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ARTICLE

Direct dihalo-alkoxylation of nitroalkenes leading to β,β-dihalo-β-nitroethyl alkyl ethers

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A highly efficient one-pot synthesis of β,β-dihalo- β -nitroethyl alkyl ethers is achieved by treatment of nitroalkenes with alcohols and *N*-halosuccinimides in the presence of sodium hydride. The notable advantages of this protocol are that it involves simple experimental manipulations and tolerates a wide range of functional groups. Further transformations of the obtained ethers, such as allylation and conversion to β,β-dihalogenated vinyl ethers, are also investigated.

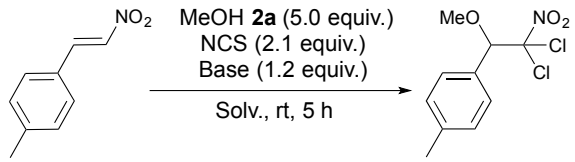
Introduction

The highly electron-deficient dihalo(nitro)methyl unit is one of the most important structural motifs found in biologically active compounds and agrochemicals.[1] The dihalo(nitro)methyl group also serves as a precursor for versatile functional groups such as dihalomethyl and amide groups.[2,3] Therefore, various approaches toward functionalized compounds containing a dihalo(nitro)methyl group have been developed, such as α,α-dihalogenation of nitroalkanes[4] and nitration of trihalonitroalkenes.[1b,5] As an alternative, dihalogenation of nitroalkenes accompanied by vicinal functionalization represents an efficient single-step approach to functionalized compounds possessing a dihalo(nitro)methyl moiety. Up to now, direct dihalo-amidation of nitroalkenes has been substantially established, using an array of nitrogen/halogen sources such as succinimide/*N*-bromosuccinimide (NBS),[6] and benzamide/NBS.[7] Direct dihalo-amidation using only *N*-bromoacetamide[8] or *N*,*N*-dichloro-*p*-toluenesulfonamide as the amido-halogenating agent[9] affords *N*-β,β-dihalo-β-nitroethylamides, which are useful precursors for functionalized 1,2-diamines.[10] While direct dihalo-amidation of nitroalkenes has been established, there is only one example of the direct halo-alkoxylation of 1-nitro-1-butene using sodium methoxide and the toxic bromine, and the substrate scope has not been investigated further.[1e] Meanwhile, we have disclosed a direct methoxy-chlorination of 1-methyl-3-nitro-2-quinolones using sodium methoxide and *N*-chlorosuccinimide (NCS).[11] On the basis of these results, we envisage that reactions of nitroalkenes with sodium alkoxide generated *in situ*[12] and readily treatable *N*-halosuccinimide facilitate the direct dihalo-alkoxylation under mild conditions, leading to diverse β,β-dihalo-β-nitroethyl alkyl ethers, which are often found as motifs in biologically active compounds.[1a,e]

Results and discussion

To evaluate the potential for vicinal functionalization, β-nitrostyrene **1a** was chosen as a model substrate. The reaction of **1a** with MeOH **2a** and NCS in the presence of *t*-BuOK in THF

Table 1 Optimization of reaction conditions



1a **3a**

Entry	Solv.	Base	Yield[a] (%)	Recov.[a] (%)
1	THF	*t*-BuOK	21	0
2	MeCN	*t*-BuOK	20	0
3	DMF	*t*-BuOK	6	0
4	MeOH	*t*-BuOK	24	0
5	Et_2O	*t*-BuOK	43	10
6	toluene	*t*-BuOK	35	10
7	$ClCH_2CH_2Cl$	*t*-BuOK	29	15
8	cyclohexane	*t*-BuOK	11	4
9	$CHCl_3$	*t*-BuOK	25	28
10	CH_2Cl_2	*t*-BuOK	51	0
11	CH_2Cl_2	Et_3N	0	100
12	CH_2Cl_2	DBU	c.m.[b]	-
13	CH_2Cl_2	NaOH	trace	0
14	CH_2Cl_2	Cs_2CO_3	trace	0
15	CH_2Cl_2	BuLi	21	0
16	CH_2Cl_2	NaH	97	0
17[c]	CH_2Cl_2	NaH	95 (90[d])	0

[a]Yield and recovery were determined by ^{1}H NMR of the reaction mixture using $C_2H_2Cl_4$ as internal standard. [b]Complex mixture. [c]The reaction involved 2.0 equiv. of MeOH. [d]Isolated yield.

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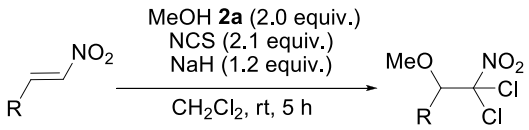
Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra data for all new products. See DOI: 10.1039/x0xx00000x

successfully afforded β,β-dichloro-β-nitroethyl methyl ether **3a** in 21% yield.[13] Aprotic solvents were more suitable for this reaction, and the yield increased to 51% when the reaction was conducted in CH_2Cl_2 (entries 1–10). In addition to *t*-BuOK, several other organic and inorganic bases were screened (entries 11–16). Although most of these bases were not effective, the yield increased to 97% when using sodium hydride, which facilitated a lower loading of MeOH without any influence on the yield (entries 16–17). Overall, the reaction conditions used in entry 16 were determined to be optimal.

With the optimized reaction conditions in hand, we screened a wide array of nitroalkenes (Table 2). Nitrostyrenes possessing an electron-donating Me or MeO group as well as a weakly electron-withdrawing Cl or Br group on the aromatic ring efficiently underwent the reaction (entries 1–7). On the other hand, β-nitrostyrene **1h** with a strongly electron-withdrawing CN group afforded the corresponding ether in a relatively low yield, and the introduction of a NO_2 group led to a complex mixture (entries 8 and 9). Additionally, the bulky naphthylnitroalkene **1j** with extended conjugation smoothly underwent dichloro-methoxylation to furnish **3j** in a good yield. While nitroalkenes with electron-rich thienyl and furyl groups afforded the corresponding ethers in good yields, the reaction of **1m** gave the dichloro-methoxylated pyridine **3m** in reduced yield (entries 10–13). When conjugated nitroalkene **1n** was subjected to this protocol, the dichloro-methoxylation regioselectively proceeded at the double bond of the nitroalkene, furnishing **3n** in 81% yield (entry 14). This protocol was also amenable to aliphatic nitroalkene **1o**, affording ether **3o** in 71% yield (entry 15).

Table 2 Dichloromethoxylation of various nitroalkenes



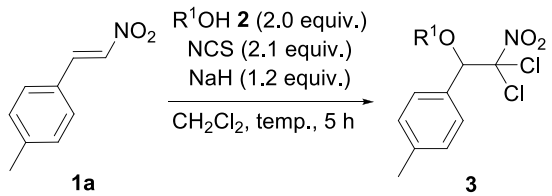
1 **3**

Entry	R		Yield[a] (%)
1	4-MeC_6H_4	**a**	90
2	4-$MeOC_6H_4$	**b**	89
3	2-$MeOC_6H_4$	**c**	76
4	3,5-$(MeO)_2C_6H_3$	**d**	79
5	C_6H_5	**e**	75
6	4-BrC_6H_4	**f**	73
7	4-ClC_6H_4	**g**	65
8	4-NCC_6H_4	**h**	42
9	4-$O_2NC_6H_4$	**i**	c.m.[b]
10	2-naphthyl	**j**	62
11	2-thienyl	**k**	75
12	2-furyl	**l**	71
13	3-pyridyl	**m**	36
14	PhCH=CH	**n**	81
15	$PhCH_2CH_2$	**o**	71

[a]Isolated yield. [b]Complex mixture.

Next, the scope of this protocol was expanded to other alcohols such as ethanol, propanol, and benzyl alcohol, which afforded the corresponding products **3p**–**r** in good yields (Table 3, entries 2–4). However, alcohols such as 2-phenylethanol **2s** and 3-methylbutanol **2t** were not sufficiently converted to the alkoxides, as release of hydrogen gas was not observed. This issue was overcome by conducting the reaction at a higher temperature to furnish **3s** and **3t** in higher yields, respectively (entries 5 and 6). While the bulky isopropanol **2u** gave **3u** in 42% yield, the bulkier *tert*-butanol **2v** furnished a highly complex mixture (entries 7 and 8). When alcohols **2w**–**y** possessing 2,2,2-trifluoro, allyl, and propargyl groups were used under the optimized reaction conditions, complex mixtures with low yields of the target products **3w**–**y** were obtained (entries 9–11). This problem was easily addressed by conducting the reaction at a lower temperature. Gratifyingly, the tolerance of the allyl and propargyl groups allowed for further chemical transformations. The feasibility of using a phenol in this transformation was also examined; however, a complex mixture was obtained without any trace of **3z** (entry 12).

Table 3 Study on the alcohol scope



1a **3**

Entry	R^1	Temp. (°C)	Product	Yield[a] (%)
1	Me	rt	**3a**	90
2	Et	rt	**3p**	80
3	Pr	rt	**3q**	75
4	4-$MeOC_6H_4CH_2$	rt	**3r**	83
5	$C_6H_5CH_2CH_2$	rt[c]	**3s**	49
6	3-methylbutyl	rt[c]	**3t**	45
7	*i*-Pr	rt	**3u**	42
8	*t*-Bu	rt	**3v**	c.m.[b]
9	CF_3CH_2	-10	**3w**	46
10	allyl	-10	**3x**	72
11	propargyl	-10	**3y**	45
12	C_6H_5	rt	**3z**	c.m.[b]

[a]Isolated yield. [b]Complex mixture. [c]Sodium alkoxides were prepared upon treatment of alcohols (5.0 equiv.) with NaH (1.2 equiv.) at 70 °C for 30 min, and then were reacted with **1a** and NCS in CH_2Cl_2 at room temperature.

In order to expand the scope of this protocol, other halogenating reagents were also employed (Scheme 1). The reaction using NBS afforded β,β-dibromo-β-nitroethyl methyl ether **4a** in excellent yield. However, diiodo-methoxylation did not occur in the case of NIS. Instead, monoiodinated product **6a** and protonated product **7a** were obtained in 35% and 15% yields, respectively, which might be due to the higher steric hindrance of the iodo group than that of the bromo group. In the case of *N*-fluorobenzenesulfonimide, a small amount of monofluorinated product **9a** was obtained without any detectable difluorinated product **8a**. When a mixture of NCS

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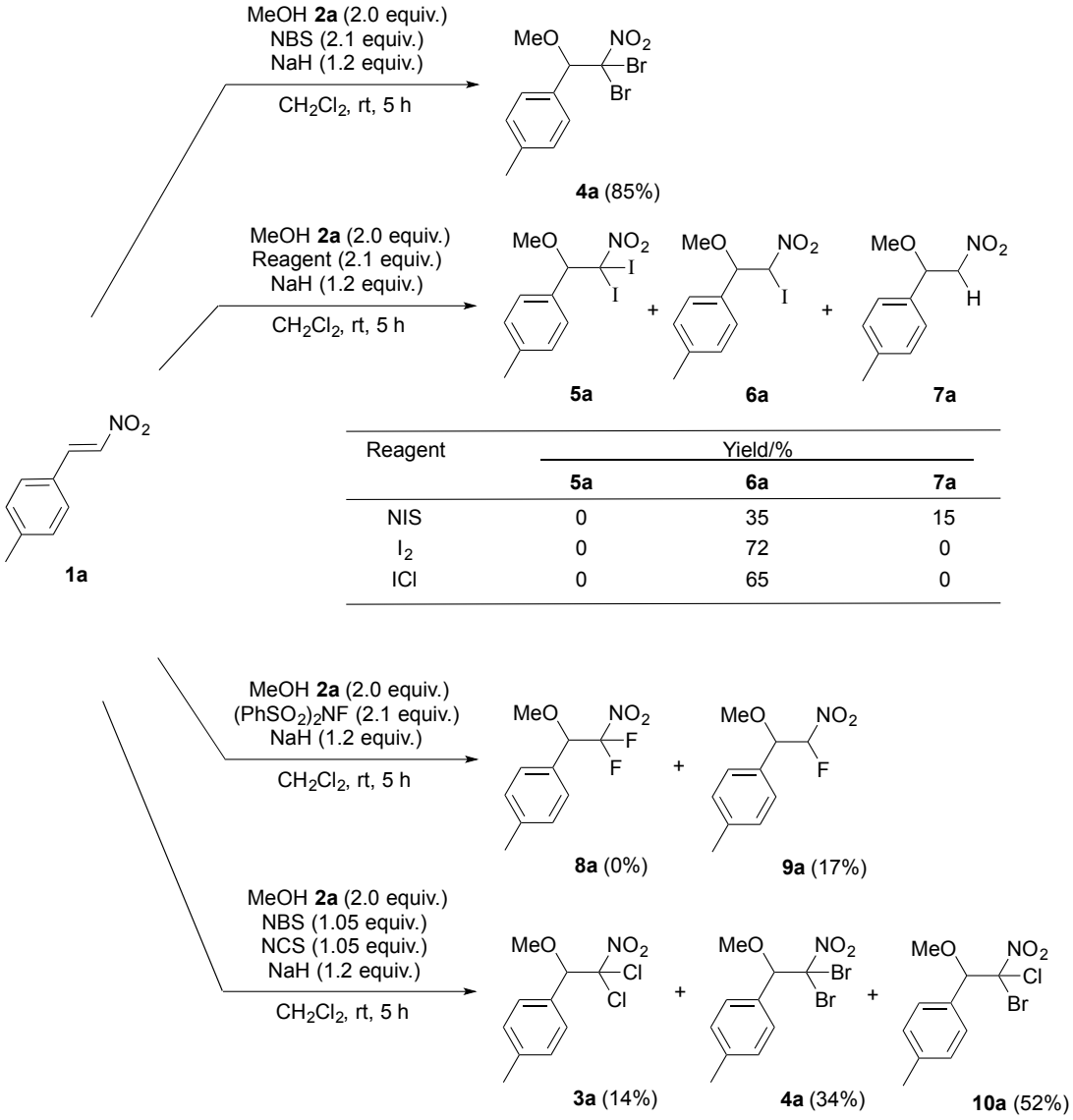
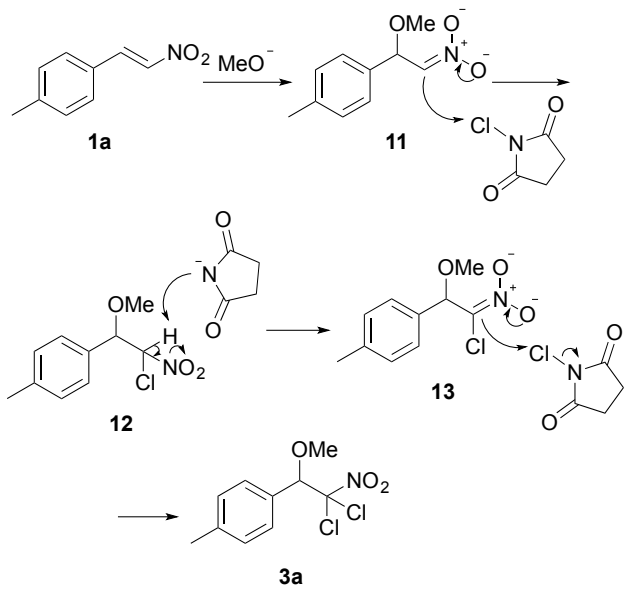


Reagent	Yield/%		
	5a	**6a**	**7a**
NIS	0	35	15
I_2	0	72	0
ICl	0	65	0

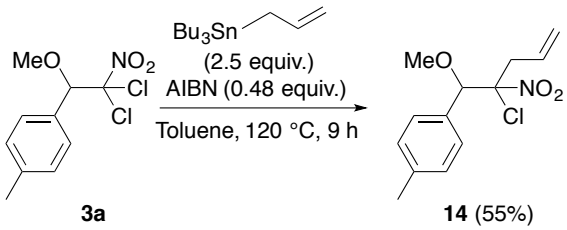
Scheme 1 Reactions involving various halogenating reagents

and NBS was used, dichlorinated product **3a**, dibrominated product **4a**, and chloro-brominated product **10a** were furnished in 14:34:52 ratio. However, **10a** could not be isolated from the reaction mixture despite several attempts, owing to the similar properties with **3a** and **4a**. In addition to the abovementioned *N*-haloamides, other halogenating reagents were also scanned in this reaction. While sodium hypochlorite hydrate yielded dichlorinated product **3a** in 75% yield, iodine and iodine monochloride increased the yield of mono-iodinated product **6a** to 72% and 65% yields, respectively.

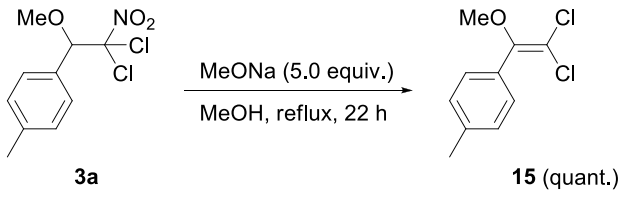


Scheme 2 A plausible mechanism for the formation of **3a**

On the basis of the above results, a plausible mechanism for the dihalo-alkoxylation is proposed (Scheme 2). The conjugate addition of sodium methoxide generated *in situ* from methanol **2a**, to nitrostyrene **1a** affords nitronate **11**. The reaction of **11** with NCS facilitates chlorination by nucleophilic substitution, affording mono-chlorinated intermediate **12**. The subsequent deprotonation and chlorination of **13** leads to the formation of β,β-dihalo-β-nitroethyl alkyl ether **3a**. Another reaction mechanism including a single-electron transfer from nitronate to NCS is also acceptable. When *p*-nitrophenyl substrate **1i** was used, no target product **3i** was not be detected (Table 2, entry 9). Since there is a possibility that good electron acceptor **1i** inhibited the single-electron transfer, the latter mechanism could not be excluded.



Scheme 3 Allylation of **3a**



Scheme 4 Elimination of nitrous acid from **3a**

Finally, to illustrate the synthetic potential of this protocol, the convertion of the resultant ethers **3** possessing a dihalo(nitro)methyl group into other useful building blocks was investigated. The reaction of **3a** with allyltributyltin in the presence of azobis(isobutyronitrile) (AIBN) afforded allylated product **14** in 55% yield,[14] leading to a extended structure with a chloronitromethene group existing in a variety of pharmaceuticals (Scheme 3).[1d,e,15] Moreover, **3a** underwent elimination of nitrous acid upon treatment with sodium methoxide to furnish 1,1-dichloro-2-methoxyethene **15** which can be further converted into other useful compounds (Scheme 4).[16]

Conclusions

A facile and efficient approach to β,β-dihalo-β-nitroethyl alkyl ethers was developed upon treatment of nitroalkenes with alcohols and *N*-halosuccinimides in the presence of sodium hydride under mild conditions. The synthetic utility was demonstrated by the transformation of the obtained ether **3a** into other useful compounds through allylation of the dihalo(nitro)methyl group and elimination of nitrous acid, respectively. Further efforts about the application of this protocol for preparing versatile functionalized compounds are ongoing in our group.

Experimental

Experimental section

The melting points were determined on SRS-Optimelt Automated Melting Point System, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with tetramethylsilane as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The high-resolution mass spectra were measured on an AB SCIEX Triple TOF 4600. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer.

General procedure for the preparation of nitroalkenes

(*E*)-Aromatic nitroalkenes **1a**–**n** were synthesized in moderate to good yields upon treatment of aromatic aldehydes with nitromethane in the presence of ammonium acetate.[17] Aliphatic nitroalkene **1o** was prepared through the condensation reaction of aliphatic aldehyde with nitromethane in the presence of sodium hydroxide followed by MsCl–mediated dehydration.[18]

General procedure for one-pot synthesis of β,β-dihalo-β-nitroethyl alkyl ethers 3

1-(2,2-Dichloro-1-methoxy-2-nitroethyl)-4-methylbenzene (3a). To a solution of sodium hydride (60% dispersion in mineral oil, 14.7 mg, 0.37 mmol) in CH_2Cl_2 (1.7 mL), were added MeOH **2a** (24.9 μL, 0.61 mmol), (*E*)-β-nitrostyrene **1a** (50.0 mg, 0.31 mmol), and NCS (86.0 mg, 0.64 mmol) successively. The resultant mixture was stirred at room temperature for 5 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow oil, which was treated by column chromatography on silica gel to afford β,β-dichloro-β-

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nitroethyl methyl ether **3a** (eluted with CH_2Cl_2/hexane = 1/5, 72.0 mg, 0.27 mmol, 90% yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.28 (s, 3H), 3.15 (s, 3H), 5.37 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6,, 100 MHz) δ 20.8 (CH_3), 57.5 (CH_3), 86.1 (CH), 114.6 (C), 128.6 (C), 128.8 (CH), 129.4 (CH), 139.5 (C); IR (ATR/cm^{-1}) ν 1330, 1587; HRMS (ESI/TOF) Calcd for $C_{10}H_{12}Cl_2NO_3$ [(M+H)$^+$]: 264.0189, found 264.0187.

When other nitroalkenes **1**, alcohols **2**, and halogenating reagents were used, experiments were conducted in a similar way.

1-(2,2-Dichloro-1-methoxy-2-nitroethyl)-4-methoxybenzene (3b). Colorless oil (75.9 mg, 0.27 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (s, 3H), 3.84 (s, 3H), 5.16 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.3 (CH_3), 57.9 (CH_3), 87.4 (CH), 113.8 (CH), 114.8 (C), 123.5 (C), 130.8 (CH), 161.0 (C); IR (ATR/cm^{-1}) ν 1330, 1585; HRMS (ESI/TOF) Calcd for $C_{10}H_{11}Cl_2NO_4Na$ [(M+Na)$^+$]: 301.9957, found 301.9960.

1-(2,2-Dichloro-1-methoxy-2-nitroethyl)-2-methoxybenzene (3c). Colorless oil (64.5 mg, 0.23 mmol, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.25 (s, 3H), 3.88 (s, 3H), 5.91 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.41 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5 (CH_3), 57.8 (CH_3), 79.8 (CH), 110.7 (CH), 115.0 (C), 120.5 (C), 120.6 (CH), 129.6 (CH), 131.1 (CH), 158.8 (C); IR (ATR/cm^{-1}) ν 1337, 1585; HRMS (ESI/TOF) Calcd for $C_{10}H_{11}Cl_2NO_4Na$ [(M+Na)$^+$]: 301.9957, found 301.9959.

1-(2,2-Dichloro-1-methoxy-2-nitroethyl)-3,5-dimethoxybenzene (3d). Colorless oil (74.2 mg, 0.24 mmol, 79%). ^{1}H NMR (CDCl3, 400 MHz) δ 3.33 (s, 3H), 3.82 (s, 6H), 5.13 (s, 1H), 6.54 (t, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5 (CH_3), 55.5 (CH_3), 58.2 (CH_3), 87.6 (CH), 101.7 (CH), 107.7 (CH), 114.4 (C), 134.0 (C), 160.6 (C); IR (ATR/cm^{-1}) ν 1318, 1586; HRMS (ESI/TOF) Calcd for $C_{11}H_{13}Cl_2NO_5Na$ [(M+Na)$^+$]: 332.0063, found 332.0068.

(2,2-Dichloro-1-methoxy-2-nitroethyl)benzene (3e). Colorless oil (56.9 mg, 0.23 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.31 (s, 3H), 5.21 (s, 1H), 7.43–7.45 (m, 3H), 7.55–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.1 (CH_3), 87.6 (CH), 114.5 (C), 128.3 (CH), 129.5 (CH), 130.0 (CH), 131.8 (C); IR (ATR/cm^{-1}) ν 1336, 1586; HRMS (ESI/TOF) Calcd for $C_9H_{10}Cl_2NO_3$ [(M+H)$^+$]: 250.0032, found 250.0031.

1-Bromo-4-(2,2-dichloro-1-methoxy-2-nitroethyl)benzene (3f). Colorless oil (72.8 mg, 0.22 mmol, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.31 (s, 3H), 5.18 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.2 (CH_3), 87.1 (CH), 113.9 (C), 124.5 (C), 130.9 (C), 131.1 (CH), 131.6 (CH); IR (ATR/cm^{-1}) ν 1336, 1587; HRMS (ESI/TOF) Calcd for $C_9H_9BrCl_2NO_3$ [(M+H)$^+$]: 327.9137, found 327.9129.

1-Chloro-4-(2,2-dichloro-1-methoxy-2-nitroethyl)benzene (3g). Colorless oil (56.0 mg, 0.20 mmol, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.31 (s, 3H), 5.20 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.2 (CH_3), 87.0 (CH), 114.1 (C), 128.7 (CH), 130.4 (C), 130.8 (CH), 136.3 (C); IR (ATR/cm^{-1}) ν 1341, 1587; HRMS (ESI/TOF) Calcd for $C_9H_9Cl_3NO_3Na$ [(M+Na)$^+$]: 306.9540, found 306.9555.

4-(2,2-Dichloro-1-methoxy-2-nitroethyl)benzonitrile (3h). Colorless oil (35.2 mg, 0.13 mmol, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (s, 3H), 5.29 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.6 (CH_3), 86.9 (CH), 113.4 (C), 114.2 (C), 118.1 (C), 130.2 (CH), 132.1 (CH), 137.2 (C); IR (ATR/cm^{-1}) ν 1341, 1587, 2232; HRMS (ESI/TOF) Calcd for $C_{10}H_9Cl_2N_2O_3$ [(M+H)$^+$]: 274.9985, found 274.9973.

2-(2,2-Dichloro-1-methoxy-2-nitroethyl)naphthalene (3j). Colorless oil (56.4 mg, 0.19 mmol, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (s, 3H), 5.39 (s, 1H), 7.52–7.57 (m, 2H), 7.67 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.87–7.91 (m, 3H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.2 (CH_3), 87.8 (CH), 114.6 (C), 125.9 (CH), 126.6 (CH), 127.2 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.3 (C), 130.0 (CH), 132.7 (C), 134.1 (C); IR (ATR/cm^{-1}) ν 1340, 1587; HRMS (ESI/TOF) Calcd for $C_{13}H_{11}Cl_2NO_3Na$ [(M+Na)$^+$]: 322.0008, found 322.0017.

2-(2,2-Dichloro-1-methoxy-2-nitroethyl)thiophene (3k). Colorless oil (58.6 mg, 0.23 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.37 (s, 3H), 5.49 (s, 1H), 7.08 (dd, *J* = 4.0, 4.8 Hz, 1H), 7.30 (d, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.3 (CH_3), 84.6 (CH), 113.9 (C), 126.7 (CH), 128.4 (CH), 130.4 (CH), 134.4 (C); IR (ATR/cm^{-1}) ν 1333, 1586; HRMS (ESI/TOF) Calcd for $C_7H_8Cl_2NO_3S$ [(M+H)$^+$]: 255.9597, found 255.9604.

2-(2,2-Dichloro-1-methoxy-2-nitroethyl)furan (3l). Colorless oil (51.9 mg, 0.22 mmol, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.36 (s, 3H), 5.33 (s, 1H), 6.48 (dd, *J* = 1.6, 3.2 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.3 (CH_3), 82.3 (CH), 110.8 (CH), 112.6 (C), 112.7 (CH), 144.3 (CH), 146.0 (C); IR (ATR/cm^{-1}) ν 1334, 1587; HRMS (ESI/TOF) Calcd for $C_7H_8Cl_2NO_4$ [(M+H)$^+$]: 239.9825, found 239.9827.

2-(2,2-Dichloro-1-methoxy-2-nitroethyl)pyridine (3m). Colorless oil (27.6 mg, 0.11 mmol, 36%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (s, 3H), 5.28 (s, 1H), 7.41 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.71 (d, *J* = 4.8 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.5 (CH_3), 85.8 (CH), 113.7 (C), 123.3 (CH), 128.0 (C), 136.7 (CH), 150.8 (CH), 151.3 (CH); IR (ATR/cm^{-1}) ν 1334, 1587; HRMS (ESI/TOF) Calcd for $C_8H_9Cl_2N_2O_3$ [(M+H)$^+$]: 250.9985, found 250.9997.

(*E*)-(4,4-Dichloro-3-methoxy-4-nitrobut-1-enyl)benzene (3n). Colorless oil (68.3 mg, 0.25 mmol, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.40 (s, 3H), 4.73 (d, *J* = 7.6 Hz, 1H), 6.13 (dd, *J* = 7.6, 16.0 Hz, 1H), 6.89 (d, *J* = 16.0 Hz, 1H), 7.32–7.40 (m, 3H), 7.47 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.8 (CH_3), 87.6 (CH), 113.6 (C), 119.7 (CH), 127.1 (CH), 128.8 (CH), 129.1 (CH), 135.1 (C), 139.7 (CH); IR (ATR/cm^{-1}) ν 1332, 1587; HRMS (ESI/TOF) Calcd for $C_{11}H_{12}Cl_2NO_3$ [(M+H)$^+$]: 276.0189, found 276.0187.

(4,4-Dichloro-3-methoxy-4-nitrobutyl)benzene (3o). Colorless oil (63.3 mg, 0.22 mmol, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03–2.12 (m, 1H), 2.18–2.26 (m, 1H), 2.72–2.80 (m, 1H), 2.93–3.00 (m, 1H), 3.48 (s, 3H), 4.20 (dd, *J* = 2.4, 9.6 Hz, 1H), 7.22–7.25 (m, 3H), 7.33 (dd, *J* = 7.6, 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.9 (CH_2), 33.1 (CH_2), 61.4 (CH_3), 86.8 (CH), 115.1 (C), 126.5 (CH), 128.3 (CH), 128.7 (CH), 140.2 (C); IR (ATR/cm^{-1}) ν 1327, 1583; HRMS (ESI/TOF) Calcd for $C_{11}H_{13}Cl_2NO_3Na$ [(M+Na)$^+$]: 300.0165, found 300.0174.

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1-(2,2-Dichloro-1-ethoxy-2-nitroethyl)-4-methylbenzene (3p). Colorless oil (67.4 mg, 0.24 mmol, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 3.38–3.45 (m, 1H), 3.47–3.54 (m, 1H), 5.27 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 21.3 (CH_3), 66.2 (CH_2), 85.8 (CH), 114.9 (C), 129.0 (CH), 129.4 (CH), 129.7 (C), 139.9 (C); IR (ATR/cm^{-1}) ν 1326, 1587; HRMS (ESI/TOF) Calcd for $C_{11}H_{13}Cl_2NO_3Na$ [(M+Na)$^+$]: 300.0165, found 300.0179.

1-(2,2-Dichloro-2-nitro-1-propoxyethyl)-4-methylbenzene (3q). Colorless oil (66.3 mg, 0.23 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.53 (ddq, *J* = 6.4, 6.4, 7.2 Hz, 2H), 2.39 (s, 3H), 3.29 (dt, *J* = 6.4, 13.2 Hz, 1H), 3.41 (dt, *J* = 6.4, 13.2 Hz, 1H), 5.25 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.3 (CH_3), 21.3 (CH_3), 22.6 (CH_2), 72.3 (CH_2), 86.1 (CH), 114.9 (C), 128.9 (CH), 129.4 (CH), 129.6 (C), 139.9 (C) ; IR (ATR/cm^{-1}) ν 1327, 1587; HRMS (ESI/TOF) Calcd for $C_{12}H_{15}Cl_2NO_3Na$ [(M+Na)$^+$]: 314.0321, found 314.0333.

1-[2,2-dichloro-1-(4-methoxybenzyloxy)-2-nitroethyl]-4-methylbenzene (3r). Colorless oil (93.8 mg, 0.25 mmol, 83%). ^{1}H NMR (CDCl3, 400 MHz) δ 2.41 (s, 3H), 3.80 (s, 3H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 5.28 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 55.3 (CH_3), 71.4 (CH_2), 84.5 (CH), 113.9 (CH), 115.0 (C), 127.9 (C), 129.0 (C), 129.1 (CH), 129.7 (CH), 129.9 (CH), 140.1 (C), 159.7 (C); IR (ATR/cm^{-1}) ν 1325, 1587; HRMS (ESI/TOF) Calcd for $C_{17}H_{17}Cl_2NO_4Na$ [(M+Na)$^+$]: 392.0427, found 392.0442.

1-[(2,2-Dichloro-2-nitro-1-(2-phenylethoxy)ethyl]-4-methyl benzene (3s). Colorless oil (52.6 mg, 0.15 mmol, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 2.81 (dd, *J* = 6.8, 6.8 Hz, 2H), 3.53–3.63 (m, 2H), 5.27 (s, 1H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.20–7.27 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 36.0 (CH_2), 71.2 (CH_2), 86.1 (CH), 114.7 (C), 126.4 (CH), 128.3 (CH), 128.9 (CH), 129.0 (CH), 129.2 (C), 129.4 (CH), 138.0 (C), 140.0 (C); IR (ATR/cm^{-1}) ν 1328, 1587; HRMS (ESI/TOF) Calcd for $C_{17}H_{17}Cl_2NO_3Na$ [(M+Na)$^+$]: 376.0478, found 376.0493.

1-[2,2-Dichloro-1-(3-methylbutoxy)-2-nitroethyl]-4-methyl benzene (3t). Colorless oil (43.7 mg, 0.14 mmol, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 1.33–1.47 (m, 2H), 1.58–1.68 (m, 1H), 2.39 (s, 3H), 3.32–3.38 (m, 1H), 3.43–3.48 (m, 1H), 5.24 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 22.3 (CH_3), 22.5 (CH_3), 24.7 (CH), 38.1 (CH_2), 69.1 (CH_2), 86.1 (CH), 114.9 (C), 128.9 (CH), 129.4 (CH), 129.6 (C), 139.9 (C); IR (ATR/cm^{-1}) ν 1326, 1588; HRMS (ESI/TOF) Calcd for $C_{14}H_{19}Cl_2NO_3Na$ [(M+Na)$^+$]: 342.0634, found 342.0646.

1-(2,2-Dichloro-1-isopropoxy-2-nitroethyl)-4-methylbenzene (3u). Colorless oil (37.6 mg, 0.13 mmol, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 2.39 (s, 3H), 3.60 (qq, *J* = 6.4, 6.4 Hz, 1H), 5.33 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (CH_3), 21.2 (CH_3), 22.9 (CH_3), 72.5 (CH), 84.1 (CH), 115.4 (C), 128.8 (CH), 129.4 (CH), 130.6 (C), 139.8 (C); IR (ATR/cm^{-1}) ν 1324, 1587; HRMS (ESI/TOF) Calcd for $C_{12}H_{15}Cl_2NO_3Na$ [(M+Na)$^+$]: 314.0321, found 314.0331.

1-[2,2-Dichloro-2-nitro-1-(2,2,2-trifluoroethoxy)ethyl]-4-methylbenzene (3w). Colorless oil (46.2 mg, 0.14 mmol, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 3.70–3.87 (m, 2H), 5.46 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 66.8 (q, *J* = 35.2 Hz, CH_2), 86.6 (CH), 113.9 (C), 123.0 (q, *J* = 277.0 Hz, CF_3), 127.3 (C), 129.3 (CH), 129.4 (CH), 140.9 (C); IR (ATR/cm^{-1}) ν 1331, 1590; HRMS (ESI/TOF) Calcd for $C_{11}H_{10}Cl_2F_3NO_3Na$ [(M+Na)$^+$]: 353.9882, found 353.9892.

1-[1-(3-propenyloxy)-2,2-dichloro-2-nitroethyl]-4-methyl benzene (3x). Colorless oil (63.8 mg, 0.22 mmol, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 3.82 (dddd, *J* = 1.2, 1.2, 6.8, 12.8 Hz, 1H), 4.03 (dddd, *J* = 1.2, 1.2, 5.2, 12.8 Hz, 1H), 5.15–5.20 (m, 2H), 5.33 (s, 1H), 5.71–5.81 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 70.8 (CH_2), 84.8 (CH), 114.9 (C), 118.7 (CH_2), 129.0 (CH), 129.1 (C), 129.5 (CH), 132.7 (CH), 140.1 (C); IR (ATR/cm^{-1}) ν 1339, 1587; HRMS (ESI/TOF) Calcd for $C_{12}H_{13}Cl_2NO_3Na$ [(M+Na)$^+$]: 312.0165, found 312.0176.

1-[2,2-Dichloro-2-nitro-1-(prop-2-ynyloxy)ethyl]-4-methyl benzene (3y). Colorless oil (39.0 mg, 0.14 mmol, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 2.47 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.96 (dd, *J* = 2.4, 16.0 Hz, 1H), 4.25 (dd, *J* = 2.4, 16.0 Hz, 1H), 5.57 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 56.8 (CH_2), 76.4 (CH), 77.1 (C), 84.1 (CH), 114.7 (C), 128.0 (C), 129.2 (CH), 129.7 (CH), 140.4 (C); IR (ATR/cm^{-1}) ν 1333, 1589, 2124; HRMS (ESI/TOF) Calcd for $C_{12}H_{11}Cl_2NO_3Na$ [(M+Na)$^+$]: 310.0008, found 310.0018.

1-(2,2-Dibromo-1-methoxy-2-nitroethyl)-4-methylbenzene (4a). Colorless oil (91.1 mg, 0.26 mmol, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 3.31 (s, 3H), 5.13 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 57.9 (CH_3), 88.1 (CH), 93.3 (C), 128.9 (CH), 129.4 (C), 129.8 (CH), 140.0 (C); IR (ATR/cm^{-1}) ν 1329, 1576; HRMS (ESI/TOF) Calcd for $C_{10}H_{11}Br_2NO_3Na$ [(M+Na)$^+$]: 373.8998, found 373.9016.

1-(2-Iodo-1-methoxy-2-nitroethyl)-4-methylbenzene (6a). Colorless oil (33.8 mg, 0.11 mmol, 35%). A pair of diastereoisomers were detected with a ratio of 76/24. ^{1}H NMR ($CDCl_3$, 400 MHz) of the major isomer: δ 2.39 (s, 3H), 3.22 (s, 3H), 4.82 (d, *J* = 10.0 Hz, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 57.3 (CH), 57.9 (CH_3), 86.0 (CH), 128.3 (CH), 129.5 (CH), 131.2 (C), 139.8 (C). ^{1}H NMR ($CDCl_3$, 400 MHz) of the minor isomer: δ 2.24 (s, 3H), 3.33 (s, 3H), 4.57 (d, *J* = 7.6 Hz, 1H), 6.24 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2 (CH_3), 57.5 (CH), 60.0 (CH_3), 84.1 (CH), 127.4 (CH), 129.7 (CH), 131.2 (C), 139.8 (C); IR (ATR/cm^{-1}) ν 1351, 1559; HRMS (ESI/TOF) Calcd for $C_{10}H_{12}INO_3Na$ [(M+Na)$^+$]: 343.9754, found 343.9756.

1-(1-Methoxy-2-nitroethyl)-4-methylbenzene (7a). Colorless oil (9.0 mg, 0.05 mmol, 15%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.26 (s, 3H), 4.37 (dd, *J* = 3.2, 12.8 Hz, 1H), 4.60 (dd, *J* = 10.0, 12.8 Hz, 1H), 4.91 (dd, *J* = 3.2, 10.0 Hz, 1H), 7.21 (d, *J* =

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8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2 (CH_3), 57.0 (CH_3), 79.9 (CH), 80.5 (CH_2), 126.8 (CH), 129.7 (CH), 132.9 (C), 139.1 (C); IR (ATR/cm^{-1}) ν 1330, 1559; HRMS (ESI/TOF) Calcd for $C_{10}H_{13}NO_3Na$ [(M+Na)$^+$]: 218.0788, found 218.0796.

1-(2-Fluoro-1-methoxy-2-nitroethyl)-4-methylbenzene (9a). Colorless oil (11.1 mg, 0.05 mmol, 17%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 3.31 (s, 3H), 4.68 (dd, *J* = 5.6, 13.6 Hz, 1H), 5.84 (dd, *J* = 5.6, 50.0 Hz, 1H), 7.23–7.24 (d, 4H, overlap); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 57.4 (CH_3), 81.6 (d, *J* = 22.8 Hz, CH), 111.1 (d, *J* = 238.9 Hz, CH), 127.8 (CH), 129.5 (C), 129.7 (CH), 139.9 (C); IR (ATR/cm^{-1}) ν 1346, 1515; HRMS (ESI/TOF) Calcd for $C_{10}H_{12}FNO_3Na$ [(M+Na)$^+$]: 236.0693, found 236.0704.

Allylation of 3a

To a solution of **3a** (51.9 mg, 0.20 mmol) in toluene (1.6 mL), were added allyltributyltin (151.2 μL, 0.49 mmol) and azobis(isobutyronitrile) (0.1 mmol, 15.6 mg) successively. The resultant mixture was heated at 120 ℃for 9 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow oil, which was treated by column chromatography on silica gel to afford **14** (eluted with Et_2O/hexane = 1/120, 29.1 mg, 0.11 mmol, 55% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 2.89 (dddd, *J* = 1.2, 1.2, 6.4, 14.4 Hz, 1H), 2.99 (dddd, *J* = 1.2, 1.2, 7.2, 14.4 Hz, 1H), 3.22 (s, 3H), 4.35 (s, 1H), 5.16 (dddd, *J* = 1.2, 1.2, 2.8, 16.8 Hz, 1H), 5.20 (dddd, *J* = 1.2, 1.2, 2.8, 10.4 Hz, 1H), 5.90–6.00 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3), 48.2 (CH_2), 57.6 (CH_3), 89.0 (CH), 93.2 (C), 120.4 (CH_2), 128.5 (CH), 129.7 (CH), 131.7 (CH), 132.0 (C), 138.7 (C); IR (ATR/cm^{-1}) ν 1346, 1565; HRMS (ESI/TOF) Calcd for $C_{13}H_{16}ClNO_3Na$ [(M+Na)$^+$]: 292.0711, found 292.0724.

Elimination of nitrous acid from 3a

To a solution of **3a** (36.1 mg, 0.14 mmol) in MeOH (1.0 mL), was added MeONa (0.69 mmol, 37.0 mg). The resultant mixture was heated at 70 ℃for 22 h. Then, the solvent was evaporated to afford a reaction mixture as a yellow oil, which was treated by column chromatography on silica gel to afford **15** (eluted with CH_2Cl_2/hexane = 1/6, 29.6 mg, 0.14 mmol, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 3.45 (s, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (CH_3), 58.1 (CH_3), 108.5 (C), 128.5 (C), 129.1 (CH), 129.2 (CH), 139.6 (C), 152.2 (C); IR (ATR/cm^{-1}) ν 1610; HRMS (ESI/TOF) Calcd for $C_{10}H_{11}Cl_2O$ [(M+H)$^+$]: 217.0182, found 217.0190.

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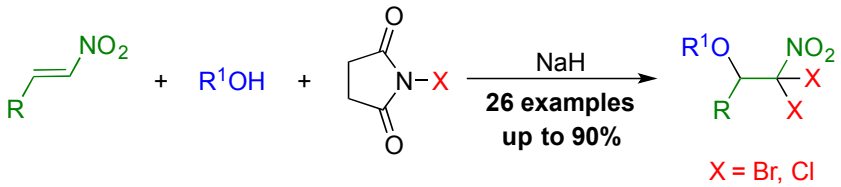

A direct alkoxy-dihalogenation method of nitroalkenes was developed by three component reaction using alcohol and *N*-halosuccinimide.