side-product that needs to be separate by chromatography. This is also the case with the tosyl derivative (**24**, **33**). A plausible mechanism for the formation of the side-products is discussed in the mechanism investigation section. This side reaction is not observed with the other substrates. Substrates **1n-o**, bearing no heteroatom, gave the corresponding halides (**25-26**, **34-35**) in

excellent yields. Once again, tri-substituted alkenes such as citronellol and its benzoyl derivatives (**1s**) afford the halides in excellent yields. Acetylation of the free alcohol is still observed. Surprisingly, when geraniol was subjected to the reaction conditions, the trihalogenated product was formed (**29**, **38**). The presence of an allylic alcohol may be responsible for this transformation. The tribromide **29** could not be isolated with a satisfactory purity (85% as estimated by NMR analysis) as it was found to be unstable and start decomposing readily upon isolation. Alkenes **1a**, **1h-i** and **1m** produced an impurity that was identified as 1,3-dibromo-3-methylbutane or 1,3-diiodo-3-methylbutane. These reactions therefore needed silica gel chromatography purification to isolate the desired compound.

Scheme 4. Hydrobromination and iodination of alkenes using a MsOH/LiBr or a MsOH/LiI combination^a



^aSee the Experimental Section for the detailed experimental procedures. All the reactions were performed on a 0.2 mmol scale. Isolated yield of the halide after work-up.

^bDetermined by ¹H NMR analysis. ^cThe purity was estimated at 85% by NMR analysis.

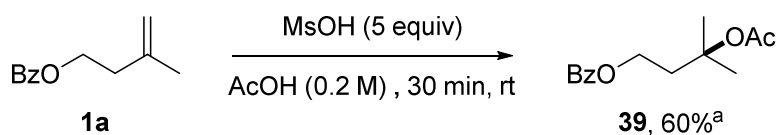
Finally, we performed a series of experiments in order to probe the mechanism. One of our main concern was the potential addition of acetic acid on the alkene to generate the corresponding acetate. To test if that addition occurred, we tried the reaction without any

halogen. However, in these conditions, the product decomposed into several byproducts, the main one being the acetate, but only in a 5% yield. However, when we reduced the reaction time to only 30 minutes, the acetate (**39**) was formed in a 60 % yield (**Scheme 5a**). In a second experiment, we tried the hydrochlorination directly on the acetate to determine if an *in situ* generated acetate could be converted to the chloride (**Scheme 5b**). Indeed, the chloride was formed in an 89% yield, the same yield as from the alkene. We then turned our attention to deuterium incorporation, both from the point of view of mechanism elucidation, but also for potential application for the generation of isotopically labelled molecules. Deuterium enriched methanesulfonic acid being expensive and not easy to obtain, we envisioned that using commercially available and widely accessible deuterated acetic acid⁷ instead could lead to the labelled product if an exchange could take place between deuterated acetic acid and methanesulfonic acid prior to the protonation of the alkene. We were pleased to see an incorporation of more than 95% in deuterium using this method (**Scheme 5c**). The reaction without methanesulfonic acid yields the chloride in only 9% (**Table 1, entry 15**), supporting the fact that methanesulfonic acid is necessary and serves as the protonating species. Moreover, only one deuterated compound was generated, hinting that once the carbocation is formed, it does not eliminate to isomerize the alkene. Interestingly, methods for deuteriohalogenation reactions are limited. Common methods require the use of preformed DX usually from the reaction of D₂O with a halide source (BzOCl, AcCl, TiCl₄, PCl₃, PBr₃, BBr₃) that needs to be distilled and dried.^{3k,8} Alternatively, Snyder reported an interesting method using D₂O-saturated nitromethane as the source of deuterium.^{3c} Deuterium incorporation is excellent, but the solution of nitromethane must be made prior to the reaction.

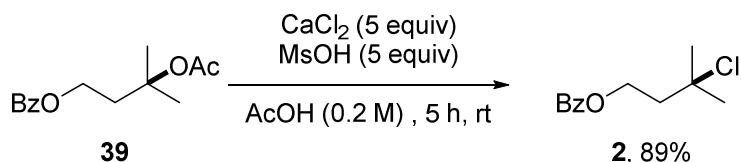
With these data in hand, we propose that the reaction proceeds as described in **Scheme 5d**. Methanesulfonic acid generates the tertiary carbocation by protonation of the alkene. This carbocation can either react with a chloride (to generate the desired chlorinated product) or with acetic acid to produce the corresponding acetate. However, the latter, under the reaction conditions, is in an equilibrium with the carbocation and eventually will be transformed into the chloride. We assume that a similar mechanism is operating for the hydrobromination and hydroiodination.

Scheme 5. Mechanistic investigations for the hydrochlorination^a

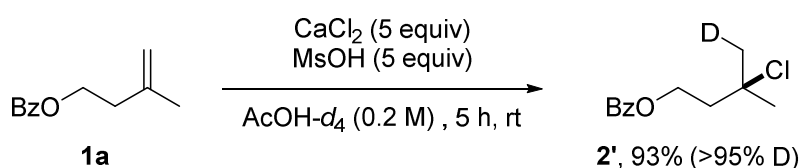
a) Probing the formation of an acetate intermediate



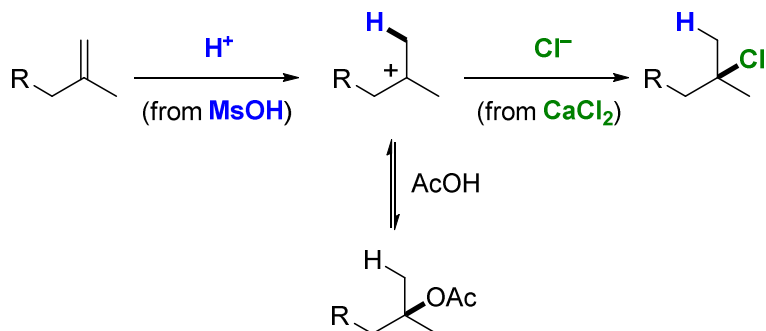
b) Reactivity of the putative acetate intermediate



c) Deuteration using AcOH-d₄



d) Proposed mechanism



^aYield estimated by ¹H NMR using 1,4-dimethoxybenzene as the internal standard.

CONCLUSION

In summary, we have described the use of a combination of methanesulfonic acid and halide salts (CaCl₂, LiBr, LiI) for the efficient hydrohalogenation of alkenes. This method provides tertiary halide in up to 99% yield using readily available and easy-to-handle reagents. The use of deuterated acetic acid allows for a deuteriochlorination reaction.

General information. The following includes general experimental procedures, specific details for representative reactions, isolation and spectroscopic information for the new compounds prepared. All commercial compounds were used as received. Solvents were used as purchased unless stated as dry. THF and CH₂Cl₂ were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All air and water sensitive reactions were carried out under argon atmosphere. Reactions were monitored by TLC on pre-coated plates (Silicycle silica gel 60 Å F254 230-240 mesh) and products were visualized under 254 nm UV light followed by staining with KMnO₄ when appropriate. Purification by flash column chromatography was carried out on silica gel (Silicycle silica gel 60 Å F254). NMR spectra were recorded on an Agilent DD2 500 MHz spectrometer or on a Varian Inova 400 MHz spectrometer in the indicated solvent at 298 K. Chemical shifts for ¹H and ¹³C spectra are reported on the delta scale in ppm and were referenced to residual solvent references or internal TMS reference. For ¹⁹F spectra, calibration was performed using a unified scale.⁹ Resonances are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br. s = broad signal

or a combination of the above), coupling constant (Hz), integration. NMR yields were determined by ^1H NMR analysis of the crude mixture after work-up using 1,4-dimethoxybenzene as the internal standard. High-resolution mass (HRMS) spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI). Low resolution mass spectra (GC-MS) were obtained on a GC-MS Thermo ITQ 900 Trace GC Ultra using chemical ionisation (CI). Infrared spectra were recorded on an ABB MB3000 FT-IR spectrometer. Alkenes **1r** and **1t** are commercially available.

Synthesis of starting alkenes. Alkenes **1a-1n**,⁵ **1o**,¹⁰ **1p**,¹¹ **1q**,¹² **1s**⁵ were synthesized according to previously reported procedures.

Hydrochlorination reaction (General procedure A). To a solution of the alkene (0.2 mmol, 1 equiv.) in acetic acid (1 mL, 0.2 M) was added calcium chloride (111.0 mg, 5 equiv.). Methanesulfonic acid (65 μL , 5 equiv.) was added and the reaction was stirred at room temperature. After 5 hours, the reaction was quenched with a saturated aqueous solution of NaHCO_3 and extracted with CH_2Cl_2 (3x). The organic layers were combined and then washed with a saturated aqueous solution of Na_2CO_3 , dried with Na_2SO_4 , and concentrated under reduced pressure. The desired product was obtained without further purification unless otherwise noted.

3-Chloro-3-methylbutyl benzoate (2). Following general procedure A using 3-methylbut-3-en-1-yl benzoate (**1a**, 38 mg, 0.2 mmol), the desired product was obtained as a colorless oil (40 mg, 0.18 mmol, 89%). Spectroscopic data agreed with the literature.^{4a}

3-Chloro-3-methylbutyl 4-(tert-butyl)benzoate (3). Following general procedure A using 3-methylbut-3-en-1-yl 4-(tert-butyl)benzoate (**1b**, 49 mg, 0.2 mmol), the desired product was obtained as a colorless oil (53 mg, 0.19 mmol, 93%). IR (ATR, diamond), $\nu = 2966, 2907, 1717, 1610, 1464, 1273, 1188, 1115, 1016, 773, 708 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.00 – 7.92 (m, 2H), 7.49 – 7.42 (m, 2H), 4.55 (t, $J = 6.7 \text{ Hz}$, 2H), 2.25 (t, $J = 6.7 \text{ Hz}$, 2H), 1.68 (s, 6H), 1.34 (s, 9H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 166.5, 156.7, 129.4, 127.4, 125.4, 68.6, 61.9, 44.1, 35.1, 32.9, 31.1; HRMS-ESI calcd for $\text{C}_{16}\text{H}_{24}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 283.1459, found 283.1460.

3-Chloro-3-methylbutyl [1,1'-biphenyl]-4-carboxylate (4). Following general procedure A using 3-methylbut-3-en-1-yl [1,1'-biphenyl]-4-carboxylate (**1c**, 53 mg, 0.2 mmol), the desired product was obtained as a white solid (52 mg, 0.17 mmol, 86%). M.p. = 70.3 – 73.3 °C; IR (ATR, diamond), $\nu = 2976, 1709, 1610, 1485, 1448, 1271, 1117, 1009, 852, 744, 696 \text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.13 – 8.07 (m, 2H), 7.69 – 7.63 (m, 2H), 7.66 – 7.59 (m, 2H), 7.50 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 4.59 (t, $J = 6.7 \text{ Hz}$, 2H), 2.27 (t, $J = 6.7 \text{ Hz}$, 2H), 1.69 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 166.3, 145.7, 139.9, 130.1, 128.9, 128.6, 128.2, 127.3, 127.1, 68.5, 62.1, 44.1, 32.9; HRMS-ESI calcd for $\text{C}_{18}\text{H}_{20}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 303.1146, found 303.1140.

3-Chloro-3-methylbutyl 4-chlorobenzoate (5). Following general procedure A using 3-methylbut-3-en-1-yl 4-chlorobenzoate (**1d**, 45 mg, 0.2 mmol), the desired product was

obtained as a colorless oil (46 mg, 0,18 mmol, 89%). Spectroscopic data agreed with the literature.¹³

3-Chloro-3-methylbutyl 4-bromobenzoate (6). Following general procedure A using 3-methylbut-3-en-1-yl 4-bromobenzoate (**1e**, 54 mg, 0.2 mmol), the desired product was obtained as a colorless oil (52 mg, 0.17 mmol, 85%). IR (ATR, diamond), $\nu = 2970, 2926, 1720, 1591, 1483, 1398, 1269, 1101, 1013, 754 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92 – 7.87 (m, 2H), 7.61 – 7.56 (m, 2H), 4.56 (t, $J = 6.8 \text{ Hz}$, 2H), 2.25 (t, $J = 6.8 \text{ Hz}$, 2H), 1.67 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 165.8, 131.8, 131.1, 129.0, 128.2, 68.3, 62.3, 44.0, 32.9; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{15}\text{BrClO}_2$ $[\text{M}+\text{H}]^+$ 304.9938, found 304.9920.

3-Chloro-3-methylbutyl 4-nitrobenzoate (7). Following general procedure A using 3-methylbut-3-en-1-yl 4-nitrobenzoate (**1f**, 47 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (50 mg, 0.18 mmol, 92%). IR (ATR, diamond), $\nu = 2976, 1724, 1609, 1526, 1348, 1271, 1117, 1101, 1014, 874, 717 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.34 – 8.26 (m, 2H), 8.24 – 8.18 (m, 2H), 4.63 (t, $J = 6.8 \text{ Hz}$, 2H), 2.28 (t, $J = 6.8 \text{ Hz}$, 2H), 1.69 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 164.6, 150.6, 135.5, 130.7, 123.6, 68.0, 63.0, 43.9, 32.9; GCMS-CI $M = 271,06$, found 272,47 ($[\text{M}+\text{H}]^+$). All tentative of HRMS (ESI, APPI) only found $\text{C}_{12}\text{H}_{14}\text{NO}_4$ $[\text{M}-\text{Cl}]^+$: calculated 236.0917, found 236.0906.

3-Chloro-3-methylbutyl 3,5-bis(trifluoromethyl)benzoate (8). Following general procedure A using 3-methylbut-3-en-1-yl 3,5-bis(trifluoromethyl)benzoate (**1g**, 65 mg, 0.2 mmol), the desired product was obtained as a colorless oil (65 mg, 0.18 mmol, 90%). IR (ATR, diamond), $\nu = 2978, 2928, 1732, 1277, 1248, 1176, 1128, 1126, 912, 770, 700 \text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 2H), 8.07 (s, 1H), 4.65 (t, $J = 7.0 \text{ Hz}$, 2H), 2.29 (t, $J = 7.0 \text{ Hz}$, 2H), 1.69 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.8, 132.3, 132.3 (q, $J = 34.2 \text{ Hz}$), 129.7 (q, $J = 3.9 \text{ Hz}$), 126.4 (hept, $J = 3.7 \text{ Hz}$), 122.9 (q, $J = 272.9 \text{ Hz}$), 67.9, 63.3, 43.8, 32.9; ^{19}F NMR (376 MHz, CDCl_3) δ -63.02 (s, 6F); HRMS-ESI calcd for $\text{C}_{14}\text{H}_{17}\text{ClF}_6\text{NO}_2$ $[\text{M}+\text{NH}_4]^+$ 380.0847, found 380.0835.

3-Chloro-3-methylbutyl furan-2-carboxylate (9). Following general procedure A using 3-methylbut-3-en-1-yl furan-2-carboxylate (**1h**, 36 mg, 0.2 mmol), the desired product was obtained as a colorless oil (41 mg, 0.19 mmol, 95%). Spectroscopic data agreed with the literature.¹³

3-Chloro-3-methylbutyl thiophene-2-carboxylate (10). Following general procedure A using 3-methylbut-3-en-1-yl thiophene-2-carboxylate (**1i**, 39 mg, 0.2 mmol), the desired product was obtained as a colorless oil (41 mg, 0.17 mmol, 87%). Spectroscopic data agreed with the literature.^{3c}

3-Chloro-3-methylbutyl nicotinate (11). Following general procedure A using 3-methylbut-3-en-1-yl nicotinate (**1j**, 38 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (42 mg, 0.19 mmol, 93%). IR (ATR, diamond), $\nu = 2974, 2928, 1720, 1591, 1420, 1277, 1111, 1024, 739, 702 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.22 (dd, $J = 2.2, 0.9 \text{ Hz}$, 1H), 8.79 (dd, $J = 4.9, 1.7 \text{ Hz}$, 1H), 8.30 (dt, $J = 7.9, 1.9 \text{ Hz}$, 1H), 7.40 (ddd, $J = 8.0, 4.8, 0.9 \text{ Hz}$, 1H), 4.61 (t, $J = 6.8 \text{ Hz}$, 2H), 2.27 (t, $J = 6.8 \text{ Hz}$, 2H), 1.69 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 165.2, 153.5, 150.9, 137.0, 126.0, 123.3, 68.2, 62.5, 43.9, 32.9; HRMS-ESI calcd for $\text{C}_{11}\text{H}_{15}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$ 228.0786, found 228.0768.

3-Chloro-3-methylbutyl tetradecanoate (12). Following general procedure A using 3-methylbut-3-en-1-yl tetradecanoate (**1k**, 59 mg, 0.2 mmol), the desired product was obtained as a colorless oil (62 mg, 0.19 mmol, 94%). IR (ATR, diamond), $\nu = 2955, 2922, 2853, 1740, 1466, 1456, 1369, 1167, 1119, 721 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.30 (t, $J = 6.9 \text{ Hz}$, 2H), 2.29 (t, $J = 7.4 \text{ Hz}$, 2H), 2.10 (t, $J = 6.9 \text{ Hz}$, 2H), 1.65 – 1.57 (m, 8H), 1.32 – 1.23 (m, 20H), 0.88 (t, $J = 6.7 \text{ Hz}$, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 173.8, 68.4, 61.3, 44.0, 34.4, 32.8, 31.9, 29.68, 29.65 (2C), 29.6, 29.5, 29.4, 29.3, 29.2, 24.9, 22.7, 14.1; HRMS-ESI calcd for $\text{C}_{19}\text{H}_{38}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 333.2555, found 333.2536.

((3-Chloro-3-methylbutoxy)methyl)benzene (13). Following general procedure A using (((3-methylbut-3-en-1-yl)oxy)methyl)benzene (**1l**, 35 mg, 0.2 mmol), the desired product was obtained as a colorless oil (38 mg, 0.18 mmol, 89%). Spectroscopic data agreed with the literature.^{3c}

3-Chloro-3-methylbutyl 4-methylbenzenesulfonate (14). Following general procedure A using 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (**1m**, 48 mg, 0.2 mmol), the desired product was obtained as a colorless oil (48 mg, 0.17 mmol, 86%). Spectroscopic data agreed with the literature.¹⁴

(3-Chloro-3-methylbutyl)benzene (15). Following general procedure A using (3-methylbut-3-en-1-yl)benzene (**1n**, 29 mg, 0.2 mmol), the desired product was obtained as a colorless oil (31 mg, 0.17 mmol, 84%). Spectroscopic data agreed with the literature.^{4a}

(4-Chloro-4-methylcyclohexyl)benzene (18). Following general procedure A using (4-methylenecyclohexyl)benzene (**1q**, 34 mg, 0.2 mmol), the desired product was obtained as a colorless oil (39 mg, 0.19 mmol, 94%, 1:6 d.r.). Spectroscopic data agreed with the literature.^{4a}

7-Chloro-3,7-dimethyloctyl acetate (19). Following general procedure A using 3,7-dimethyloct-6-en-1-ol (citronellol) (**1r**, 31.3 mg, 0.2 mmol), the desired product was obtained as a colorless oil (45.2 mg, 0.193 mmol, 96%). Spectroscopic data agreed with the literature.¹⁵

7-Chloro-3,7-dimethyloctyl benzoate (20). Following general procedure A using 3,7-dimethyloct-6-en-1-yl benzoate (**1s**, 52 mg, 0.2 mmol), the desired product was obtained as a colorless oil (57 mg, 0.19 mmol, 96%). IR (ATR, diamond), $\nu = 2943, 1717, 1452, 1313, 1271, 1176, 1111, 1026, 710 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.08 – 8.01 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 4.40 – 4.33 (m, 2H), 1.87 – 1.79 (m, 1H), 1.75 – 1.64 (m, 3H), 1.57 (s, 6H), 1.64 – 1.46 (m, 3H), 1.44 – 1.34 (m, 1H), 1.29 – 1.20 (m, 1H), 0.99 (d, $J = 6.5 \text{ Hz}$, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 166.7, 132.8, 130.5, 129.5, 128.3, 71.2, 63.4, 46.2, 36.9, 35.5, 32.5, 32.4, 29.9, 22.5, 19.5; HRMS-ESI calcd for $\text{C}_{17}\text{H}_{29}\text{ClNO}_2 [\text{M}+\text{NH}_4]^+$ 314.1881, found 314.1855.

3-Chloro-3-methylbutyl-4-d benzoate (2'). Following general procedure A using 3-methylbut-3-en-1-yl benzoate (**1a**, 38 mg, 0.2 mmol) and deuterated acetic acid ($\text{AcOD-}d_4$, 1 mL, 0.2 M), the desired product was obtained as a colorless oil (43 mg, 0.19 mmol, 94%). IR (ATR, diamond), $\nu = 2970, 2928, 1717, 1603, 1452, 1269, 1176, 1111, 1026, 708 \text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.05 – 8.02 (m, 2H), 7.59 – 7.54 (m, 1H), 7.47 – 7.42 (m, 2H), 4.57 (t, $J = 6.7 \text{ Hz}$, 2H), 2.26 (t, $J = 6.7 \text{ Hz}$, 2H), 1.69 – 1.65 (m, 5H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 166.5, 133.0, 130.2, 129.6, 128.4, 68.4 (t, $J = 7.7 \text{ Hz}$), 62.1, 44.1 (t, $J = 2.9 \text{ Hz}$), 32.9 (d, $J = 3.3 \text{ Hz}$), 32.7 (t, $J = 19.6 \text{ Hz}$); HRMS-ESI calcd for $\text{C}_{12}\text{H}_{15}\text{DClO}_2 [\text{M}+\text{H}]^+$ 228.0896, found 228.0895.

Hydrobromination reaction (General procedure B). To a solution of the alkene (0.2 mmol, 1 equiv.) in acetic acid (1 mL, 0.2 M) was added on lithium bromide (86.9 mg, 5 equiv.). Methanesulfonic acid (65 μL , 5 equiv.) was added and the reaction was stirred at

room temperature. After 4 hours, the reaction was quenched with a saturated aqueous solution of NaHCO₃ and extracted with CH₂Cl₂ (3x). The organic layers were combined and then washed with a saturated aqueous solution of Na₂CO₃, dried with Na₂SO₄, and concentrated under reduced pressure. The desired product was obtained without further purification unless otherwise noted.

3-Bromo-3-methylbutyl benzoate (21). Following general procedure B using 3-methylbut-3-en-1-yl benzoate (**1a**, 38 mg, 0.2 mmol), the desired product was obtained as a colorless oil (45.1 mg, 0.166 mmol, 83%) after purification by silica gel chromatography (10% EtOAc/Hexanes). Spectroscopic data agreed with the literature.¹⁶

3-Bromo-3-methylbutyl furan-2-carboxylate (22). Following general procedure B using 3-methylbut-3-en-1-yl furan-2-carboxylate (**1h**, 36.0 mg, 0.2 mmol), the desired product was obtained as a colorless oil (36.6 mg, 0.140 mmol, 70%) after purification by silica gel chromatography (10% EtOAc/Hexanes). Spectroscopic data agreed with the literature.¹⁷

3-Bromo-3-methylbutyl thiophene-2-carboxylate (23). Following general procedure B using 3-methylbut-3-en-1-yl thiophene-2-carboxylate (**1i**, 39.2 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (41.5 mg, 0.150 mmol, 75%) after purification by silica gel chromatography (10% EtOAc/Hexanes). IR (ATR, diamond), $\nu = 2966, 2918, 1705, 1526, 1418, 1360, 1259, 1094, 910, 860, 717 \text{ cm}^{-1}$; ¹H NMR (4.00 MHz, CDCl₃) δ

7.80 (dd, $J = 3.8, 1.3$ Hz, 1H), 7.56 (dd, $J = 5.0, 1.3$ Hz, 1H), 7.11 (dd, $J = 5.0, 3.7$ Hz, 1H), 4.56 (t, $J = 6.7$ Hz, 2H), 2.29 (t, $J = 6.7$ Hz, 2H), 1.85 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.1, 133.6, 133.5, 132.5, 127.8, 64.3, 63.3, 45.4, 34.7; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{14}\text{BrO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 276.9892, found 276.9898.

3-Bromo-3-methylbutyl 4-methylbenzenesulfonate (24). Following general procedure B using 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (**1m**, 48 mg, 0.2 mmol), the desired product was obtained as a colorless oil after purification by silica gel chromatography (15% EtOAc/Hexanes) (53.7 mg, 0.167 mmol, 83%) after purification by silica gel chromatography (15% EtOAc/Hexanes). Spectroscopic data agreed with the literature.¹⁸

(3-Bromo-3-methylbutyl)benzene (25). Following general procedure B using (3-methylbut-3-en-1-yl)benzene (**1n**, 29.3 mg, 0.2 mmol), the desired product was obtained as a colorless oil (41.8 mg, 0.184 mmol, 92%). Spectroscopic data agreed with the literature.¹⁹

(4-Bromo-4-methylcyclohexyl)benzene (26). Following general procedure B using (4-methylenecyclohexyl)benzene (**1o**, 34.5 mg, 0.2 mmol), the desired product was obtained as a white solid (46.7 mg, 0.184 mmol, 92%). Spectroscopic data agreed with the literature.²⁰

7-Bromo-3,7-dimethyloctyl acetate (27). Following general procedure B using 3,7-dimethyloct-6-en-1-ol (citronellol) (**1r**, 31.3 mg, 0.20 mmol), the desired product was obtained as a brownish oil (49.4 mg, 0.177 mmol, 88%). IR (ATR, diamond), $\nu = 2962, 1740, 1460, 1369, 1232, 1138, 1049, 737\text{cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.15 – 4.06 (m, 2H), 2.05 (s, 3H), 1.80 – 1.70 (m, 8H), 1.70 – 1.64 (m, 1H), 1.58 – 1.43 (m, 4H), 1.37 – 1.30 (m, 1H), 1.22 – 1.16 (m, 1H), 0.93 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 171.24, 68.48, 62.95, 47.68, 36.75, 35.46, 34.27, 29.74, 23.63, 21.07, 19.43; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{24}\text{BrO}_2$ $[\text{M}+\text{H}]^+$ 279.0954, found 279.0933.

7-Bromo-3,7-dimethyloctyl benzoate (28). Following general procedure B using 3,7-dimethyloct-6-en-1-yl benzoate (**1s**, 52.1 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (63.7 mg, 0.187 mmol, 93%). IR (ATR, diamond), $\nu = 2961, 2928, 1717, 1603, 1452, 1271, 1111, 1026, 710\text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.10 – 7.97 (m, 2H), 7.59 – 7.50 (m, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 4.40 – 4.34 (m, 2H), 1.85 – 1.73 (m, 3H), 1.75 (s, 6H), 1.67 – 1.49 (m, 4H), 1.44 – 1.37 (m, 1H), 1.27 – 1.21 (m, 1H), 0.99 (d, $J = 6.5$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 166.7, 132.8, 130.5, 129.5, 128.3, 68.5, 63.4, 47.7, 36.8, 35.5, 34.27, 34.26, 29.9, 23.7, 19.6; HRMS-ESI calcd for $\text{C}_{17}\text{H}_{26}\text{BrO}_2$ $[\text{M}+\text{H}]^+$ 343.1077, found 343.1092.

1,3,7-tribromo-3,7-dimethyloctane (29). Following general procedure B using (E)-3,7-dimethylocta-2,6-dien-1-ol (**geraniol**, 30.9 mg, 0.2 mmol), the desired product was obtained as a brownish oil (71.1 mg, 0.188 mmol, 94%, 85% of purity as estimated by

NMR analysis). The product is highly unstable and completely degrades within a day. IR (ATR, diamond), $\nu = 2978, 2964, 2918, 2870, 1740, 1456, 1381, 1230, 1134, 1107, 739$ cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.63 – 3.51 (m, 2H), 2.46 (ddd, $J = 14.5, 11.1, 5.4$ Hz, 1H), 2.32 (ddd, $J = 14.5, 11.0, 5.4$ Hz, 1H), 1.82 – 1.76 (m, 10H), 1.76 – 1.73 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ 70.1, 67.5, 48.3, 47.1, 45.5, 34.3, 34.2, 31.1, 28.5, 22.6. No HRMS or GC-MS could be obtained due to the instability of the compound.

Hydroiodination reaction (General procedure C). To a solution of the alkene (0.2 mmol, 1 equiv.) in acetic acid (1 mL, 0.2M) was added lithium iodide (133.9 mg, 5 equiv.). Methanesulfonic acid (65 μL , 5 equiv.) was added, and the reaction was stirred at room temperature. After 4 hours, the reaction was extracted with hexanes (3x). The organic layers were combined, dried with Na_2SO_4 , and concentrated under reduced pressure. The desired product was obtained without further purification unless otherwise noted.

3-Iodo-3-methylbutyl benzoate (30). Following general procedure C using 3-methylbut-3-en-1-yl benzoate (**1a**, 38 mg, 0.2 mmol), the desired product was obtained as a colorless oil (46 mg, 0.144 mmol, 72%) after purification by silica gel chromatography (10% EtOAc/Hexanes). Spectroscopic data agreed with the literature.²¹

3-Iodo-3-methylbutyl furan-2-carboxylate (31). Following general procedure C using 3-methylbut-3-en-1-yl furan-2-carboxylate (**1h**, 36.0 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (36.9 mg, 0.120 mmol, 60%) after purification by silica gel

chromatography (10% EtOAc/Hexanes). IR (ATR, diamond), $\nu = 3142, 2962, 2856, 1724, 1474, 1400, 1294, 1180, 1115, 1014, 762 \text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.58 (dd, $J = 1.8, 0.9 \text{ Hz}$, 1H), 7.18 (dd, $J = 3.5, 0.9 \text{ Hz}$, 1H), 6.51 (dd, $J = 3.5, 1.8 \text{ Hz}$, 1H), 4.54 (t, $J = 6.9 \text{ Hz}$, 2H), 2.15 (t, $J = 6.9 \text{ Hz}$, 2H), 2.02 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 158.5, 146.4, 144.6, 118.1, 111.9, 65.1, 48.0, 45.9, 38.5; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{14}\text{IO}_3$ $[\text{M}+\text{H}]^+$ 308.9982, found 308.9966.

3-Iodo-3-methylbutyl thiophene-2-carboxylate (32). Following general procedure C using 3-methylbut-3-en-1-yl thiophene-2-carboxylate (**1i**, 39.2 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (44.5 mg, 0.137 mmol, 69%) after purification by silica gel chromatography (10% EtOAc/Hexanes). IR (ATR, diamond), $\nu = 2959, 2910, 1705, 1526, 1418, 1358, 1277, 1257, 1225, 1092, 746, 717 \text{ cm}^{-1}$; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.80 (dd, $J = 3.7, 1.3 \text{ Hz}$, 1H), 7.56 (dd, $J = 5.0, 1.3 \text{ Hz}$, 1H), 7.11 (dd, $J = 5.0, 3.7 \text{ Hz}$, 1H), 4.54 (t, $J = 6.7 \text{ Hz}$, 2H), 2.16 (t, $J = 6.7 \text{ Hz}$, 2H), 2.03 (s, 6H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 162.0, 133.59, 133.55, 132.5, 127.8, 65.2, 48.1, 46.2, 38.5; HRMS-ESI calcd for $\text{C}_{10}\text{H}_{14}\text{IO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 324.9754, found 324.9742.

3-Iodo-3-methylbutyl 4-methylbenzenesulfonate (33). Following general procedure C using 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (**1m**, 48 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (40.3 mg, 0.109 mmol, 55%) after purification by silica gel chromatography (10% EtOAc/Hexanes). IR (ATR, diamond), $\nu = 2980, 2920, 1599, 1452, 1360, 1175, 1119, 964, 758, 662 \text{ cm}^{-1}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.81 (d,

$J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 4.27 (t, $J = 6.8$ Hz, 2H), 2.46 (s, 3H), 2.04 (t, $J = 6.8$ Hz, 2H), 1.91 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.0, 132.9, 129.9, 127.9, 70.6, 48.0, 45.0, 38.4, 21.7; HRMS-ESI calcd for $\text{C}_{12}\text{H}_{27}\text{INO}_2$ $[\text{M}+\text{NH}_4]^+$ 344.1081, found 344.1087.

(3-Iodo-3-methylbutyl)benzene (34). Following general procedure C using (3-methylbut-3-en-1-yl)benzene (**1n**, 29 mg, 0.2 mmol), the desired product was obtained as a yellowish oil (53.7 mg, 0.196 mmol, 98%). Spectroscopic data agreed with the literature.²⁰

(4-Iodo-4-methylcyclohexyl)benzene (35). Following general procedure C using (4-methylenecyclohexyl)benzene (**1o**, 34.5 mg, 0.2 mmol), the desired product was obtained as a white solid (57.9 mg, 0.193 mmol, 96%). Spectroscopic data agreed with the literature.²²

7-Iodo-3,7-dimethyloctyl acetate (36). Following general procedure C using 3,7-dimethyloct-6-en-1-ol (citronellol) (**1r**, 31 mg, 0.2 mmol), the desired product was obtained as a brownish oil (64.2 mg, 0.197 mmol, 98%) IR (ATR, diamond), $\nu = 2957, 2958, 1740, 1460, 1456, 1367, 1132, 1051, 1032$ cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.15–4.06 (m, 2H), 2.05 (s, 3H), 1.97–1.87 (m, 7H), 1.71–1.64 (m, 1H), 1.61–1.53 (m, 4H), 1.53–1.43 (m, 2H), 1.40–1.32 (m, 1H), 1.25–1.18 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 3H); ^{13}C

NMR (126 MHz, CDCl₃) δ 171.2, 62.9, 52.7, 50.6, 38.07, 38.06, 36.5, 35.5, 29.7, 25.9, 21.1, 19.4; HRMS-ESI calcd for C₁₂H₂₇INO₂ [M+NH₄]⁺ 344.1081, found 344.1087.

7-Iodo-3,7-dimethyloctyl benzoate (37). Following general procedure C using 3,7-dimethyloct-6-en-1-yl benzoate (**1s**, 52.1 mg, 0.2 mmol), the desired product was obtained as a brownish oil (77.3 mg, 0.199 mmol, 99%). IR (ATR, diamond), ν = 2957, 2868, 1717, 1450, 1269, 1109, 1026, 708 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07 – 8.02 (m, 2H), 7.58 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 4.42 – 4.33 (m, 2H), 1.97 – 1.80 (m, 7H), 1.73 – 1.66 (m, 1H), 1.64 – 1.49 (m, 5H), 1.46 – 1.39 (m, 1H), 1.29 – 1.25 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 166.7, 132.8, 130.5, 129.6, 128.3, 63.4, 52.7, 50.6, 38.1, 36.6, 35.6, 29.9, 25.9, 19.6; HRMS-ESI calcd for C₁₇H₂₆IO₂ [M+H]⁺ 389.0972, found 389.0973.

1,3,7-Triiodo-3,7-dimethyloctane (38). Following general procedure C using (E)-3,7-dimethylocta-2,6-dien-1-ol (**geraniol**, 30.9 mg, 0.2 mmol), the desired product was obtained as a brownish oil (96.3 mg, 0.185 mmol, 93%). IR (ATR, diamond), ν = 2978, 2951, 2860, 1740, 1452, 1153, 1101, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.38 – 3.28 (m, 2H), 2.40 (ddd, *J* = 14.6, 11.9, 5.1 Hz, 1H), 2.17 (ddd, *J* = 14.5, 12.1, 4.9 Hz, 1H), 1.95 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H), 1.87 – 1.82 (m, 1H), 1.76 – 1.70 (m, 2H), 1.68 – 1.62 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 57.3, 52.5, 51.3, 49.9, 47.5, 38.1, 38.0, 34.3, 26.9, 1.6. No HRMS or GC-MS could be obtained due to the instability of the compound.

3-Acetoxy-3-methylbutyl benzoate (39).

Procedure from alcohol: To a solution of 3-hydroxy-3-methylbutyl benzoate (104.2 mg, 0.5 mmol) in pyridine (1 mL, 0.5 M) was added acetic anhydride (95 μ L, 1 mmol) and 4-dimethylaminopyridine (6 mg, 0.05 mmol). The reaction was stirred overnight and then quenched with a saturated aqueous solution of NaHCO₃ and extracted with CH₂Cl₂ (3x). The organic layers were combined, dried with Na₂SO₄, and concentrated under reduced pressure. After purification by silica gel chromatography (10% EtOAc/Hexanes), the product was obtained as a colorless oil (95.4 mg, 0.38 mmol, 76%). IR (ATR, diamond), ν = 2978, 1717, 1603, 1452, 1367, 1273, 1252, 1111, 710 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.06 – 8.01 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 4.43 (t, J = 6.8 Hz, 2H), 2.28 (t, J = 6.8 Hz, 2H), 1.96 (s, 3H), 1.54 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 170.5, 166.6, 133.0, 130.2, 129.5, 128.4, 80.8, 61.2, 39.1, 26.5, 22.4; HRMS-ESI calcd for C₁₄H₂₂NO₄ [M+NH₄]⁺ 268.1549, found 268.1553.

Procedure from alkene: Methanesulfonic (65 μ L, 5 eq.) was added on a solution of 3-methylbut-3-en-1-yl benzoate (**1a**, 38 mg, 0.2 mmol) in acetic acid (1 mL, 0.2 M). After 30 minutes, the reaction was quenched with a saturated aqueous solution of NaHCO₃ and extracted with CH₂Cl₂ (3x). The organic layers were combined and then washed with a saturated aqueous solution of Na₂CO₃, dried with Na₂SO₄, and concentrated under reduced pressure. Analysis of the crude mixture with an internal standard indicated a 60% NMR yield. Spectral data agreed with the previously described procedure.

ASSOCIATED CONTENT

Supporting Information

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

NMR spectra for the known (^1H) and new compounds (^1H , ^{13}C , ^{19}F) prepared (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

¹ Solomons, T. W. G.; Fryhle, C. B.; Snyder, S. A. *Organic Chemistry*, 12th ed.; Wiley, 2016; p 340.

² a) Tanemura, K. Silica gel-mediated hydrohalogenation of unactivated alkenes using hydrohalogenic acids under organic solvent-free conditions. *Tetrahedron Lett.* **2018**, *59*, 4293–4298. b) Liang, S.; Hammond, G. B.; Xu, B. Metal-Free Regioselective Hydrochlorination of Unactivated Alkenes via a Combined Acid Catalytic System. *Green Chem.* **2018**, *20*, 680–684. c) Olah, G. A.; Hockswender, T. R. Radical Reactions. II. Lewis Base Catalyzed Anti-Markovnikov Addition of Hydrogen Bromide to Alkenes. *J. Org. Chem.* **1974**, *39*, 3478–3481. d) Nishio, Y.; Mifune, R.; Sato, T.; Ishikawa, S. ich; Matsubara, H. Preparation and Properties of a Novel Solution of Hydrogen Bromide (HBr) in 1,4-Dioxane: An Alternative Reagent to HBr Gas without Protic Solvents. *Tetrahedron Lett.* **2017**, *58*, 1190–1193. e) Galli, M.; Fletcher, C. J.; Del Pozo, M.; Goldup, S. M. Scalable Anti-Markovnikov Hydrobromination of Aliphatic and Aromatic Olefins. *Org. Biomol. Chem.* **2016**, *14*, 5622–5626. f) Li, Z.; Ebule, R.; Kostyo, J.; Hammond, G. B.; Xu, B. HBr-DMPU: The First Aprotic Organic Solution of Hydrogen Bromide. *Chem. Eur. J.* **2017**, *23*, 12739–12743.

³ a) Delaude, L.; Laszlo, P. Regioselective Hydrochlorination of Olefins Is Favored by an Acidic Solid Catalyst. *Tetrahedron Lett.* **1991**, *32*, 3705–3708. b) Yadav, V.; Ganesh. K. G. A Remarkably Efficient Markovnikov Hydrochlorination of Olefins and Transformation of Nitriles into Imidates by Use of AcCl and an Alcohol. *Eur. J. Org. Chem.* **2005**, *2005*, 452–456. c) Schevenels, F. T.; Shen, M.; Snyder, S. A. Isolable and Readily Handled Halophosphonium Pre-Reagents for Hydro- and Deuteriohalogenation. *J. Am. Chem. Soc.* **2017**, *139*, 6329–6337. d) Chen, W.; Oestreich, M. Metal-Free Transfer

Hydrobromination of C-C Triple Bonds. *Org. Lett.* **2019**, *21*, 4531–4534. e) Sanseverino, A. M.; De Mattos, M. C. S. Hydrobromination of Alkenes with PBr₃/SiO₂: A Simple and Efficient Regiospecific Preparation of Alkyl Bromides. *J. Braz. Chem. Soc.* **2001**, *12*, 685–687. f) Xiao, J.; Han, L. B. Ready Access to Organoiodides: Practical Hydroiodination and Double-Iodination of Carbon-Carbon Unsaturated Bonds with I₂. *Tetrahedron* **2019**, *75*, 3510–3515. g) Turhanen, P. A.; Vepsäläinen, J. J. A Powerful Tool for Acid Catalyzed Organic Addition and Substitution Reactions. *RSC Adv.* **2015**, *5*, 26218–26222. h) Kishan Reddy, C.; Periasamy, M. A New, Simple Procedure for the Generation and Addition of HI to Alkenes and Alkynes Using B13:N,N-Diethylaniline Complex and Acetic Acid. *Tetrahedron Lett.* **1990**, *31*, 1919–1920. i) Das, B.; Srinivas, Y.; Holla, H.; Narender, R. An Efficient and Facile Hydroiodination of Alkenes and Alkynes Using Polymethylhydrosiloxane-Iodine System. *Chem. Lett.* **2007**, *36*, 800–801. j) Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. A Facile Synthesis of Alkyl Iodides and Deuterated Alkyl Iodides by Hydroiodination and Deuterioiodination of Olefins. *Synth.* **1988**, *1988*, 366–369. k) Campos, P. J.; García, B.; Rodríguez, M. A. A Simple and Versatile Method for the Hydroiodination of Alkenes and Alkynes Using I₂ and Et₃SiH in the Presence of Copper(II). *Tetrahedron Lett.* **2002**, *43*, 6111–6112.

⁴ a) Gaspar, B.; Carreira, E. M. Catalytic Hydrochlorination of Unactivated Olefins with *Para*-Toluenesulfonyl Chloride. *Angew. Chem. Int. Ed.* **2008**, *47*, 5758–5760. b) Zeng, C.; Shen, G.; Yang, F.; Chen, J.; Zhang, X.; Gu, C.; Zhou, Y.; Fan, B. Rhodium-Catalyzed Generation of Anhydrous Hydrogen Iodide: An Effective Method for the Preparation of Iodoalkanes. *Org. Lett.* **2018**, *20*, 6859–6862. c) Shimizu, M.; Toyoda, T.; Baba, T. An

Intriguing Hydroiodination of Alkenes and Alkynes with Titanium Tetraiodide. *Synlett* **2005**, 2005, 2516–2518.

⁵ Bertrand, X.; Paquin, J. F. Direct Hydrofluorination of Methallyl Alkenes Using a Methanesulfonic Acid/Triethylamine Trihydrofluoride Combination. *Org. Lett.* **2019**, 21, 9759–9762.

⁶ For a review on the hydrofluorination of alkenes, see: Bertrand, X.; Chabaud, L.; Paquin, J. Hydrofluorination of Alkenes: A Review. *Chem. – An Asian J.* **2021**, 16, 563–574.

⁷ We used AcOH-*d*₄ for convenient and accessibility reasons, but AcOD-*d*₁ should also be compatible.

⁸ (a) Brown, H. C.; Groot, C. A Convenient Procedure for the Preparation of Deuterium Chloride. *J. Am. Chem. Soc.* **1942**, 64, 2223–2224. (b) Skell, P. S.; Allen, R. G. Stereospecific *trans* Radical Addition of DBr to the 2-Butenes. Syntheses of Erythro- and threo-3-Deuterio-2-Bromobutanes. *J. Am. Chem. Soc.* **1959**, 81, 5383–5385. (c) Dewar, J. M. S.; Fahey, R. C. Electrophilic Addition to Olefins. I. The Stereochemistry of Addition of Deuterium Halides to Acenaphthylene. *J. Am. Chem. Soc.* **1963**, 85, 2245–2248. (d) Brown, H. C.; Liu, K.-T. Additions to Bicyclic Olefins. VII. Electrophilic Addition of Hydrogen Chloride and Deuterium Chloride to Norbornene, 2-Methylenenorbornane, and Related Bicyclic Olefins. Evidence for a Carbonium Ion Process and the Capture of Unsymmetrical (Classical) 2-Norbornyl Cations. *J. Am. Chem. Soc.* **1975**, 97, 600–610. (e) Hassner, A.; Fibiger, R. F. A Convenient Method for in situ Generation of Deuterium Chloride and its Addition to Olefins. *Synthesis* **1984**, 1984, 960.

- ⁹ Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Goodfellow, R.; Granger, P. NMR nomenclature nuclear spin properties and conventions for chemical shifts. *Pure Appl. Chem.* **2001**, *73*, 1795–1818.
- ¹⁰ Wang, F.; Xu, P.; Cong, F.; Tang, P. Silver-Mediated Oxidative Functionalization of Alkylsilanes. *Chem. Sci.* **2018**, *9*, 8836–8841.
- ¹¹ Nagasawa, S.; Sasano, Y.; Iwabuchi, Y. Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts. *Angew. Chem. Int. Ed.* **2016**, *55*, 13189–13194.
- ¹² Villa, G.; Povie, G.; Renaud, P. Radical Chain Reduction of Alkylboron Compounds with Catechols. *J. Am. Chem. Soc.* **2011**, *133*, 5913–5920.
- ¹³ Lin, Z.; Lan, Y.; Wang, C. Reductive Allylic Defluorinative Cross-Coupling Enabled by Ni/Ti Cooperative Catalysis. *Org. Lett.* **2019**, *21*, 8316–8322.
- ¹⁴ Canestrari, D.; Lancianesi, S.; Badiola, E.; Strinna, C.; Ibrahim, H.; Adamo, M. F. A. Desulfurative Chlorination of Alkyl Phenyl Sulfides. *Org. Lett.* **2017**, *19*, 918–921.
- ¹⁵ Nishimoto, Y.; Yasuda, M.; Baba, A. Coupling Reaction of Alkyl Chlorides with Silyl Enolates Catalyzed by Indium Trihalide. *Org. Lett.* **2007**, *9*, 4931–4934.
- ¹⁶ Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11562–11565.
- ¹⁷ Chen, H.; Jia, X.; Yu, Y.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Allylation of Tertiary Alkyl Halides with Allylic Carbonates. *Angew. Chem. Int. Ed.* **2017**, *56*, 13103–13106.
- ¹⁸ Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of Gem-Difluoroalkenes with

Unactivated Secondary and Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2017**, *139*, 12632–12637.

¹⁹ Ajvazi, N.; Stavber, S. Direct Halogenation of Alcohols with Halosilanes under Catalyst- and Organic Solvent-Free Reaction Conditions. *Tetrahedron Lett.* **2016**, *57*, 2430–2433.

²⁰ Dudnik, A. S.; Fu, G. C. Nickel-Catalyzed Coupling Reactions of Alkyl Electrophiles, Including Unactivated Tertiary Halides, To Generate Carbon–Boron Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697.

²¹ Kiyokawa, K.; Takemoto, K.; Minakata, S. Ritter-Type Amination of C–H Bonds at Tertiary Carbon Centers Using Iodic Acid as an Oxidant. *Chem. Commun.* **2016**, *52*, 13082–13085.

²² Chierchia, M.; Xu, P.; Lovinger, G. J.; Morken, J. P. Enantioselective Radical Addition/Cross-Coupling of Organozinc Reagents, Alkyl Iodides, and Alkenyl Boron Reagents. *Angew. Chem. Int. Ed.* **2019**, *58*, 14245–14249.