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Thiourea-Mediated Halogenation of Alcohols

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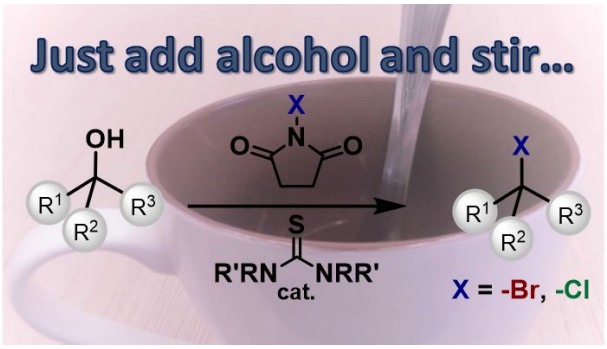


Abstract

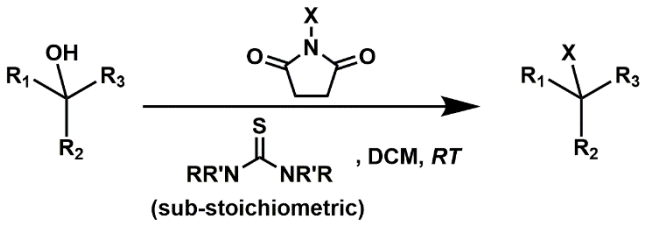
The halogenation of alcohols under mild conditions expedited by the presence of sub-stoichiometric amounts of thiourea additives is presented. The amount of thiourea added dictates the pathway of the reaction, which may diverge from the desired halogenation reaction towards oxidation of the alcohol, in the absence of thiourea, or towards starting material recovery when excess thiourea is used. Both brominations and chlorinations were highly efficient for primary, secondary, tertiary and benzyl alcohols and tolerate a broad range of functional groups. Detailed EPR studies, isotopic labeling and other control experiments suggest a radical based mechanism. The fact that the reaction is carried out at ambient conditions, uses ubiquitous and inexpensive reagents, boasts a wide scope, and can be made highly atom economic, makes this new methodology a very appealing option for this archetypical organic reaction.

Introduction

Halogen-containing compounds have numerous industrial and practical uses.[1,2] For instance, several organic halides are produced in large scale and used for PVC production, pharmaceuticals and synthesis of agrochemicals, among other uses.[3] Their value can be attributed to the polarized carbon-halogen bond, the source of their reactivity and the starting point for various synthetic transformations. Notwithstanding their importance, many halogenation protocols provide low sustainability for the overall process based on environmental and economic indicators.[4] On the other hand, alcohols stand out as ubiquitous renewable compounds and are among the prime candidates for replacing petrochemical derived substrates.[5] Indeed, OH activation for nucleophilic substitution is one of the most important chemical reactions that need to be further developed for a sustainable future.[6]

Classical halogenation of alcohols is well known, and mostly proceeds by converting an alcohol into an intermediate that can be readily displaced by a halide nucleophile.[7] Indeed, the Mitsunobu reaction[8] is a widely used method. However, it is not preferred for large scale because of the thermal hazards associated with azodicarboxylates and because it is a highly atom-inefficient process.[9] Similarly, the ubiquitous Appel reaction suffers from limited substance scope, requires tetrahalomethanes and also produces waste.[10] The much improved catalytic version of this reaction[11] developed by Denton *et al*., solves many of these problems, although tertiary and sterically hindered alcohols are still not compatible. More recently, Nguyen *et al.* demonstrated that *N*-heterocyclic carbenes (NHCs) and *N*-halosuccinimides can be used as stoichiometric redox reagents for Appel-type halogenation reactions of primary and secondary alcohols, although also in this case tertiary alcohols were not suitable starting materials.[12] Other recent efforts for catalytic nucleophilic halogenations of alcohols, pinpoint the general trend of transitioning from stoichiometric alcohol activation towards more environmentally benign sub-stoichiometric processes.[13] Notably, thioureas have important roles in a wide range of transformations.[14,15,16,17] Thiourea derivatives have also proven efficient in asymmetric reactions,[16,17] highlighting their versatility to operate via diverse mechanistic pathways.[18,19,20,21]

Herein, we present a straightforward methodology for the direct transformation of a wide scope of alcohols to alkyl bromides and chlorides using thioureas and *N*-halosuccinimides (NXS), in a single step under mild conditions (Scheme 1). The availability and low cost of the reagents and the possibility to recycle the succinimide by-product, makes this reaction highly economic and atom efficient and thus very desirable for both academia and industry.



Scheme 1. Direct halogenation of alcohols using NXS (X = Br, Cl) as halogen source and thioureas as additives.

Results and Discussion

Initially, bromination of 1-phenylethanol, **1a,** in the presence of varying amounts of *N,N'*-dimethylthiourea (DMTU) with *N*-bromosuccinimide (NBS) was studied (Figure 1). The choice of reagents poses several advantages, namely: i) **1a** and NBS are readily available substrates; ii) reaction progress may be easily monitored by several spectroscopic and mass spectrometry methods, and iii) the alcohol is commercially available either as a racemic mixture or in enantiomerically pure form.

Indeed, the preliminary results of this study were quite surprising. In line with several previously reported reactions of alcohols with NBS,[20,22] acetophenone (**3a**) was obtained almost quantitatively in absence of DMTU. Moreover, in one of these previous publications,[20] Mukherjee and Tripathi showed that 0.1 equivalents of a thiourea could be added to improve the selectivity of oxidation of secondary and benzylic alcohols if the reaction is run at low temperatures. Indeed, under these low thiourea loadings oxidation is still the main reaction also under our conditions. However, the addition of 0.45 equivalents of DMTU resulted in complete suppression of the oxidation reaction and high conversion towards the brominated product, **2a**. Moreover, adding more than two DMTU equivalents led to quantitative recovery of the starting material (Figure S2).

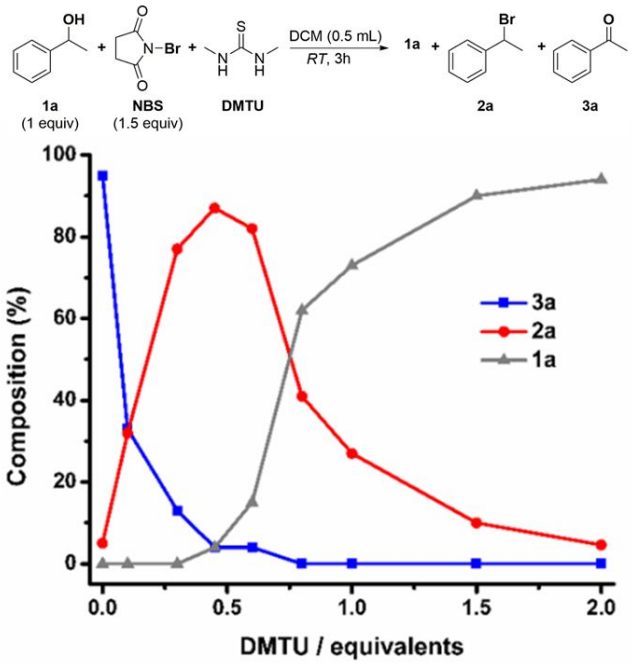


Figure 1. Reactions of **1a** with NBS and DMTU. Reaction conditions: **1a** (0.12 mmol), NBS (0.18 mmol) and DMTU (0-0.24 mmol) in CD_2Cl_2. Progress was monitored by ^1H NMR.

The remarkable effect of differing stoichiometry of substrate, NBS and DMTU were further scrutinized and the results are shown in Table 1. The main observation that arises from these results is that bromination proceeds smoothly just as long as there is about one more equivalent of NBS over DMTU. Moreover, adding more DMTU (*e.g.* entries 2 and 3) slows down the reaction. In effect, all reactions were quenched when excess DMTU was used (entries 4-5). Thus, three different compounds were obtained as the main reaction product just by changing the amount of thiourea added.

Table 1. Reaction of **1a** with NBS and DMTU[a]

Entry	NBS (eq.)	DMTU (eq.)	Time (h)	Yield (%)[a]		
				1a	2a	3a
1[b]	1.5	0.45	3	4	88	4
2	2	1	2	33	46	trace
			7	24	64	trace
3	3	2	2	46	46	0
			7	41	53	0
4	1	2	3	98	trace	0
5	3	4	3	89	9	trace

[a] **1a** (0.12 mmol). Yields determined by GC-MS. [b] Yields determined by ^1H NMR.

In continuation, bromination of a non-benzylic alcohol, hexadecanol (Figure 2, **1k**), was also examined. As expected, no oxidation was observed by mixing the primary alcohol with NBS; in accordance to the accepted oxidation mechanism.[23] Most gratifyingly, the addition of DMTU again led to efficient bromination to afford **2k**. In this case, the optimal amount was 0.3 eq. of DMTU with 1.5 eq. of NBS. Furthermore, adding excess thiourea also inhibited the halogenation and at two equivalents of DMTU, the conversion dropped to less than 10%. Indeed, the

halogenation proceeded in an efficient manner for both benzylic and primary alcohols under very similar conditions.

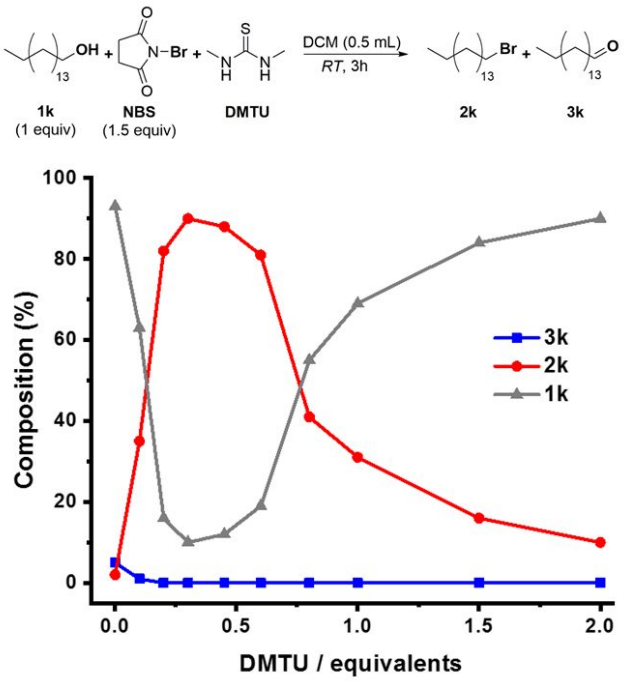


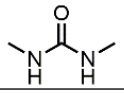
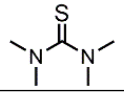
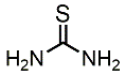
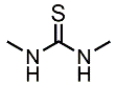
Figure 2. Reactions of **1k** with NBS and DMTU. Reaction conditions: **1k** (0.12 mmol), NBS (0.18 mmol) and DMTU (0-0.24 mmol) in CD_2Cl_2. Reaction progress followed by GC-MS (Figures S8.1-S8.10 in supporting information).

Summarizing, when no DMTU is added, NBS either oxidizes the alcohol (with benzylic alcohols) or simply does not react. Addition of sub-stoichiometric amounts of DMTU brings about a change in the mechanistic pathway, resulting in effective bromination. Excess DMTU leads to inhibition of all reactions.

To further investigate the influence of the thiourea, other additives were probed (Table 2). Tetramethyl thiourea (TMTU), or thiourea; were also found to be useful bromination promoting agents. However, *N,N*'-dimethylurea did not have the same effect as its thio analogue. The successful reaction with TMTU clearly rules out a hydrogen bonding mechanism assisted by the N-H protons. Nonetheless, DMTU was still the most efficient additive (see also Tables S1 and S2 in supporting information). In addition, replacing the bromine donor by other sources proved mostly ineffective (Table 2, entries 4-6), with the exception of molecular bromine (entry 7), clearly hinting that NBS may be releasing low amounts of bromine as part of the mechanism (typical for halogenation reactions carried out with NBS). 1,3-dibromo-5,5'-dimethyl hydantoin (DBDMH) was also examined; however, the reaction with it was less efficient than with NBS (entry 8).

The reaction was then conducted in different solvents (Table S3). In acetonitrile, a Ritter type by-product was observed as the main product (47%).[24] The use of 1,4-dioxane or THF also provided moderate yields and required longer reaction times for higher conversions. DCM and hexane were found to be the best solvents; although in hexane the reaction was somewhat slower. Suspecting a radical based mechanism because the reaction performed better in non-polar solvents, butylated hydroxyl toluene (BHT) was added as a radical scavenger, resulting in suppression of bromination (Table S3, entry 5).

Table 2. Reaction of **1a** with alternative additives. Reaction conditions: **1a** (0.12 mmol) in CD_2Cl_2 (0.5 mL). Yields determined by ^{1}H-NMR.

Entry	(thio)urea (0.45 eq.)	halogen source (1.5 eq.)	Yield (%)		
			1a	**2a**	**3a**
1[a]		NBS	-	13	44
2		NBS	8	68	16
3[b]		NBS	-	84	5
4		KBr	100	-	-
5		CBr_4	100	-	-
6		TBAB	100	-	-
7[c]		Br_2	-	100	-
8[c,d]		DBDMH (0.75 eq.)	- (24)	67 (61)	28 (3)

[a] α-Bromoacetophenone was also obtained (32%). [b] Yields reported for 0.8 eq. of thiourea. [c] Yields determined by GC-MS, 0.75 eq. of Br_2. [d] Yields reported for 1.5 eq. DBDMH and in parentheses for 0.75 eq.

Proposed Mechanism

Radical formation was studied by EPR spin-trapping – the most adequate method for tracking relatively short-lived free radicals.[25] Thus, **1a** was subjected to the bromination reaction under standard reaction conditions. Then, a DMPO spin trap (5,5-Dimethyl-1-pyrroline N-oxide) was added to the reaction mixture (Scheme S1). The resulting mixture was transferred into a glass capillary and measured by EPR. The EPR spectrum observed (Figure 3A, grey open circles) and the simulated spectrum (Figure 3A, red line) strongly suggests the presence of a single *N*-containing radical species characterized by the following hyperfine splitting parameters: a(1H) = 2.053 ± 0.005 mT, a(1N) = 1.402 ± 0.005 mT and a(1N) = 0.218 ± 0.005 mT.

Furthermore, when a control experiment without DMTU was carried out, the corresponding EPR spectra clearly showed a different radical species (Figure 3B), characterized by the following hyperfine splitting parameters: a(1N) = 0.672 ± 0.005 mT and a(2H) = 0.354 ± 0.005 mT. This radical species was found to be short-lived (lifetime of *ca*. 50 s). In contrast, the DMTU-based radical species have a lifetime of minutes and were detected in the reaction mixture even several hours after the beginning of the reaction (Figure S86).

The EPR spectra shown in Figure 3C suggest an initial reaction between DMTU and NBS to generate a reactive radical species that is responsible for alcohol halogenation. Both spectral traces (i) and (ii) show identical species; however, when excess DMTU is used (6 eq.) (see trace (iii)), the trapped radical is no longer observed, consistent with the results obtained from the reactions of **1a** and **1k** (Figures 1 and 2) where excess DMTU leads to recovery of starting material.

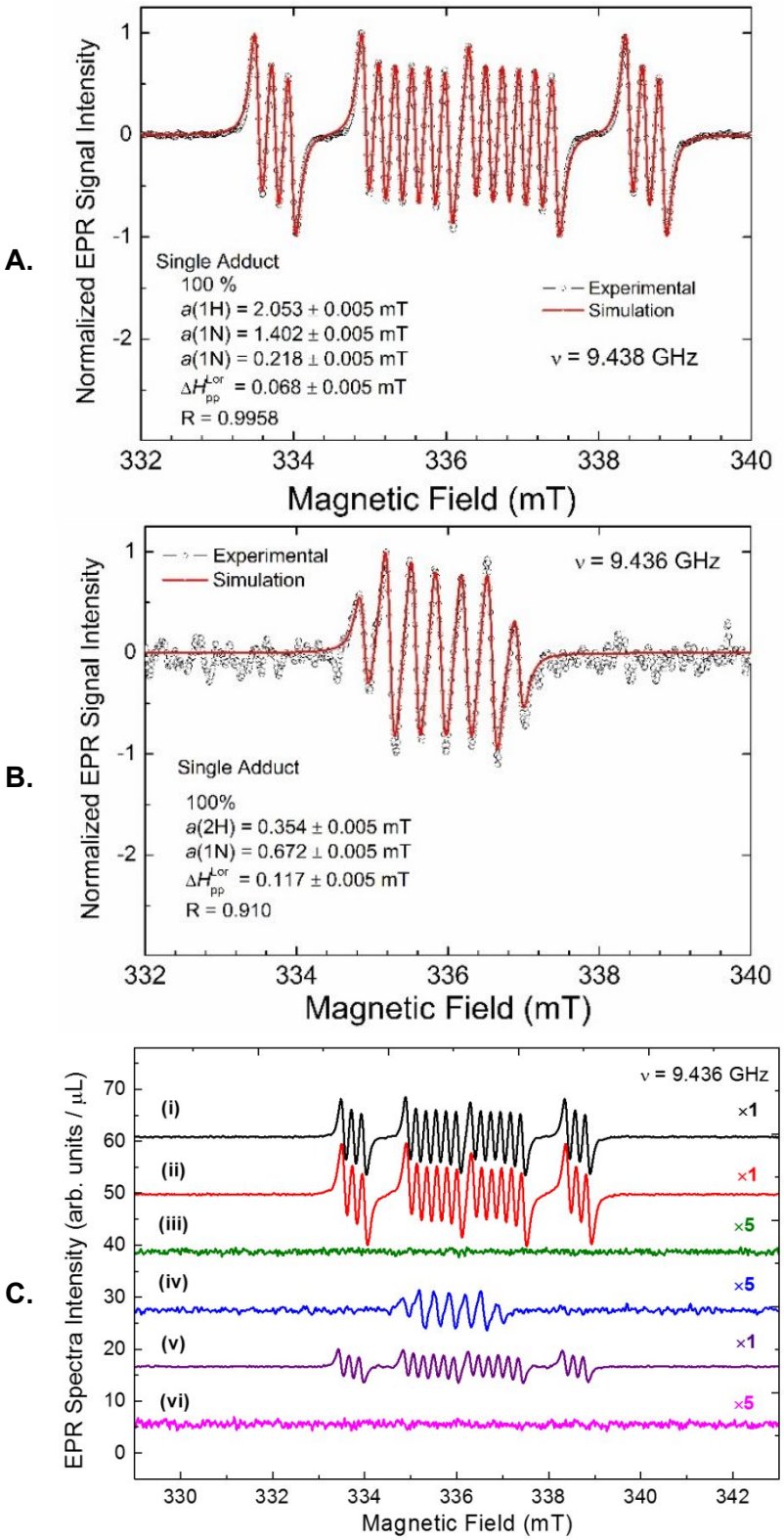
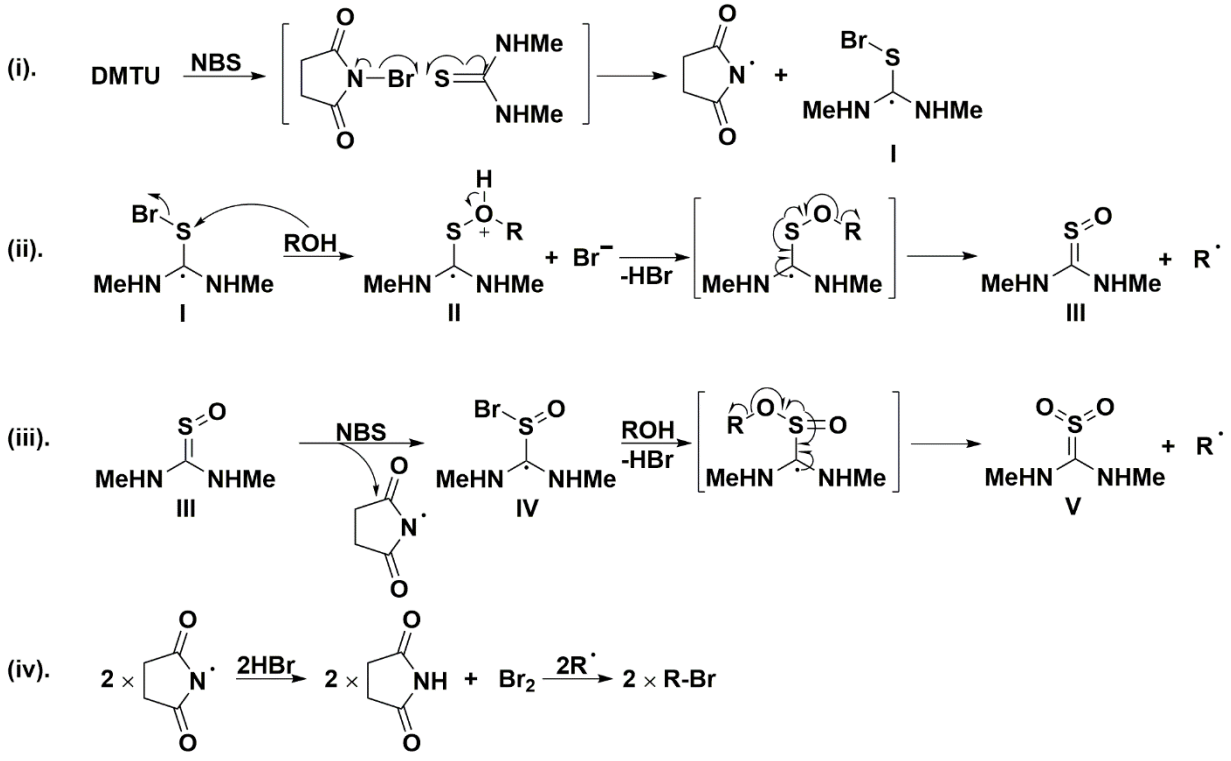


Figure 3. Experimental (grey open circles) and simulated (red line) EPR spectra following reaction of **1a** with NBS and DMTU (**A**) and without DMTU (**B**), in the presence of DMPO. Reaction conditions: **1a** (5 mg, 0.04 mmol), NBS (0.061 mmol), DMTU (0.018 mmol); concentration = 1.5 M in CD_2Cl_2 with respect to alcohol; room temperature; DMPO (0.08 mmol) was added to reaction mixture after 20 sec of stirring. **C.** EPR spectra for: (i) **1a**, NBS and DMTU; (ii) NBS and DMTU without alcohol substrate; (iii) NBS and DMTU (0.244 mmol, excess); (iv) **1a** and NBS; (v) **1f**, NBS and DMTU and (vi) no reagents.

The lack of bromination upon addition of excess amounts of DMTU is probably due to a coupling between the halo-thiourea radical (*vide infra*, proposed intermediate **I**) and another molecule of thiourea to afford a formamidine disulfide radical. Similar observations have been reported in the literature for S-hydroxy-thiourea radicals in the presence of thioureas.[26]

As expected, employing a different alcohol did not affect the EPR spectrum of the trapped radical species (v), suggesting that indeed the radical formed by DMTU and NBS is an active participant of the halogenation mechanism. Moreover, the EPR spectrum recorded for a reaction mixture containing alcohol **1a** and NBS without DMTU (spectral trace (iv)), clearly showed a different radical species that lead to alcohol oxidation.[23]

The role of the thiourea in the halogenation reaction is not trivial. As reported by Lin *et al*., the reduction potential of thiourea is relatively low (E ~ 0.8-1.0 V *vs.* SCE) and neither it, nor its corresponding radical, absorb light in the visible region.[27] Therefore, it is unlikely that thiourea itself would act as the radical initiator. Based on our experimental data, that showed complete suppression of bromination in the presence of BHT (Table S3, entry 5), a plausible mechanism should take into account an initial radical formation reaction between DMTU and NBS (Scheme 2).



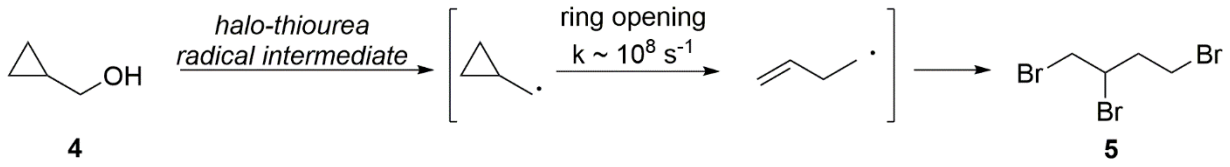
Scheme 2. Proposed mechanism of the bromination of alcohols in reaction mixture containing DMTU and NBS.

Accordingly, we propose the initial formation of a reactive radical species **I** and the succinimide radical (Scheme 2, reaction (i)). As detailed above, radical species **I** is consistent with the EPR analysis and is quite persistent. Next, the alcohol substitutes the bromide to generate intermediate **II**, which is transformed to the thiourea monoxide intermediate **III** after the release of a radical R (Scheme 2, reaction (ii)). In the same manner, thiourea monoxide **III** can be further halogenated on the sulfur atom by NBS and the reaction repeats itself to afford intermediate **IV** and then thiourea dioxide **V**, a known metabolite of DMTU *via* S-oxygenation pathways (Scheme 2, reaction (iii)).[28]

The organic halide can then be readily obtained by a typical reaction between an organic radical and trace amounts of bromine, generated from NBS and trace HBr (Scheme 2, reaction (iv)). Unfortunately, compound **V** was not observed after the reaction completion, possibly due to its decomposition or further oxidation to the thiourea trioxide.[29,30]

Indeed, three different divergent 'regions' for the reaction of alcohols with NBS are observed. Without DMTU, oxidation of the alcohol transpires (mostly with benzylic alcohols).[31] When specific sub-stoichiometric amounts of DMTU are added to the reaction mixture, then bromination dominates for all types of alcohols. Finally, if excess DMTU is added, then the radical reactions are quenched and the starting alcohol is recovered.

Following the proposed radical mechanism in Scheme 2, we hypothesized that a radical clock substrate could provide some further support to the radical mechanism and further insights into the species involved in this reaction. Accordingly, the bromination reaction of cyclopropyl carbinol **4** with NBS and DMTU in dichloromethane at room temperature was studied (Scheme 3). If the reaction follows a radical pathway, the subsequent radical undergoes irreversible ring-opening driven by the relief of ring strain to provide 1-butenyl radical.[32] The latter is then brominated at positions 1, 2 and 4 to afford 1,2,4-tribromobutane **5** (Figure S84).[33] Thus, the peak's retention time at 5.3 min. in the GCMS chromatogram was identified as the expected product and confirmed by both NMR data and HRMS analysis (see experimental section). In a control experiment where **4** was mixed with NBS in the absence of DMTU, compound **5** was not detected neither by GCMS based on retention time nor by ^{1}H NMR. This result supports the proposed role of intermediate **I** (Scheme 2, reaction (ii)) in generating cyclopropyl carbinyl radical.



4 **5**

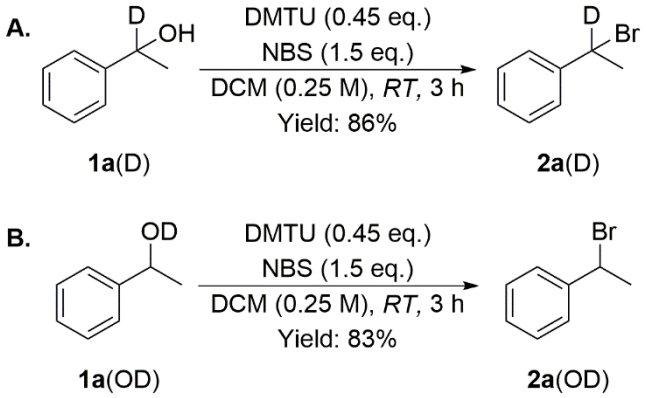
Scheme 3. Ring opening of radical clock substrate **4** and bromination.

More information was also revealed when the bromination reaction of **4** was studied systematically by EPR spin trap measurements. Hence, DMPO (2 eq.) was added to a series of samples containing: (a) **4**, NBS and DMTU; (b) NBS and DMTU; (c) **4** and NBS; (d) **4**, and DMTU and (e) only **4**. The first two samples exhibited the same EPR signals as observed in Figure 3A and 3C trace (ii), respectively. Similarly, sample (c) showed an identical EPR spectrum to that observed in Figure 3B and 3C trace (iv), whereas no signal was observed when DMPO was mixed with either **4** and DMTU or **4** only (samples (d) and (e), respectively).

The above set of five experiments were performed in excess concentration of DMPO (×10) (see figure S87) to attempt trapping of short-lived radical adducts. Under these experimental conditions two spin adducts were detected. For samples (a) and (b) the expected previous spin adduct was observed (~80% of the overall spectrum) with almost identical hyperfine splitting parameters, combined with an additional radical species (~20%) which showed a quasi-three component signal (marked by asterisks in Figure S87), originated from a single nitrogen *a*(1N) = 1.40 ± 0.01 mT and, most probably, a single proton with *a*(1H) = 0.09 ± 0.01 mT. This radical species has a longer life time and after 3 hours took over the spectral profile in all experiments, hinting on self-decomposition of DMPO.

The most interesting result was obtained from the addition of DMPO to a mixture containing **4** and NBS (sample (c)): the observed EPR signal was found to be identical to the main signal observed for samples (a) and (b) (Figure S87 trace (iii): over 95% of the spectrum), but gradually changed its pattern to the form of spectrum as observed in Figure 3B. In contrast, no noteworthy EPR signal was detected when DMPO was mixed with **4** and DMTU (sample (d)). These two results reveal the important role of NBS in forming two different radical species which would lead to the bromination of alcohols when DMTU is present or to oxidation of alcohol in its absence.. All together, the above EPR studies and the use of the radical clock substrate present additional evidence for the proposed mechanism.

Isotope-labelling experiments were also conducted. As expected, no isotope scrambling was observed with C-D deuterium labelled alcohol **1a**(D) and, more revealing, deuterated succinimide was detected as a by-product when **1a**(OD) was used as the starting material (Scheme 4).



Scheme 4. Bromination of **1a**(D) (**A**) and **1a**(OD) (**B**).

Scope

Following this basic set of reactions, an extensive substrate scope for both the bromination and chlorination (by using NBS and NCS) was scrutinized. Figure 4 summarizes the results, typically affording good to excellent yields. It should be noted that the chlorination reaction proceeded faster and more efficiently when the mixture was irradiated with UV-A light. This can be understood because of the greater of N-Cl bond strength compared to the N-Br bond in the corresponding halosuccinimides (*i.e.* light is needed to efficiently disrupt the N-Cl bond in NCS).[34] Irradiation of the bromination reaction had no visible effect.

During the scope survey, some functional groups were found to be incompatible with the reaction conditions (Table S5). These include carbon-carbon double bonds, which also undergo bromination, thiols (oxidation to disulfides) and basic amines (reactions were sluggish); although pyridines were found to be compatible. The scope also revealed that the reaction proceeds with a wide variety of alcohols: primary, secondary, tertiary and benzylic. Both electron withdrawing and electron releasing functional groups are tolerated in the aromatic groups of the benzylic alcohols.

Naturally, bromine could also be used “as is” for the reaction (Table 2, entry 7); however, this may be less convenient for safety purposes under certain settings. Significantly, the halogenations of **1f** led to **2f** and **2f’** as major products, discouraging a cationic mechanism that would probably lead to rearrangement to the benzylic position. Chlorination of the alcohol functionality in **2m’** took precedence over halogen exchange with complete selectivity.

Moreover, the reaction of **1e** also highlights the tolerance of the reaction to acid sensitive boronic esters, which may be further used in Pd-catalyzed coupling reactions.

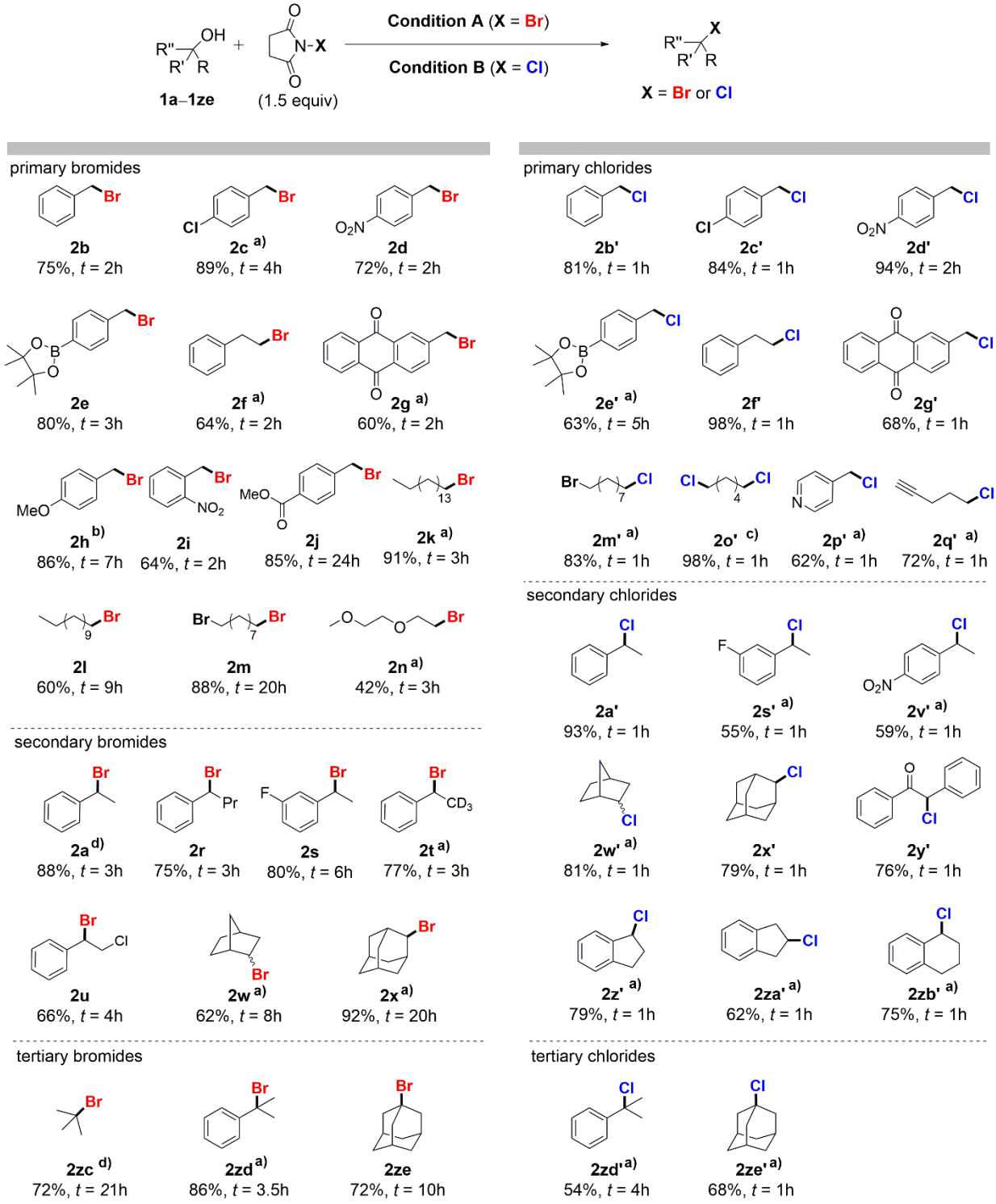
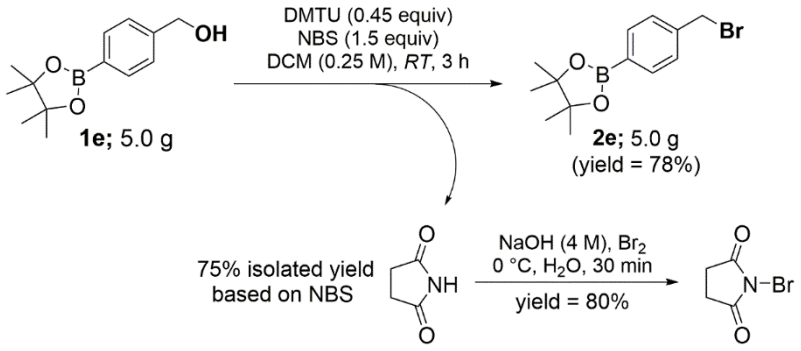


Figure 4. Halogenation of alcohols. Conversions were determined by GC-MS. Reaction conditions: alcohol (0.25M in DCM) and DMTU (0.45 eq.) at r.t., (**Condition A**) NBS (1.5 eq.); (**Condition B**) NCS (1.5 eq.); irradiation at λ = 350 nm. [a] GC-MS yields; [b] alcohol **1h**, NBS (3 eq.), DMTU (0.9 eq.); [c] alcohol **1o** (hexane-1,6-diol), NCS (3 eq.), DMTU (0.9 eq.); [d] ^{1}H NMR conversion.

Decidedly, the main advantage of this methodology over existing methods is its simplicity and cost. In order to improve the "environmental friendliness" of the process, the succinimide side product in a gram scale synthesis of compound **2e**, was filtered and brominated in a bromine solution to recycle NBS[35] (Scheme 5). This additional step makes this novel reaction highly atom economic; which, when coupled with the mild reaction conditions (room temperature), inexpensive reagents and broad scope, uncovers a novel and most convenient procedure for this important synthetic transformation.



Scheme 5: Gram scale synthesis of **2e** and recovery of NBS.

Conclusions

A general pathway for halogenation of alcohols by using thioureas under very mild conditions and in a surprisingly facile manner is presented. The reaction can be carried out on many different types of alcohols, including primary, secondary and tertiary alcohols and is compatible with several functional groups. The fact that alcohols are ubiquitous natural products, that thioureas, NCS and NBS are notably inexpensive, available in bulk quantities, safe, and amenable to industrial scale-up and that the reaction can be made highly atom efficient by recycling the succinimide obtained at the end of the reaction, makes this approach an extremely exciting opportunity to make a strong impact on sustainable organic synthesis methodologies and become the paradigm for the transformation of alcohols to alkyl chlorides and bromides. Further investigation on the scope and mechanism of this reaction is underway, especially regarding the use of chiral thioureas to advance asymmetric halogenation sequences and to expand the methodology to the other halogens.

Experimental Section

General Information. All reagents, compound **4** and solvents were purchased from commercial sources and used as received. Alcohols **1e**[36], **1o**[37], **1p**[38], **1v**[39], **1a**(D)[40], **1a**(OD), **1r**[41] and **1j**[42] were synthesized and purified according to literature procedures. NBS was recrystallized from hot water, stored under dark and used as required. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated aluminum backed plates. ^{1}H and ^{13}C NMR spectra were recorded in an AVIII400 Bruker spectrometer. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale[43]: GC-MS spectra were recorded by using an Agilent 6850 instrument. A Luzchem LZC-ORG instrument was used as the photo reactor for the chlorination reactions (λ = 350 nm). Continuous wave X-band (9.4 GHz) EPR measurements were carried out at room temperature (RT, *T* ~295 K) using a Bruker EMX - 220 spectrometer equipped with an Agilent 53150A frequency counter. Purification of certain compounds was performed by silica gel column chromatography.

General procedure for bromination of alcohols

Alcohols **1** (0.9-1.1 mmol, 1 eq.) and *N,N'*-dimethylthiourea (DMTU) (0.45 eq.) in dry dichloromethane (DCM) (4 mL) were stirred at room temperature until the starting materials were completely dissolved. The reaction mixture was vigorously stirred and *N*-bromosuccinimide (1.5 eq.) was added in a single portion. After completion of reaction, the mixture was diluted with DCM (5 mL) and an aliquot (1 μL) injected to the GC-MS. Then, the organic layer was concentrated over rotary evaporator to produce crude product, which was purified by silica gel flash chromatography over n-hexane (100%) as mobile phase to afford the corresponding bromides, **2** (*vide infra*). The yields of known bromides **2a,c,f-h,k,n,t,w,x, 2zc** and **2zd**, were determined by GC-MS (see supporting information Figures S43-S82).

General procedure for chlorination of alcohols

Alcohols **1** (1 mmol, 1 eq.) and DMTU (0.45 eq.) in dry DCM (4 mL) were stirred at room temperature until the starting materials were completely dissolved. The reaction mixture was vigorously stirred and *N*-chlorosuccinimide (1.5 eq.) was added in a single portion, and reaction vessel kept in the photo reactor set for wavelength 350 nm. After completion of reaction, the mixture was diluted with DCM (5 mL) and an aliquot (1μL) injected to the GC-MS. Then, the organic layer was concentrated over rotary evaporator to produce crude product, which was purified by silica gel flash chromatography over n-hexane (100%) as mobile phase to afford the corresponding chlorides **2'** (*vide infra*). The yields of chlorides **2a',e',m',p',q',s',v',w',z', 2za'**, **2zb'**, **2zd'** and **2ze'** were determined by GC-MS (see supporting information Figures S43-S82).

Benzyl bromide, (**2b**).[44]

Reaction time: 2 h; obtained as liquid (130 mg, 75%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.46-7.35 (m, 5H), 4.57 (s, 2H); GCMS (ESI) m/z calcd for C_7H_7Br 169.9 [M], found: 169.9.

1-(bromomethyl)-4-chlorobenzene (**2c**)[45]

Reaction time: 4 h; Yield: 89%

1-(bromomethyl)-4-nitrobenzene (**2d**)[46]

Reaction time: 2 h; obtained as pale yellow solid (162 mg, 72%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.53 (s, 2H), 7.55 (d, J = 8 Hz, 2H), 8.18 (d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 147.7, 145, 130.1, 129.8, 124, 123.8, 31.2; GCMS (ESI) m/z calcd for $C_7H_6BrNO_2$ [M] 214.9, found: 214.9.

2-(bromoethyl)benzene (**2f**)[47]

Reaction time: 2 h; Yield: 64%

2-(bromomethyl)anthracene-9,10-dione (**2g**)[48]

Reaction time: 2 h; Yield: 60%.

1-(bromomethyl)-4-methoxybenzene (**2h**)[45]

Reaction time: 7 h; Yield: 86%

1-(bromomethyl)-2-nitrobenzene (**2i**)[49]

Reaction time: 2 h; obtained as a pale yellow solid (140 mg, 64%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.81 (s, 2H), 7.47-7.99 (m, 3H), 8.00 (d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 133.3, 132.3, 132.1, 129.3, 125, 28.6; GCMS (ESI) m/z calcd for $C_7H_6BrNO_2$ [M-NO_2] 168.9, found: 168.9.

Methyl 4-(bromomethyl)benzoate (**2j**)[50]

Reaction time: 24 h; obtained as white solid (200 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.48 (s, 2H), 7.45 (d, *J* = 8 Hz, 2H), 8.01 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 142.5, 130, 128.9, 52.1, 32.1; GCMS (ESI) m/z calcd for $C_9H_9BrO_2$ [M] 227.9, found: 227.9

Hexadecyl bromide (**2k**)[51]

Reaction time: 3 h; Yield: 91%.

Dodecyl bromide (**2l**)[52]

Reaction time: 9 h; obtained as colorless liquid (160 mg, 60%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.42 (t, *J* = 8 Hz, 2H), 1.86 (m, 2H), 1.41-1.36 (m, 2H), 0.88 (m, 16H), 0.84 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 35.8, 34.5, 33.5, 31.2, 31.1, 31, 30.9, 30.3, 29.7, 24.3, 15.4; GCMS (ESI) m/z calcd for $C_{12}H_{25}Br$ [M] 248.1, found: 248.1

1,9-Dibromononane (**2m**)[53]

Reaction time: 20 h; obtained as colorless liquid (225 mg, 88 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.42 (t, *J* = 8 Hz, 4H), 1.86 (m, 4H), 1.43-1.40 (m, 4H), 1.38-1.29 (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 35.8, 34.4, 30.8, 30.2, 29.7; GCMS m/z calc for $C_9H_{18}Br_2$ (M-Br) 206.1, and found (M-Br) 206.9.

1-bromo-2-(2-methoxyethoxy)ethane (**2n**)[54]

Reaction time: 3 h; Yield: 42%

(1-bromobutyl)benzene (**2r**)[55]

Reaction time: 3 h; obtained as liquid (160 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 4.99 (t, *J* = 4 Hz, 1H), 2.29-2.25 (m, 1H), 2.16-2.07 (m, 1H), 1.53-1.46 (m, 1H), 1.39-1.31 (m, 1H), 0.96 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 128.6, 128.2, 127.2, 55.5, 42, 21.5, 13.3; GCMS (ESI) m/z calcd for $C_{10}H_{13}Br$ [M] 212, found: 212.

1-(1-bromoethyl)-3-fluorobenzene (**2s**)[56]

Reaction time: 6 h; obtained as liquid (174 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.16 (m, 3H), 7.03-6.98 (m, 1H) 5.21 (q, *J* = 8 Hz, 1H), 2.06 (d, *J* = 8 Hz, 3H); GCMS (ESI) m/z calcd for C_8H_8BrF [M] 201.9, found: 201.9

(1-bromoethyl-2,2,2-d3)benzene (**2t**)[57]

Reaction time: 3 h; Yield: 77%.

(1-bromo-2-chloroethyl)benzene (**2u**)[58]

Reaction time: 4 h; obtained as white solid (150 mg, 66%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.18-4.08 (m, 2H), 5.10 (dd, *J* = 8 Hz and 4 Hz, 1H), 7.42-7.34 (m,.5H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 138.4, 129.1, 128.9, 127.7, 51.6, 47.6.

(1R,4S)-2-bromobicyclo[2.2.1]heptane (**2w**)[59]

Reaction time: 8 h; Yield: 62%.

2-bromoadamantane (**2x**)[59]

Reaction time: 20 h; Yield: 92%.

tert-Butyl bromide (**2zc**)[60]

Reaction time: 21 h; Yield: 72%

(2-bromopropan-2-yl)benzene (**2zd**)[61]

Reaction time: 10 h; Yield: 72%.

1-Bromoadamantane (**2ze**)[62]

Reaction time: 10 h; obtained as white solid (152 mg, yield = 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (d, *J* = 4 Hz, 6H), 2.90 (bs, 3H), 1.72 (t, *J* = 4H, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.3, 36.5, 33. GCMS (ESI) m/z calcd for $C_{10}H_{15}Br$ [M] 214.0, found: 214.8

(1-chloroethyl)benzene (**2a'**)[63]

Reaction time: 1 h; Yield: 93%.

Benzyl chloride, (**2b'**).[64]

Reaction time: 1 h; obtained as a colorless oil (105 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (m, 5H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 128.9, 128.7, 128.5, 46.4; GCMS (ESI) m/z calcd for C_7H_7Cl [M] 126, found: 126.

1-Chloromethyl-4-chlorobenzene (**2c'**).[22]

Reaction time: 1 h; obtained as a colorless oil (143 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 4H), 4.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 134.5, 130.1, 129.1, 45.5; GCMS (ESI) m/z calcd for $C_7H_6Cl_2$ [M] 159.9, found: 159.9.

1-(bromomethyl)-4-nitrobenzene (**2d'**)[65]**:**

Reaction time: 2 h; obtained as a colorless oil (170 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8 Hz, 2H), 7.58 (q, *J* = 8 Hz, 2H), 4.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 129.5, 127.1, 124.1, 44.6; GCMS (ESI) m/z calcd for $C_7H_6ClNO_2$ [M] 171, found: 171.

2-(4-(chloromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2e'**)[66]

Reaction time: 5 h; Yield: 63%.

(2-chloroethyl)benzene (**2f'**)[22]

Reaction time: 1 h; obtained as a colorless oil (113 mg, 98%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.31-7.24 (m, 3H), 3.76 (t, *J* = 8 Hz, 2H), 3.12 (t, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.9, 128.7, 127, 45.1, 39.3; GCMS (ESI) m/z calcd for C_8H_9Cl [M] 140, found: 140.

2-(chloromethyl)anthracene-9,10-dione (**2g'**).[67]

Reaction time: 1 h; obtained as a pale yellow solid (184 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.30 (m, 4H), 7.82-7.80 (m, 3H), 4.7 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 182.8, 143.9, 134.4, 134.3, 134, 133.9, 133.6, 133.3, 128.1, 127.5, 127.5, 127, 45.1; GCMS (ESI) m/z calcd for $C_{15}H_9ClO_2$ [M] 256, found: 256.

1,9-Dichlorononane (**2m'**)[68]

Reaction time: 1 h; Yield: 83%

1,6-Dichlorohexane (**2o'**).[69]

Reaction time: 1 h; obtained as a colorless oil (155 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (t, *J* = 8 Hz, 2H), 1.82-1.75 (m, 2H), 1.49-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1, 32.5, 26; GCMS m/z (ESI) calcd for $C_6H_{12}Cl_2$ [M-Cl] 120, found: 120.

4-(chloromethyl)pyridine (**2p'**)[70]

Reaction time: 1 h; Yield: 62%.

5-chloropent-1-yne (**2q'**)[47]

Reaction time: 1 h; Yield: 72%

1-(1-chloroethyl)-3-fluorobenzene (**2s'**)[71]

Reaction time: 1 h; Yield: 55%

1-(1-chloroethyl)-4-nitrobenzene (**2v'**)[72]

Reaction time: 1 h; Yield: 59%.

(1R,4S)-2-chlorobicyclo[2.2.1]heptane (**2w'**)[73]

Reaction time: 1 h; Yield: 81%.

2-Chloroadamantane (**2x'**).[74]

Reaction time: 1 h; obtained as a colorless oil (142 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 1H), 3.28 (d, *J* = 12 Hz, 2H), 2.07 (s, 2H), 1.96-1.58 (m, 8H), 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4, 38.2, 37.8, 35.9, 31.1, 27.5, 26.9; GCMS (ESI) m/z calcd for $C_{10}H_{15}Cl$ [M] 170, found: 170.

2-chloro-1,2-diphenylethan-1-one (**2y'**).[75]

Reaction time: 1 h; obtained as a colorless oil (182 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.97-7.95 (m, 2H), 7.48-7.36 (m, 8H), 6.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 135.9, 134.4, 133.8, 129.3, 129.25, 129.23, 128.9, 128.6, 62.3.5.5, 32.6. GCMS (ESI) m/z calcd for $C_{10}H_{15}Br$ [M] 214, found: 214.8

1-Chloro-2,3-dihydro-1H-indene (**2z'**)[76]

Reaction time: 1 h; Yield: 79%.

2-Chloro-2,3-dihydro-1H-indene (**2za'**)[77]

Reaction time: 1 h; Yield: 62%

1-Chloro-1,2,3,4-tetrahydronaphthalene (**2zb'**)[76]

Reaction time: 1 h; Yield: 75%

(2-Chloropropan-2-yl)benzene (**2zd'**)[78]

Reaction time: 4 h; Yield: 54%.

1-Chloroadamantane (**2ze'**)[79]

Reaction time: 1 h; Yield: 68%

1,2,4-Tribromobutane (**5**)[33]

Cyclopropyl carbinol **4** (345 mg, 4.8 mmol) and DMTU (225 mg, 2.16 mmol) in dry dichloromethane (DCM) (20 mL) were stirred vigorously at room temperature until the starting materials were completely dissolved. Then, *N*-bromosuccinimide (1.28 g, 7.2 mmol) was added

in a single portion. After 3h, the mixture was diluted with DCM (10 mL) and washed with water (3×30 mL). The organic layer was separated, dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to give 162 mg of crude mixture. GC-MS analysis of an aliquot indicated 78% conversion to compound **5**. The product was isolated by silica gel flash chromatography over *n*-hexane (100%) as mobile phase to afford pure **5** as colorless oil (53 mg, 5%). Note: the product is volatile (72-74 °C at 3 mmHg) and the yield may be reduced after solvent evaporation under vacuum.[33c]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.4 (m, 1H), 3.90 (dd, ^2J = 10.4; ^3J = 4.4 Hz, 1H), 3.68-3.53 (m, 3H), 2.69 (m, 1H); 2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.0, 39.0, 35.7, 30.2. HRMS (APCI) m/z calcd for $C_4H_7Br_2$ [M-Br] 212.8909, found: 212.8924

Gram scale synthesis

2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2e**).[80]

Alcohol **1e** (5 g, 21.4 mmol, 1 eq.) and DMTU (1 g, 9.6 mmol) in DCM (100 mL) were vigorously stirred at room temperature until mixture was completely dissolved. Then, *N*-bromosuccinimide (5.7 g, 32 mmol) was quickly added and stirring was continued for 3.5 h. The reaction mixture was diluted with DCM (50 mL) followed by addition of water (50 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated over rotary evaporator to produce **2e** as an off-white solid (5 g; 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 4.51 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.2, 128.3, 83.9, 33.3, 24.9.

The aqueous layer was concentrated on the rotary evaporator to produce an orange residue. The residue was purified on small bed of silica gel by eluting with MeOH in DCM as mobile phase (0% to 5%) to afford succinimide as white solid (2.4 g; 75% based on starting NBS). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.7 (s, 4H).[81]

Synthesis of *N*-bromosuccinimide:[82] The previously obtained succinimide (2.4 g, 24.2 mmol) was dissolved in NaOH solution in water (4 M, 7.5 mL) and cooled to 0 ºC. To the vigorously stirred reaction mixture, bromine (4.26 mg, 26.65 mmol) was added, and the mixture was stirred for 20 min. The solid was filtered, washed with cold water and recrystallized from hot water to afford *N*-bromosuccinimide as white solid (yield = 3.5 g; 80% based on succinimide).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The synthetic procedures, reaction optimizations and characterizations of the compounds studied (^{1}H and ^{13}C NMR), EPR and secondary isotope effect studies are also provided (PDF).

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Notes

The authors declare no conflict of interest.

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