Deconstructive diversification through C-C single bond cleavage

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Abstract: Deconstructive functionalization through C-C bond cleavage can generate structures with modified carbon skeletons, which are challenging or even inaccessible to achieve otherwise. The highly desired transformations through C-C single bond cleavage are underexplored. Herein, we report a general procedure to produce halides from readily accessible alkyl alcohols through C-C single bond fragmentation. Catalyzed with iron chloride under visible light, this reaction performed efficiently to produce primary, secondary, and tertiary alkyl halides bearing various functional groups. The resulting halides are valuable synthons for versatile modifications. More importantly, because alcohol can be simply prepared from other functional groups including ester, aldehyde, ketone, alkene, etc., this method enabled a broadly useful C-C bond functionalization beyond using alcohol as the precursor through a two-step procedure. Through C-C single bond cleavage, the method establishes a general platform towards a highly valuable pool of unique synthons, which includes chiral fragments from abundant and inexpensive natural products.

Different from traditional methods, deconstructive transformation through C-C

bond fragmentation changes the backbone of a molecule, and can quickly generate unique structures from known compounds, such as complex natural products with special stereochemistry, and compounds with the potential activity of medicaments[1-6]. This strategy is like "molecular gardening", and can realize "scaffold hopping"[7,8]: through C-C bond scission, the chosen molecule fragments can undergo different transformations, which is a less common but sometimes more efficient way to achieve complexity. Deconstructive functionalization provides novel logic for molecule construction and opens new opportunities to edit important compounds and access challenging molecules. In this context, transformations involving C=C bond fragmentation have shown sufficient advances[9,10]. While methods for C-C single bond cleavage, which would explore new chemical space, are still in their infancy.

A few multistep methodologies were developed to produce structural unique alkenes, and alkanes, with stoichiometric metal regents[11,12]. For example, Kwon reported an efficient two-step procedure, to enable the hydrodealkenylative $C(sp^3)$-$C(sp^2)$ bond cleavage through oxidation of O_3 and subsequent reduction of Fe(II)[13]. Sarpong developed a rare example to produce primary alkyl halides from cyclic amines via sequential C-N and C-C single bond fragmentation with stoichiometric silver salt and oxidants. The resulting halides can be further transformed via various substitution reactions, enabling a deconstructive diversification procedure (Fig. 1a)[14]. Reported catalytic C-C single bond transformations generally suffered from limitations of substrates with preinstalled directing groups or strained rings[1-4]. Until recently, breakthroughs of transformations of C-C single bond applying linear aldehydes, and

unstrained ketones have been achieved, catalyzed with Rh[15,16], Ir[16,17], or Cu[18]. However, a general catalytic method to achieve deconstructive diversification through C-C single bond cleavage has not been established yet.

Lately, photocatalysis has shown great potentials for challenging functional group transformations and opening new chemical spaces[19-22]. Pioneered by Knowles[23,24] and Zuo[25,26], photocatalytic C-C single bond fragmentation of aliphatic alcohols has been realized, through β-scission of in-situ formed alkoxy radical intermediates[26-28]. Hydroxyl is one of the most common functional groups in natural products, bioactive compounds, and feedstock chemicals[1,3,4,29]. In addition, hydroxyl is also one of the most accessible substitutes that can be easily generated from aldehydes, ketones, esters, alkenes, etc[30]. Thus, deconstructive halogenation through C-C fragmentation of alcohols would afford alkyl halides as structurally diversified fragment links from various functional groups, offering a general pathway and multitudinous possibilities for molecule editing (Fig. 1b). Importantly, regioselective late-stage halogenation of organic compounds on different positions through C-C bond cleavage, which is unfulfillable through traditional methods, can illustrate brand new directions to produce bioactive compounds from natural abundant or readily accessible organic sources, such as Betulin, and its derivatives[31,32](Fig. 1c). However, no general method was reported to achieve the desired versatile halogenation through C-C bond cleavage. We found that iron chloride, which formed chlorine radical under visible light, catalyzed the formation of different alkoxy radicals with a base to generate primary, secondary, and tertiary carbon radicals[33,34]. As designed in Fig. 1b, the procedure may be applied to form

carbon radicals through C-C single bond fragmentation of structurally diversified alcohols from various sources. Thus, a general method can be established, to produce alkyl halides which are sometimes difficult to achieve or even inaccessible, with simple halide reagents under gentle and inexpensive conditions.

Results. Tert-butyl 4-(2-hydroxypropan-2-yl)piperidine-1-carboxylate was chosen as the substrate for the initial optimization study with NCS as a chlorine source (Fig. 1d). Under the irradiation of blue LEDs (Fig. S1, S2), iron chloride catalyzed the reaction successfully with collidine as the base, generating 44% isolated yield of the target chlorination product (entry 1). Different chlorine sources, including NCP, DCDMH, and TCICA were tested, leading to no valuable outcome (entries 2-4). Next, a series of solvents were examined, and a mixed solvent of DCM/MeCN (5: 1) was optimal (entries 5-7), presenting a 70% isolated yield. Increasing the solvent concentration to 0.2 M benefited the reaction and the best yield of 75% was observed (entry 7). However, testing LEDs with shorter wavelengths resulted in no conversion (entry 8). Control reactions without LEDs, base, or iron chloride showed a complete loss of reactivity, demonstrating the significance of each element (entry 9).

With the simple and gentle optimized conditions established, we proceeded to evaluate the scope of the deconstructive chlorination process. Not only for chlorides, this reaction is also applied to produce bromides and iodides via changing halide sources. Many compounds with important functional groups were suitable sources for alcohol substrates. As shown in Fig. 2, linear (**1**-**47**) and cyclic alcohols (**48**-**67**) all reacted successfully, giving the corresponding alkyl halides in synthetically useful to

excellent yields. To investigate the structural diversity of substrates, commercially available (**1**-**6**) or readily prepared primary, secondary, and tertiary alcohols, which were generated easily from aldehydes (**7**, **8**), ketones (**9**-**16**), and esters (**17**-**47**), were all explored. With formaldehyde (**1**-**4**, **17**), acetone (**5**, **6**, **12**, **13**, **18**-**47**), benzaldehyde (**7**), acetaldehyde (**8**), or acetophenone (**9**-**11**, **14**-**16**) as the leaving fragment, the reaction presented diverse primary, secondary, and tertiary carbon radicals to yield various alkyl halides. As coupling fragments with halides, heterocycle, ring-structured alkyl, benzyl, alkenyl, linear alkyl with or without arene replacements, and alkyl with or without heteroatoms were all tolerated. Delightfully, homobenzylic halides with different phenyl substitutes could be produced in moderate to good isolated yields from different sources (**4**-**6**, **14**-**16**, **18**-**22**). Electronic effects on benzene rings didn't show much impact on the process. A similar observation was found for benzylic radical fragments (**1**-**3**, **17**). It is notable that even when active benzylic/allylic sites were accessible, no regioisomer was found besides the desired product (**3**-**6**, **8**, **14**-**23**, **27**). The results were challenging to achieve with traditional functional group interconversion. The linear alcohols with long alkyl chains were also suitable substrates for the reaction (**7**, **9**-**11**), and both odd and even carbon halides were produced successfully. Moreover, substrates containing different-sized rings with or without heteroatoms, which were frequently observed as moieties in bioactive compounds and pharmaceuticals, were compatible with the reaction conditions, presenting novel halides as attractive coupling links (**23**-**47**). In addition, this transformation displayed good functionality tolerance, with a variety of commonly encountered substitutes,

including halide, ether, ester, amide, heteroarene, and even alkene unaffected, although simple alkenes are usually not compatible with oxidative halogenation reagents. To our surprise, with two hydroxyl groups presented (**44)**, the tertiary hydroxyl fragment was reacted, with the secondary hydroxyl group on the ring untouched. As expected, tertiary alkyl halides were also produced successfully through the carbon-carbon bond cleavage process (**4**, **12**, **13**, **45**-**47**).

Through C-C bond cleavage, ring-opening halogenation of cyclic alcohols can generate products with no leaving fragments, presenting completely different skeletons. Strained cyclic alcohols proved to be good substrates for the transformation[28,35]. For unstrained five and six-membered cyclic alcohols, photocatalytic ring-opening halogenation could only be applied to special tertiary alcohol substrates with limited functional group tolerance because of the added strong oxidants, resulting in distal alkyl bromides or iodides containing ketone group[36-38]. Our method could be readily applied to regiospecifically furnish the different position halogenated ketones and aldehydes, with both tertiary and secondary cyclic alcohols tolerated (**48**-**67**). Various cyclic ketones could be readily transformed to cyclic alcohol substrates with organometallic reagents, presenting enriched structural diversification and functional group tolerance (**58**-**67**). Phenyl (**48**-**50**, **60**-**63**, **65**, **67**), pyridyl (**64**), and methyl (**51**, **52**) were all suitable substitutes adjacent to -OH. Surprisingly, cyclohexanol containing a propyl group (**53**) also resulted in the ring-opening product solely, illustrating that the reaction selectivity is quite sensitive to the ring strain. Delightfully, the substrate with a primary OH was also tolerated to afford a chlorinated ring-opening alcohol (**54**). In the cases of

unsymmetrical β-substituted secondary cycloalkanols (**55**-**57**, **66**), the ring opening halogenation happened regioselectively via the formation of more stable secondary carbon radicals. In addition, β-substituted tertiary cycloalkanols (**58**-**63**) generated the corresponding internal alkyl halides in moderate to excellent yields, with cyano (**62**) and alkene (**63**) groups well tolerated. Heterocycles were also good substrates to generate unique linear (**65**) or cyclic (**67**) hetero atom-containing halides.

To further assess the synthetic potential of our approach, the late-stage deconstructive halogenations of natural products and complex drug structures were performed (Fig. 3, **68**-**90**). By applying the method, a large amount of abundant natural products can be transformed to difficult-to-access coupling linkers with special carbon skeletons and stereoscopic configurations. Given the ubiquity of olefins in terpenes and other organic molecules[39-42], we envisioned the facile generation of useful value-added compounds from abundant materials containing alkene groups. Merging this iron-catalyzed deconstructive chlorination with commonly used hydration of alkenes, we could achieve a formal $C(sp^2)$-$C(sp^3)$ bond cleavage and chlorination (**68**-**73**). Building blocks with chiral centers on ring structures, which have shown important applications and potentials as backbones of bioactive compounds and are difficult to synthesize with traditional methods[13,39-42], could be obtained smoothly. The transformation revealed attractive selectivity for hydroxy groups: secondary (**70**), and even tertiary (**72**) OH could be retained with acetone as the only leaving fragment. The methodology could also be applied to cyclic terpenes with alkene groups on ring structures to achieve complex ring-opening alkyl halides (**87**-**90**). Substrates from natural products or drugs

containing aldehyde (**74**), ketone (**75**, **76**), ester (**77**-**79**), or hydroxy group (**80**-**86**) proceeded in good yields and excellent regioselectivities. Interestingly, the elimination of the chloride group leading to more stable conjugated structures was not observed under basic conditions (**69**, **71**, **73**-**75**, **83**). Furthermore, derivatives of complicated bioactive drugs, such as steroidal drugs (**76**, **84**, **85**), Gemfibrozil (**77**, **78**), antimalarial drug (**79**), Sclareolide (**83**), and Indomethacin (**86**), could be efficiently converted into halides, thereby demonstrating the promising potential of this procedure for providing an additional entry for further derivatization of drugs.

To demonstrate the synthetic applicability of this methodology, the deconstructive chlorination was amenable to scale-up to gram quantities using continuous-flow reactors (Fig. 4a**,** Fig. S3)[43]. To our delight, under flow conditions, primary (**3**), secondary (**68**), and tertiary (**4**) alkyl chlorides can all be generated in good yields more rapidly (less than 3 h) than using standard conditions. Applying the dealkenylative halogenation procedure (Fig. 3, **68**-**73**), the alkene group embedded in readily available (+)-Isopulegol framework could be successfully transformed, affording a chlorinated (**91**) or brominated (**92**) androgen modulator (Fig. 4b)[44] which can be further modified. Notably, as a challenging selective C-C bond cleavage problem mentioned before (Fig. 1c), with betulin as the starting material, we could achieve chlorinated products selectively through dehydroxymethylative and dealkenylative chlorination, with 44% (**93**) and 61% (**94**) isolated yield, respectively (Fig. 4c). In addition, the cyclic alcohol moiety could undergo the ring-opening procedure successfully, to produce an unstable iodide, which transformed to an alkene under the basic conditions (**95**). The late-stage

functionalization products were hard to achieve with traditional methods. Our procedure provided new pathways for molecule diversification toward a wide range of pharmacological activities.

Since halides are versatile functional groups in organic synthesis, we further showcased the synthetic applications of this procedure to prepare compounds with other important functional groups. As shown in Fig. 4d-i, several transformations of some chlorides produced from natural products or drug sources were conducted. Applying (-)-Nopol as the substrate, a one-pot sequence of dehydroxymethylative chlorination and the following substitution with 4-^{t}BuC$_6$H$_4$SH afforded **96** in 41% yield (Fig. 4d). Through HCl elimination of the in-situ formed chlorides, conjugated alkenes (**97**, **98**) could be formed directly (Fig. 4e, f) under the optimized conditions. A rearranged chlorination reaction was observed to produce a chiral tertiary alkyl chloride with a terminal vinyl group (**99**) when the hydrated derivative of (+)-3-Carene (**99a**) was applied. The rearrangement was performed through a radical clock procedure of a cyclopropane intermediate (Fig. 4g), illustrating the radical character of the deconstructive reaction. As an interesting example to achieve novel structures, chlorinated compound **68** could be readily converted to a highly strained multi-loop structure (**100**) smoothly in the presence of sodium hydride, together with an isomer containing cyclopropane skeleton (**101**, Fig. 4h). Product **101** shared the same core structure with many natural products showing important bioactivities[45]. Moreover, **68** could react with sodium azide to form a new C-N$_3$ bond (**102**), which enabled click reaction[46] with a dipeptide smoothly (**103**). As a synthetic challenge, selectively

installing chlorine at the β site of the farnesyl group is difficult. Our method enabled employing the inexpensive farnesylacetone as the starting material to provide farnesyl chloride **104** successfully via a two-step process (classical Grignard reaction and this deconstructive chlorination). Farnesyl chloride can act as a useful synthon for further transformations to give valuable organic compounds, such as primary ether (**105**), thioether (**106**), imide (**107**), and azide (**108**) (Fig. 4i), with the farnesyl moiety untouched. Compounds with farnesyl or similar groups are important precursors of terpenoids or relevant derivatives. Promoted with an acid, the farnesyl chloride (**104**) was successfully transformed to a bicyclic chloride (**109**), with the same core structure of many important terpenoids[29,31,22,39].

Mechanistically, the carbon radical intermediate formed from 2-(1-tosylpiperidin-4-yl)propan-2-ol could be trapped by TEMPO (**110**), with the yield of chloride **31** decreasing sharply (Fig. S4). The radical clock experiment in Fig. 4g also showed good evidence of the radical mechanism of this procedure. The quantum yield of the reaction (based on the formation of **48**) was 0.0388 (see Fig. S5, S6), which implied that a radical chain process made little contribution to the target C–X bond. Meanwhile, a light on/off experiment was also performed, and no reaction was observed without LEDs, ruling out the radical chain mechanism with a long length (See Fig. S7). To further support the proposed mechanism (Fig. 1b), the time-resolved UV-vis spectra of $FeCl_3$ (Fig. S8) and $FeCl_2$ with NCS (Fig. S9) were collected, illustrating the LMCT course of Fe(III)-Cl species and the Fe(II)/Fe(III) cycle with the oxidant NCS, which consisted with our formal mechanistic studies[33,34].

Conclusions. In conclusion, we developed a general photocatalytic method to produce alkyl halides from readily available alcohols through C-C single bond cleavage under gentle conditions. Catalyzed with abundant iron chloride under visible light, the deconstructive halogenation reaction performed smoothly to produce primary, secondary, and tertiary alkyl halides, many of which contained unique stereoscopic skeletons and were challenging to achieve or even inaccessible from traditional methods. In addition, this simple reaction is compatible with numerous functional groups and has a wide substrate scope, providing a highly valuable synthon pool including unique chiral backbones for synthesis. Beyond alcohols, the reaction also enables a new route to synthesize alkyl halides from other fundamentally important functional groups, such as ester, aldehyde, ketone, alkene, etc., through a two-step pathway. Thus, the challenging selective deconstructive halogenation can be realized through C-C single bond cleavage of different substitute moieties, illustrating an attractive logic for molecular skeleton modification on different positions, especially for late-stage functionalization of complex compounds.

Online Methods

The details of general information, preparation of starting materials, deconstructive halogenation of alcohols, gram-scale reaction, transformation of products, and mechanistic studies can be found in Supplementary Information.

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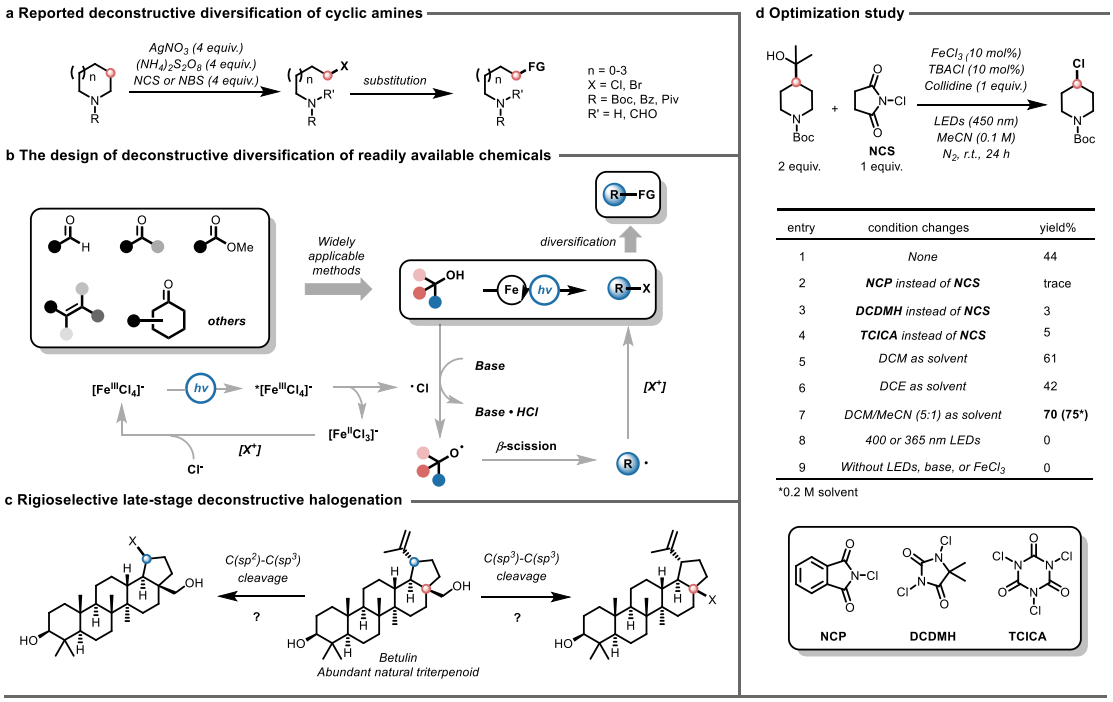
Competing interests: The authors declare no competing interests.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

Additional information: Correspondence and requests for materials should be addressed to P.H. (hupeng8@mail.sysu.edu.cn)



entry	condition changes	yield%
1	*None*	44
2	***NCP** instead of **NCS***	trace
3	***DCDMH** instead of **NCS***	3
4	***TCICA** instead of **NCS***	5
5	*DCM as solvent*	61
6	*DCE as solvent*	42
7	*DCM/MeCN (5:1) as solvent*	**70 (75*)**
8	*400 or 365 nm LEDs*	0
9	*Without LEDs, base, or $FeCl_3$*	0

*0.2 M solvent

Fig. 1 | Deconstructive diversification through C-C single bond fragmentation. **a**, Deconstructive halogenation of cyclic amines and the following substitution enables the formation of diversified amines with modified skeletons through C-N and C-C single bond cleavage. **b**, A design of a general pathway to produce halides from readily available chemicals bearing different functional groups through C-C bond cleavage, with alcohols as the pivot substrates. The resulting halides can be transformed to various functional groups (FG) easily. Under visible light, iron chloride can generate chlorine radicals, which can promote the formation of alkoxy radicals from alcohols with a base. Through a *β*-scission procedure, the formed alkoxy radical can generate an alkyl radical, which may be easily transferred to alkyl halides with oxidizing halide sources. **c**, Halogenation though C-C bond cleavage may be applied for regioselective late-stage functionalization of compounds on special positions that are inaccessible with traditional methods, illustrating new strategies for complex structure modification. Betulin is an abundant natural product, of which the derivatives show a wide spectrum of pharmacological activities. **d**, Optimization study. 0.2 mmol scale. Isolated yields are shown. TBACl = Tetrabutyl ammonium chloride, Collidine = 2,4,6-trimethylpyridine, NCS = N-Chlorosuccinimide, NCP = N-Chlorophthalimide, DCDMH = 1,3-Dichloro-5,5-dimethylhydantoin, TCICA = Trichloroisocyanuric acid.

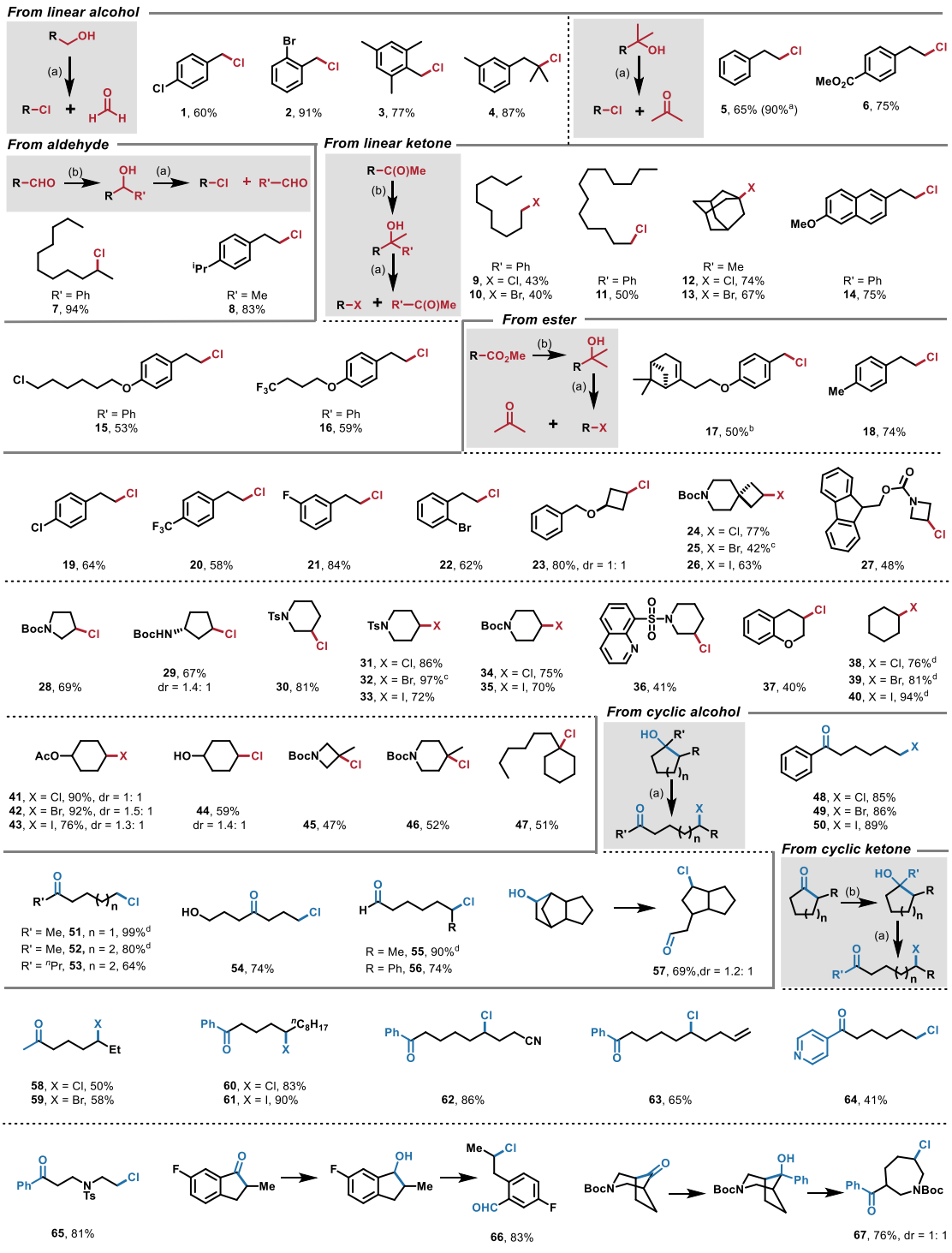


Fig. 2. | Scope of simple substrates. Reaction conditions: (a) alcohol (0.4 mmol), NCS, NBSac or NIS (0.2 mmol), $FeCl_3$ (10 mol%), TBACl (10 mol%), Collidine (1 equiv.), LEDs (450 nm), DCM/MeCN = 5: 1 (1 mL), r.t., N_2, 24 h. Isolated yields are reported unless otherwise noted. Values of diastereomeric ratio (dr) were determined by ^{1}H NMR. (b) R'[M] (R' = Me, Ph; [M] = MgBr, Li), $LiAlH_4$ or $NaBH_4$ was used. See Supplementary Information for details. [a]2,4-diphenylbutan-2-ol was used. Acetophenone was the leaving fragment. [b]2-aryl-ethanol was used. Formaldehyde was the leaving fragment. [c]TBCA was used as the bromide reagent. [d]Determined by GC-MS due to volatility. NBSac = N-Bromosaccharin. TBCA = TribroMocyanuric acid. NIS = N-Iodosuccinimide.

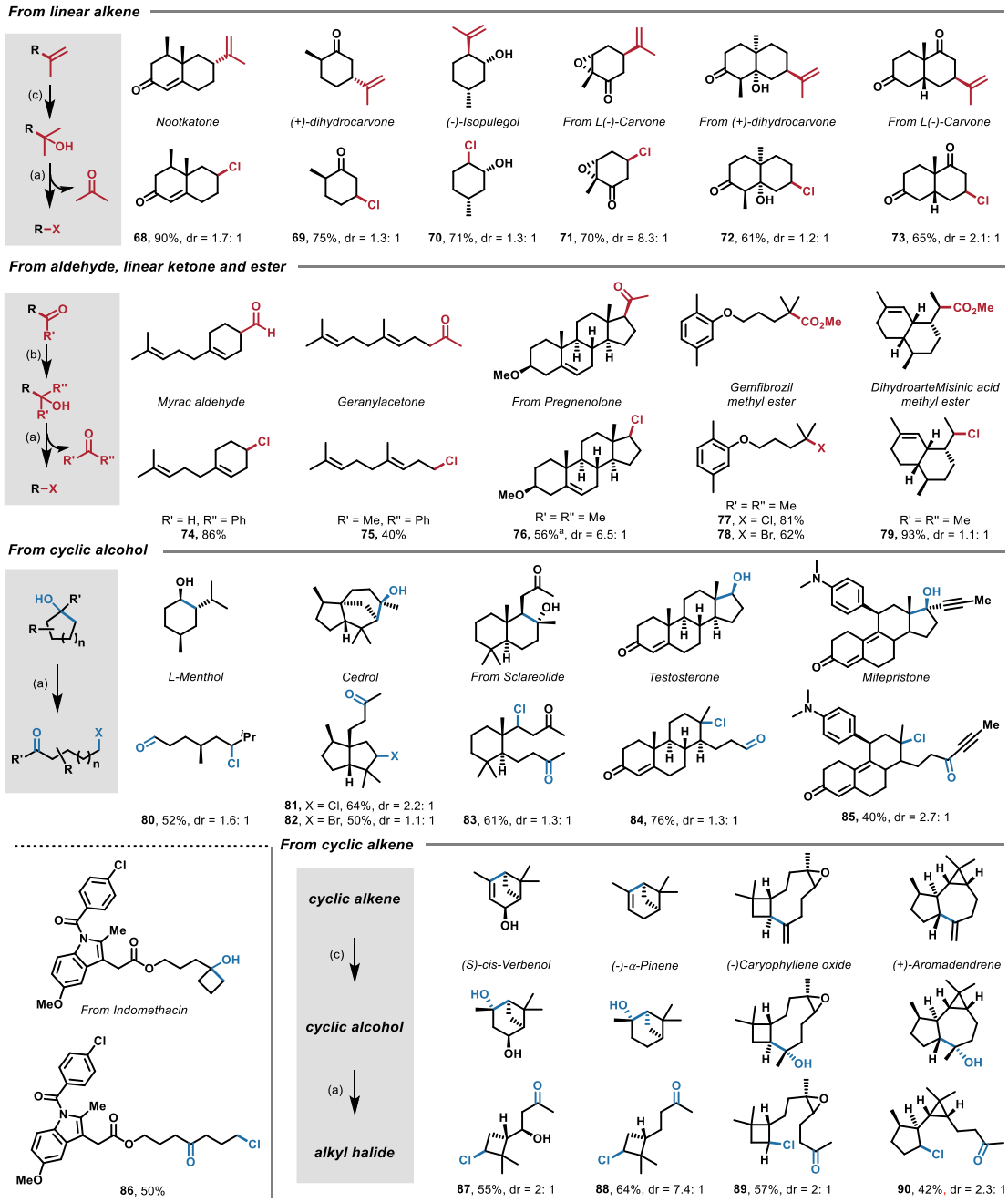


Fig. 3. | Deconstructive halogenation of natural products and pharmaceuticals. Conditions (a), (b), see **Fig. 2**. Conditions (c): $Fe(acac)_3$, $ArNO_2$, $PhSiH_3$; or 40% H_2SO_4. See Supplementary Information for details. Isolated yields are reported. dr values were determined with ^1H NMR, HPLC or GC-MS. [a]2 mL solvent.

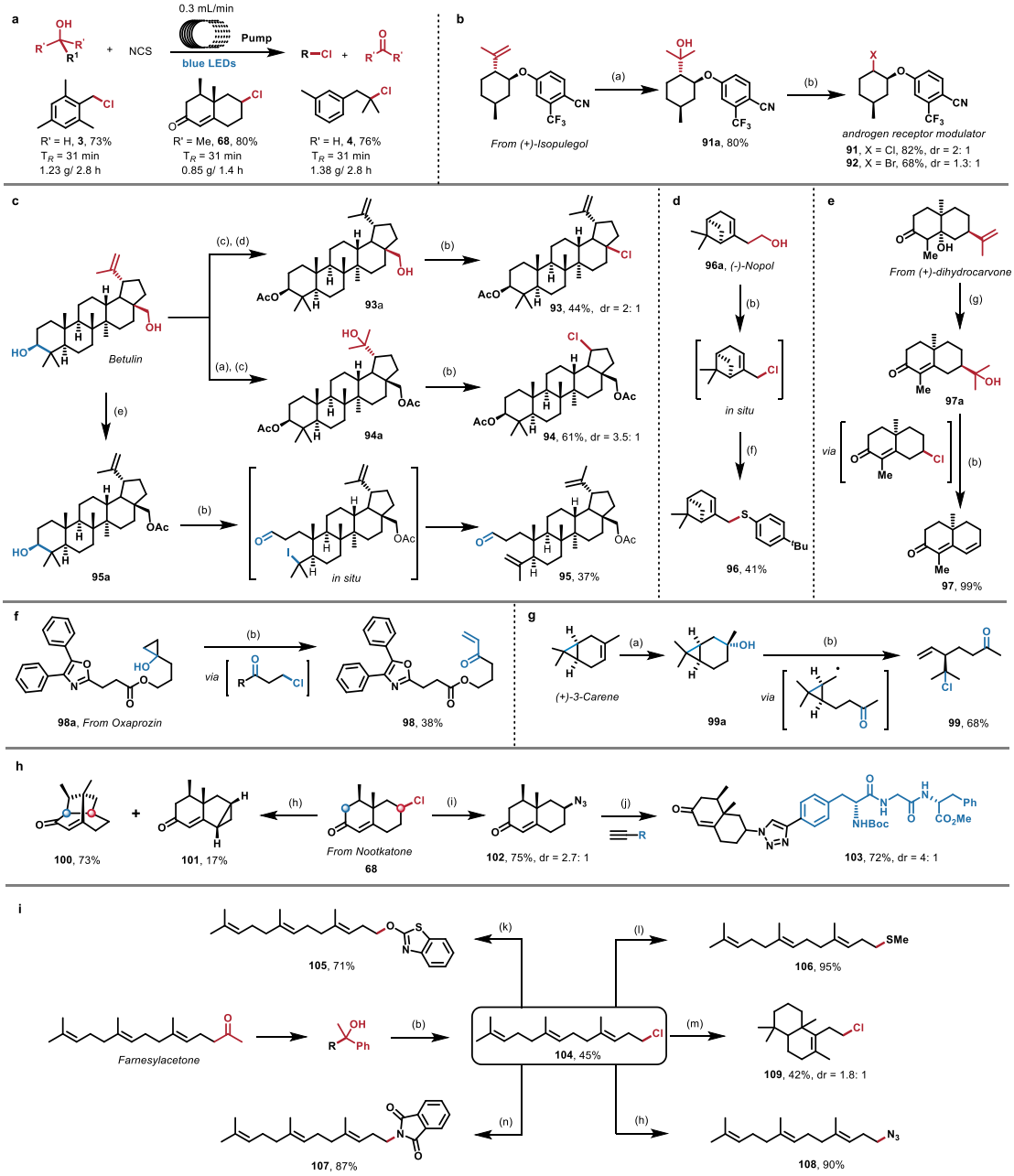


Fig. 4. | Synthetic application. a, Gram scale reactions under flow conditions. **b**, Halogenation through a formal $C(sp^2)$-$C(sp^3)$ bond fragmentation to produce bioactive compound from abundant (+)-Isopulegol. **c**, Late-stage selective chlorination/transformation of Betulin through C-C single bond cleavage. **d-f**, Transformation of in situ formed chlorides from natural product sources (**d**, **e**) and Oxaprozin (**f**). **g-i**, Transformation of chlorides from natural product sources. Isolated yields are reported. (a) $Fe(acac)_3$, $ArNO_2$, $PhSiH_3$; (b) alcohol (0.4 mmol), NCS, NBSac or NIS (0.2 mmol), $FeCl_3$ (10 mol%), TBACl (10 mol%), Collidine (1 equiv), LEDs (450 nm), DCM/ MeCN = 5: 1 (1 mL), r.t., N_2, 24 h; (c) Ac_2O, pyridine; (d) $Al(O^iPr)_3$; (e), Ac_2O, $CHCl_3$; (f) NaH, 4-*tert*-butylthiophenol; (g) 40% H_2SO_4; (h) NaH; (i) NaN_3; (j) $CuSO_4•H_2O$, Na-ascorbate; (k) NaH, 2-hydroxybenzothiazole; (l) NaSMe; (m) $MeSO_3H$; (n) NaI, potassium phthalimide.