VIP C–H Functionalization Very Important Paper

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Site Selective Chlorination of C(sp^3)–H Bonds Suitable for Late-Stage Functionalization

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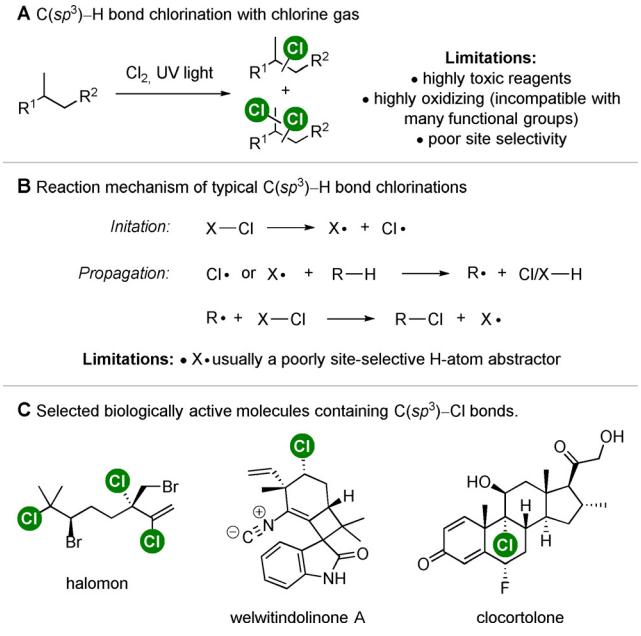
Abstract: *C(sp^3)–Cl bonds are present in numerous biologically active small molecules, and an ideal route for their preparation is by the chlorination of a C(sp^3)–H bond. However, most current methods for the chlorination of C(sp^3)–H bonds are insufficiently site selective and tolerant of functional groups to be applicable to the late-stage functionalization of complex molecules. We report a method for the highly selective chlorination of tertiary and benzylic C(sp^3)–H bonds to produce the corresponding chlorides, generally in high yields. The reaction occurs with a mixture of an azidoiodinane, which generates a selective H-atom abstractor under mild conditions, and a readily-accessible and inexpensive copper(II) chloride complex, which efficiently transfers a chlorine atom. The reaction's exceptional functional group tolerance is demonstrated by the chlorination of >30 diversely functionalized substrates and the late-stage chlorination of a dozen derivatives of natural products and active pharmaceutical ingredients.*

Introduction

C(sp^3)–H bond functionalization reactions enable the introduction of functional groups at previously inert sites, circumventing the synthesis of pre-functionalized substrates and streamlining the preparation of new organic molecules.[1] Such reactions have been heralded as one of many emerging synthetic strategies that could revolutionize how we prepare organic molecules[2] for application in medicinal chemistry,[3] total synthesis,[4] and the late-stage functionalization of natural products.[5] However, the development of site-selective functionalizations of C(sp^3)–H bonds, particularly those destined to be applied to late-stage functionalization, is challenging because of the need to distinguish between multiple non-activated C(sp^3)–H bonds possessing similar steric and electronic properties.[6] While many advances have been made toward the functionalization of C(sp^2)–H bonds with high site-selectivity,[7] far fewer methods functionalize C(sp^3)–H bonds with high site-selectivity,[8] especially those within complex molecules.[2–5]

The archetypal C(sp^3)–H bond functionalization is the radical chlorination of alkanes initiated by the homolysis of chlorine gas by ultraviolet light (Scheme 1 A). This reaction is an industrially important process for the production of small chlorinated molecules from light alkanes, but its use on the benchtop for the chlorination of more complex small molecules is greatly limited by the toxicity of chlorine gas, the strongly oxidizing nature of this reagent, and the low site selectivity with which these chlorinations occur.[9,6d] The site selectivity of these chlorinations is low because the reaction is initiated by the homolysis of chlorine gas, giving two chlorine radicals, and is propagated by the reaction of Cl_2 with an alkyl radical (Scheme 1 B); because the chlorine radical undergoes unselective abstraction of a C(sp^3)–H bond, mixtures of isomeric mono-chloride and poly-chloride products are often produced.[10]

Interest in the development of C(sp^3)–H bond chlorination reactions has been driven by the high value of alkyl chlorides. C(sp^3)–Cl bonds are present in numerous natural products[11] and can imbue beneficial properties to biologically-active molecules,[12] such as increased lipophilicity, modulation of the electronic properties of nearby functional groups, and the prevention of metabolic oxidation at the site of chlorination (for some selected examples of biologically active molecules containing C(sp^3)–Cl bonds, see Scheme 1 C). Furthermore, alkyl chlorides can be used as a site for diversification by substitution at the C(sp^3)–Cl bond.[13]



Scheme 1. Classical C(sp^3)–H bond chlorination with chlorine gas and its reaction mechanism, and selected biologically-active molecules containing C(sp^3)–Cl bonds.

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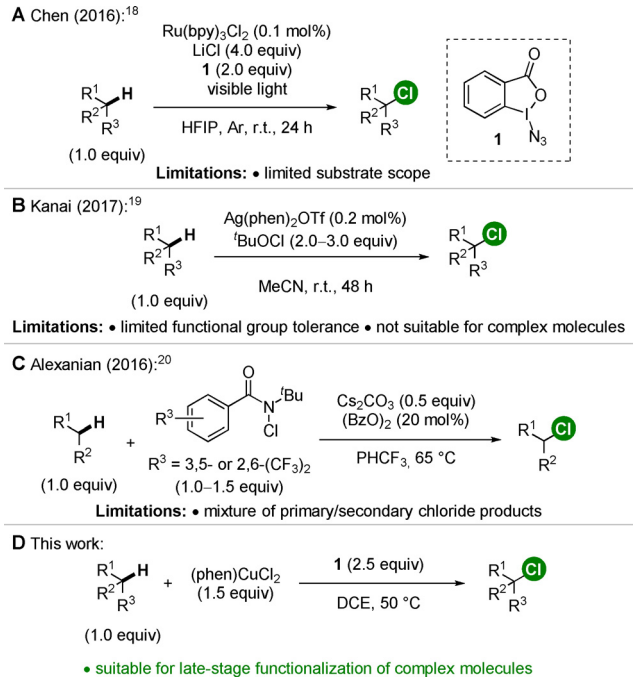
Therefore, the development of methods capable of selectively incorporating a chlorine atom into biologically-active small-molecules or natural products at a late stage could positively alter their efficacy and expedite the discovery of pharmaceuticals based on these scaffolds.[14]

These potential benefits and the drawbacks of the classical C(sp^3)–H bond chlorination methods have led to the development of alternative methods for the chlorination of C(sp^3)–H bonds,[15–20] but many of these methods rely on common reagents (such as *N*-chlorosuccinimide, TCCA, or *tert*-butyl hypochlorite) with the chlorine atom bound to an electronegative heteroatom. With these reagents, the X–Cl bond is sufficiently weak to undergo homolysis and initiate/propagate the reaction, but, after such a step, generates a heteroatom-centered radical that is poorly chemo-selective and site-selective for H-atom abstraction. As a consequence, multiple products form, and C(sp^3)–H bond chlorination reactions require a large excess of the substrate in which the C–H bond reacts. The exceptions to this trend include chlorinations of benzylic C(sp^3)–H bonds, which can be conducted often with high site selectivity because this bond is weaker than others,[16] and chlorination reactions that are directed intramolecularly to a particular site by a pre-installed functional group.[17]

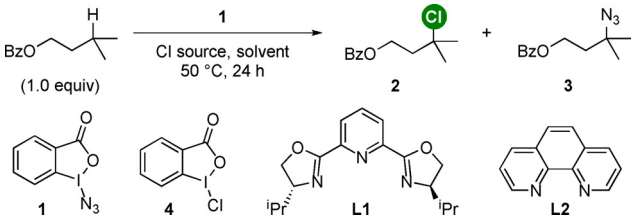
Three recent publications describe the chlorination of C(sp^3)–H bonds with the substrate as the limiting reagent. First, Chen[18] reported that a mixture of Zhdankin's azidoiodinane (**1**), lithium chloride, and a ruthenium photocatalyst in HFIP under visible light irradiation chlorinated tertiary C(sp^3)–H bonds (Scheme 2A). However, just six substrates were evaluated, and studies described here reveal the limited tolerance of this process for auxiliary functional groups, perhaps due to the high concentration of oxidant and presence of a photoredox catalyst. Next, Kanai[19] reported the chlorination of tertiary and benzylic C(sp^3)–H bonds by *tert*-butyl hypochlorite in the presence of a silver catalyst (Scheme 2B). Again, the substrate scope and functional group tolerance was limited to small molecules containing few potentially reactive C(sp^3)–H bonds, in this case because the promiscuous *tert*-butyloxy radical, which is generated by the reaction of the silver catalyst or an alkyl radical with *tert*-butyl hypochlorite, abstracts the C(sp^3)–H bond. More complex molecules, even those derived from simple natural products such as menthol and citronellol, underwent reaction to form complex mixtures of products. In contrast to these two studies, Alexanian[20] reported recently the chlorination of primary and secondary C(sp^3)–H bonds with *N*-chloroamide reagents, a reaction whose site selectivity complements that of other radical chlorinations (Scheme 2C). Although this method was applied to the chlorination of sclareolide with high selectivity in the total synthesis of chlorolissoclimide,[20a] the chlorination of other small molecules was less selective,[20b] and an excess of substrate was required in some cases. In these reactions, an N-centered radical, which is generated by the homolytic cleavage of the N–Cl bond or by its reaction with an alkyl radical, abstracts the H-atom and, thus, dictates the reaction's site selectivity.[21] These prior studies show that new methods are needed for the chlorination of C(sp^3)–H bonds to create a suite of systems that are highly site selective and tolerate a wide range of functional groups.

Previously, we reported the azidation of C(sp^3)–H bonds in a range of complex small molecules[22] with 10 mol% of (**L1**)Fe(OAc)$_2$ (**L1** = ^{i}PrPybox, Table 1) and 2.0 equivalents of Zhdankin's azidoiodinane reagent (**1**) (Scheme 3).[23] We later exploited the high selectivity of this reaction to achieve the late-stage azidation of a wide range of natural products and active pharmaceutical ingredients.[24] While details of the mechanism of this azidation reaction are under study and will be reported elsewhere, abstraction of a C(sp^3)–H bond by a benzoyloxy radical generated by the homolysis of the weak



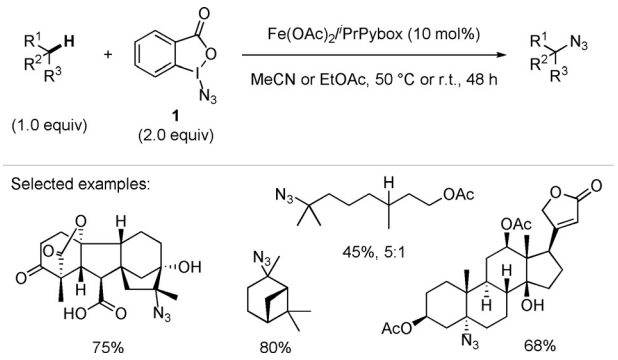
Scheme 2. Recent progress in the site-selective chlorination of C(sp^3)–H bonds.

Table 1: Evaluation of reactions conditions for the chlorination of the tertiary C(sp^3)–H bond of isopentyl benzoate.



Entry	Equiv **1**	Chloride source	**2** (**3**) [%][a]
1	2.0	$FeCl_2$/**L1** (10 mol%)	20 (41)
2	2.0	$FeCl_2$/**L1** (1.0 equiv)	13 (10)
3	–	$FeCl_2$/**L1** (10 mol%), **4** (2.0 equiv)	0
4	2.0	$FeCl_3$, $NiCl_2$, $CoCl_2$, or $MnCl_2$ (1.0 equiv)	<5 (0)
5	2.0	$CuCl_2 \cdot 2H_2O$ (1.0 equiv)	16 (0)
6	2.0	$CuCl_2 \cdot 2H_2O$ (1.0 equiv), **L2** (1.0 equiv)	69 (0)
7	2.0	(**L2**)$CuCl_2$ (1.0 equiv)	54 (0)
8	2.5	(**L2**)$CuCl_2$ (1.5 equiv)	92 (0)[b]

[a] Yields determined by ^{1}H NMR. [b] Allowed to react for 48 h in DCE solvent.



Scheme 3. Our previously reported iron-catalyzed azidation of C(sp^3)–H bonds suitable for the late-stage azidation of complex molecules.

N–I bond[25] of Zhdankin's azidoiodinane leads to an alkyl radical that is trapped by an iron-azide complex. Because of the exquisite site selectivity and functional group tolerance of this method, we sought to develop new functionalizations of C(sp^3)–H bonds based on the combination of Zhdankin's reagent and a transition metal complex that transfers the new functional group.

Here, we report the design and implementation of a method for the chlorination of tertiary, as well as benzylic, C(sp^3)–H bonds, that occurs with high site-selectivity and functional group tolerance (Scheme 2D). The design involves a mechanism that is distinct from those of previous studies and divorces the H-atom abstraction and chlorine atom transfer agents: Zhdankin's azidoiodinane reagent[23] is used to generate the *o*-iodobenzoyloxy radical, which is highly selective for H-atom abstraction under mild conditions, and the cheap and readily-accessible copper(II) complex, (phen)$CuCl_2$,[26] is used to mediate the controlled, rapid delivery of a chlorine atom to an alkyl radical without the generation of reactive radical byproducts. The mild conditions and high site selectivity of this system made possible the isolation of a single product in high yield from the chlorination of a range small molecules, as well as a number of derivatives of complex natural products and active pharmaceutical ingredients. These studies bring C(sp^3)–H bond chlorination into the lexicon of late-stage C(sp^3)–H bond functionalizations.[3–5]

Results and Discussion

We sought to identify conditions that would enable the chlorination of C(sp^3)–H bonds using our previously developed azidation conditions as a starting point. We began our investigations by studying the reaction of isopentyl benzoate with **1** and metal-chloride salts (Table 1). The product of C(sp^3)–H bond chlorination was first observed from reactions with $FeCl_2$ in place of $Fe(OAc)_2$ to form the (**L1**)FeX_2 complex under conditions typical for the azidation reaction.[22,24] In this case, 20% of the tertiary chloride **2** was observed, alongside 41% of the tertiary azide **3** (Table 1, entry 1). The yield of **2** from this reaction did not increase with increased equivalents of $FeCl_2$ (entry 2), and the reaction with the chloride analog of Zhdankin's reagent, chloroiodinane **4** (entry 3), resulted in no observable chloride product. The last result was consistent with the unusual ability of **1** to generate a species that abstracts a tertiary C(sp^3)–H bond.

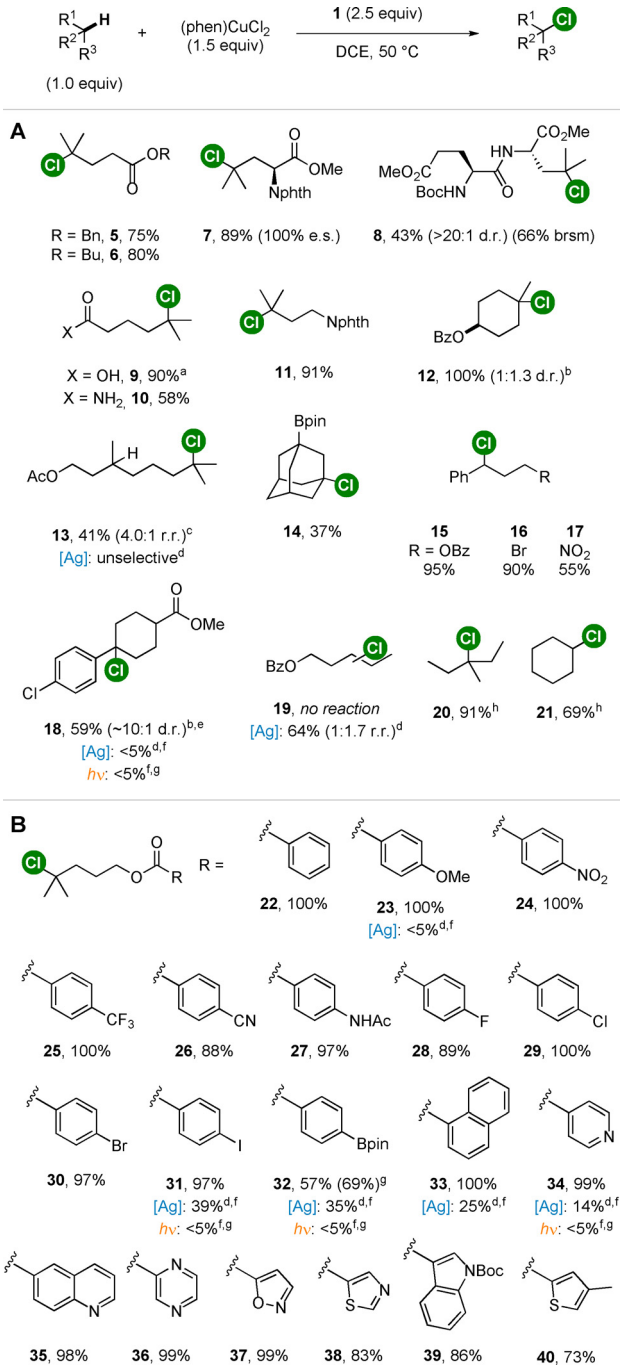
We considered that the weak C(sp^3)–H bonds in **L1** (those α to the oxygen and nitrogen atoms, and the tertiary C(sp^3)–H bond of the isopropyl group) could interfere with abstraction of the tertiary C(sp^3)–H bond in the substrate, and our results made clear that a species was needed that would transfer a chlorine atom without reacting with **1** to form a metal azide complex that would transfer an azide unit to an alkyl radical. On the basis of this logic, we tested a series of additional metal chloride salts in the presence of **1** and isopentyl benzoate under otherwise identical conditions. The reactions with iron(III), nickel(II), cobalt(II) and manganese(II) chlorides formed the alkyl chloride product **2** in trace quantities (entry 4). In all of these reactions, the presence of alkyl azide **3** was not observed.

Reactions with copper(II) chlorides bore more fruit. The reaction with $CuCl_2{\cdot}2H_2O$, formed **2** in 16% yield, again, without formation of azide **3** (entry 5). The addition of 1,10-phenanthroline (phen, **L2**),[26] a simple and readily-available nitrogen ligand lacking weak C–H bonds, to this reaction resulted in the formation of **2** in 69% yield (entry 6), but this result was not consistently reproducible. Fortunately, conducting the reaction with the preformed, isolated copper chloride complex (phen)$CuCl_2$ reproducibly formed **2** in 54% yield (entry 7). This (phen)$CuCl_2$ complex is convenient and easily prepared in one step on multigram scale by simply mixing cheap $CuCl_2{\cdot}2H_2O$ ($0.08 g^{-1}, Acros Organics) and 1,10-phenanthroline ($0.60 g^{-1}, Combi-Blocks) or can be purchased from common chemical suppliers and is fully air-stable over extended periods of time.

To further increase the yield of **2**, we increased the equivalents of **1**, increased the reaction time, and changed the solvent to 1,2-dichloroethane (DCE), resulting in 92% of **2** (90% isolated yield) (entry 8). While we primarily foresee this method being valuable for the preparation of functionalized small molecules on the small scales appropriate for investigation of biological activity, the reaction also occurred in equally high yield on gram scale. The chlorination of 1.0 g of isopentyl benzoate gave 1.08 g of isolated **2**, corresponding to a yield of 91%.

These newly developed conditions led to chlorination reactions occurring in higher yields than those previously reported by others[18,19] on similar substrates and, more important, enabled the chlorination of a much broader scope of complex molecules with high site selectivity (vide infra). Furthermore, the reaction assembly and work-up are simple. All chlorination reactions were conducted on the benchtop in laboratory-grade solvents, and a brief purging of the reaction vessel headspace with nitrogen gas was the only precaution taken that was required to maintain high yields. In most cases, the (phen)$CuCl_2$ complex and unreacted azidoiodinane reagent was safely and quantitatively removed by washing the diluted reaction mixture with an aqueous solution of sodium hydroxide to deliver crude products with few contaminants.

As shown in Scheme 4A, the chlorination of a set of small organic molecules containing C(sp^3)–H bonds in a range of



Scheme 4. Scope of small molecules that undergo C(sp^3)–H bond chlorination. Reaction conditions: **1** (2.5 equiv), (phen)$CuCl_2$ (1.5 equiv) and 0.2 mmol of the substrate in DCE (1.5 mL, 0.13 M) at 50 °C. Isolated yields of chloride products are reported. [a] Isolated as the methyl ester. [b] The ratio of isomers was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by the ratio of the obtained masses of the two constitutional isomers following column chromatography. [d] [Ag] = Ag(phen)$_2$OTf (0.2 mol%), ^{t}BuOCl (2.0–3.0 equiv), MeCN, r.t., 48 h.[19] [e] Reaction was conducted at ambient temperature in MeCN. [f] Yield determined by ^{1}H NMR analysis of the crude reaction mixture. [g] $h\nu$ = $Ru(bpy)_3Cl_2$ (0.1 mol%), LiCl (4.0 equiv), **1** (2.0 equiv), visible light, HFIP, r.t., 24 h.[18] [h] Yield determined by GC-FID analysis of the crude reaction mixture.

chemical environments and possessing a series of common functional groups occurred under the developed conditions to give products **5**–**21** in high yield. The reactions of benzyl (**5**) and butyl (**6**) esters of 4-methylvaleric acid formed the corresponding tertiary chlorides in good to excellent yields. These results demonstrate that the C(sp^3)–H bonds of linear aliphatic chains and the weak benzylic C(sp^3)–H bonds of the benzyl ester are not chlorinated under our conditions. Derivatives of leucine (**7**) and a Leu-Glu dipeptide (**8**) also underwent chlorination at the tertiary C(sp^3)–H bond on the side-chain without epimerization of any of the stereocenters, indicating the potential utility of this method for the chlorination of leucine residues in polypeptides. Substrates containing a free carboxylic acid (**9**), a primary amide (**10**), a phthalimide-protected amine (**11**), and a cyclohexyl group (**12**), all underwent chlorination in excellent yields, further demonstrating the tolerance of this method for common functional groups. The reaction of dihydrocitronellyl acetate, which contains two sterically similar but electronically differentiated tertiary C(sp^3)–H bonds formed the 7- and 3-chlorinated products in a 4.0:1 mixture (only major isomer **13** shown). These ratios are similar to that observed in our previously reported iron-catalyzed azidation reaction of the same substrate,[22] indicating that the site selectivity of these reactions does not depend on the functional group transfer reagent; rather, it depends on the properties of the common azidoiodinane reagent, which forms the species that abstracts the H-atom. Finally, adamantyl pinacol boronic ester, which contains 12 weak secondary C(sp^3)–H bonds and a potentially labile boronic ester, underwent chlorination with selectivity for the tertiary C(sp^3)–H bond (**14**). This site selectivity can be attributed to steric repulsion between the bulky putative benzoyloxy radical and the axial protons, which favors abstraction from the stronger[27] but more sterically accessible bridgehead tertiary C(sp^3)–H bonds.[28]

Benzylic C(sp^3)–H bonds also underwent chlorination with excellent site selectivity. A secondary benzylic C(sp^3)–H bond in a series of functionalized 3-phenylpropanes containing a benzoate (**15**), bromide (**16**) and nitro group (**17**) were chlorinated in good to excellent yields. The tertiary benzylic C(sp^3)–H bond of a derivative of a precursor to the antiparasitic drug atovaquone[29] (**18**) also was successfully chlorinated, a functionalization that we found did not occur under published chlorination conditions[18,19] and, in general, is a poorly precedented transformation.

The precursors to alkyl chlorides **5**–**18** all possess electron-withdrawing functional groups that inductively deactivate nearby C(sp^3)–H bonds and could be responsible for enabling the high site-selectivity observed. To test this hypothesis, *n*-pentyl benzoate, which features an electron-withdrawing benzoate functional group, was subjected to our chlorination conditions. This substrate did not react, demonstrating the high sensitivity of our system to electronic effects. In contrast, the same substrate underwent chlorination at the γ and δ sites to give a mixture of products (**19**) in a 1:1.7 ratio under Kanai's conditions,[19,30] and underwent chlorination at all positions except that α to the electron-withdrawing functional group under Alexanian's conditions with the corresponding acetate substrate.[20b] These results clearly demonstrate that

the intermediate that abstracts the H-atom in our system, a benzoyloxy radical, is much more selective than those in Kanai's (a *tert*-butyloxy radical)[19] and Alexanian's (an N-centered radical) toward tertiary and benzylic C(sp^3)–H bonds that are deactivated only weakly by a nearby electron-withdrawing functional group.

To assess whether the presence of electron-withdrawing functional groups was required to achieve our high site-selectivity, we conducted the chlorination of the unfunctionalized alkane, 3-methylpentane. The product of tertiary chlorination, compound **20**, formed in 91% yield, as determined by GC-FID; the chlorides produced by functionalization of the secondary and primary C(sp^3)–H bonds were not observed. These results contrast sharply with a classical photochemical chlorination of the same substrate with carbon tetrachloride,[31] which formed products from chlorination of primary and secondary C(sp^3)–H bonds of 3-methylpentane in 82% yield, with the tertiary chloride detected as a minor reaction product in only 18% yield. Furthermore, under our conditions, chlorocyclohexane (**21**) was produced by the chlorination of cyclohexane in 69% yield; higher molecular-weight products, such as dichlorocyclohexanes, were not observed, and this result contrasts strongly with the outcomes obtained by other methods involving more reactive chlorinating reagents.[20a]

The tolerance of the reaction toward functional groups was further investigated by conducting the chlorination of a series of 4-methylpentyl aryl esters containing a variety of functional groups on the aryl ring (Scheme 4B). Good to excellent yields of the tertiary chloride products **22**–**40** were obtained from the corresponding substrates, showing that this method is tolerant of numerous functional groups and pharmaceutically important heteroarenes.[32] For example, substrates bearing aryl halides (**28**–**31**) and pinacol boronic esters (**32**) underwent chlorination in good yield without modification of the functional groups.[33] Furthermore, a fused polycyclic arene (**33**) and electron-poor heteroarenes, such as pyridine (**34**), quinoline (**35**), and pyrazine (**36**), were well tolerated and did not undergo alkylation by a Minisci-type reaction. The tertiary C(sp^3)–H bond of the 4-methylpentyl group of a thienyl ester was selectively chlorinated in the presence of three weak primary benzylic C(sp^3)–H bonds of the methyl group on the thienyl ring; 73% of the tertiary chloride was isolated (**40**), with only a trace of the bis-chlorinated product observed. The product of mono-chlorination at the benzylic position was not detected.

By contrast, electron-rich arenes and polycyclic arenes, aryl iodides, boronic esters, and heteroarenes gave products from arene halogenation or complex mixtures of products by halogenation procedures published previously,[18,19] highlighting the higher functional group tolerance of our chlorination method.

While the tolerance for functional groups was high, some common functional groups, such as primary and secondary alcohols, alkenes, and alkynes, were not tolerated under any of these conditions for chlorination (see Supporting Information for details of substrates containing tertiary C(sp^3)–H bonds that did not react to give an isolable tertiary chloride product). Such limitations are consistent with those of other C(sp^3)–H bond functionalization reactions that proceed by H-atom abstraction to form radical intermediates.

To determine whether this reaction is amenable to the late-stage chlorination of molecules that already are densely functionalized, we conducted the chlorination of a series of natural products and active pharmaceutical ingredients containing tertiary C(sp^3)–H bonds or, in one case, benzylic C(sp^3)–H bonds. These results highlight the value of this new, mild, method for achieving chlorination of such C(sp^3)–H bonds in complex substrates.

Complex molecules that underwent chlorination are shown in Figure 1. The monoterpenoid (−)-menthone, a flavoring and fragrance molecule that is responsible for the

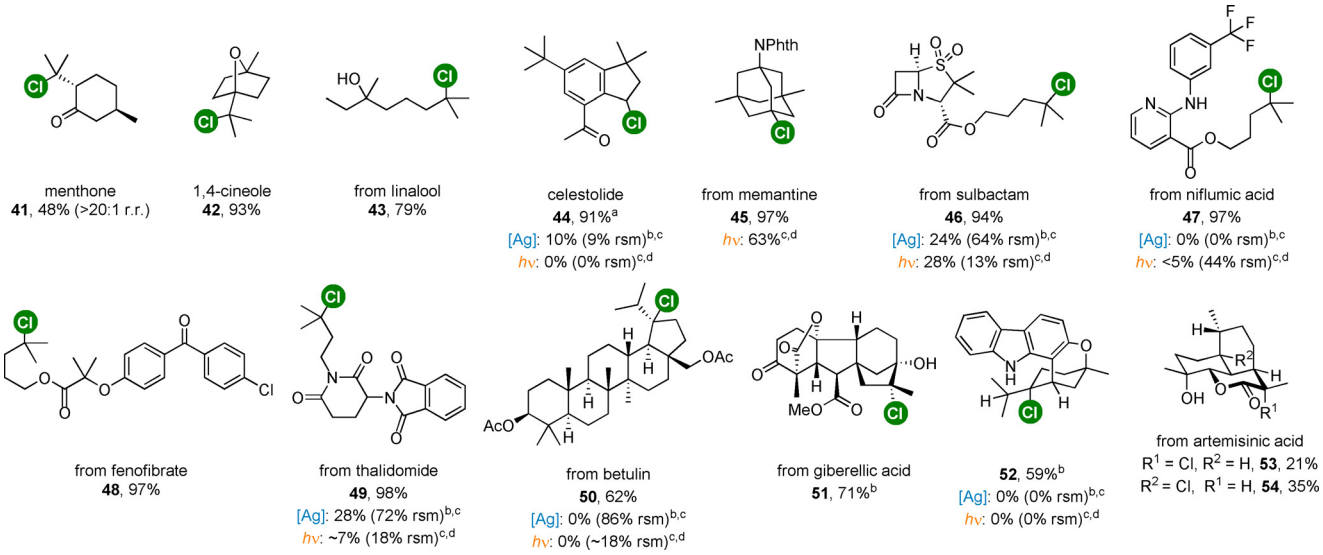


Figure 1. Scope of natural product and drug derivatives that undergo C(sp^3)–H bond chlorination. Reaction conditions: **1** (2.5 equiv), (phen)$CuCl_2$ (1.5 equiv) and the substrate in DCE (0.13 M) at 50 °C. Isolated yields of chloride products are reported. [a] Reaction was conducted at ambient temperature in MeCN. [b] [Ag] = $Ag(phen)_2OTf$ (0.2 mol%), ^{t}BuOCl (2.0–3.0 equiv), MeCN, r.t., 48 h.[19] [c] Yield determined by ^{1}H NMR analysis of the crude reaction mixture. [d] $h\nu$ = $Ru(bpy)_3Cl_2$ (0.1 mol%), LiCl (4.0 equiv), **1** (2.0 equiv), visible light, HFIP, r.t., 24 h.[18]

characteristic taste and aroma of peppermint, was selectively chlorinated at the tertiary C(sp^3)–H bond of its pendent isopropyl group (>20:1 regioselectivity) to give chloride **41**. This product was isolated in 48% isolated yield, albeit with small amounts of impurities that we assumed to be minor constitutional isomers. Likewise, the tertiary C(sp^3)–H bond of the pendent isopropyl group of the bicyclic monoterpenoid 1,4-cineole, which is an isomer of eucalyptol and a component of the flavor components of lime juice, was chlorinated to give **42** in 93% yield. The fully hydrogenated derivative of the ubiquitous fragrance molecule linalool, tetrahydrolinalool, also was selectively chlorinated at its tertiary C(sp^3)–H bond to give **43** in 79% yield. This result contrasts with the chlorination of tetrahydrolinalool acetate with Alexanian's chlorination system (Scheme 2C), which produced a mixture of primary and secondary chlorinated products.[20b] The secondary benzylic C(sp^3)–H bond of the indane musk celestolide underwent chlorination to give the benzylic chloride **44** in 80% yield, and a derivative of the adamantane-based Alzheimer's drug Memantine was selectively chlorinated at the tertiary bridgehead position to give adamantyl chloride **45** in quantitative yield.

The 4-methylpentyl esters of sulbactam, a β-lactamase inhibitor used in combination with the antibiotic ampicillin for the treatment of bacterial infections resistant to β-lactam antibiotics, niflumic acid, a drug used for the treatment of joint and muscular pain, and the acid derived from fenofibrate, a drug used to treat abnormal blood lipid levels, all underwent chlorination selectively at the tertiary C(sp^3)–H bonds of the 4-methylpentyl moiety to give chlorides **46**, **47** and **48**, respectively, in excellent yields. An *N*-2-methylbutyl derivative of thalidomide, a multipurpose drug which is used for the treatment of multiple myeloma, was also chlorinated with perfect site selectivity for the tertiary C(sp^3)–H bond of the pendent 2-methylbutyl group to give chloride **49** in excellent yield. In these examples, the complex biologically-active cores remained unfunctionalized and intact, highlighting both the mild conditions and functional-group tolerance of our chlorination process.

The site-selective chlorination of natural product and drug derivatives with more topologically complex structures containing multiple tertiary C(sp^3)–H bonds was also investigated. A derivative of betulin, a naturally-occurring pentacyclic triterpene that exhibits a broad spectrum of biological effects, including anti-cancer activity,[34] and that contains seven electron-rich tertiary C(sp^3)–H bonds, was chlorinated in 62% yield with high selectivity for a single tertiary C(sp^3)–H bond (**50**) (no other isomeric chloride products could be isolated or identified). A derivative of the plant and fungi growth hormone gibberellic acid, a pentacyclic diterpene, was also chlorinated in good yield and with high selectivity for a single tertiary C(sp^3)–H bond out of four others, giving chloride **51**. A pyrano[3,2-a]carbazole, a common precursor to the murrayamine natural product family developed recently by Sarpong,[35] was selectively chlorinated at the non-benzylic tertiary C(sp^3)–H bond on the cyclohexane ring to give tertiary chloride **52** in good yield. The two other tertiary C(sp^3)–H bonds did not react. The one in the pendent isopropyl group is sterically inaccessible because it is positioned toward the aromatic system to minimize steric repulsion between these two groups, and the benzylic one is likewise sterically inaccessible due to being almost co-planar with the aromatic system. Finally, the chlorination of a precursor to the anti-malarial drug artemisinin gave a mixture of chloride products. The two main products were the result of chlorination of the C(sp^3)–H bonds at C2 and C5, giving tertiary chlorides **53** and **54**, respectively, in modest yields. The most electron-rich tertiary C(sp^3)–H bond at C6, which is farthest from the electron-withdrawing ester, did not undergo chlorination because it is on the concave face of the molecule and thus sterically inaccessible.

To compare the value of other reported methods for C(sp^3)–H bond chlorination to our procedure closely, we tested Chen[18] and Kanai's[19] systems (Scheme 2A and B) for the chlorination of several complex molecules. In all cases, the yields of these chlorination reactions were much lower than those obtained under our conditions. Memantine was the most complex molecule reported to undergo chlorination under Chen's[18] conditions (63% yield of **45** vs. 97% under the newly developed conditions), and no other substrates gave yields higher than 7% under these conditions. Likewise, the highest yield for any example under Kanai's silver-catalyzed conditions was the chlorination of the *N*-alkyl thalidomide substrate, which gave just 28% yield, a reaction that gave a yield of 98% under our conditions.

Conclusion

In summary, we have developed a method for the chlorination of tertiary C(sp^3)–H bonds embedded within a diverse set of small organic molecules featuring a broad array of functional groups to form the corresponding tertiary chlorides in good to excellent yields and with excellent site selectivity. This method also was suitable for the transformation of secondary and tertiary benzylic C(sp^3)–H bonds into the corresponding alkyl chlorides. Furthermore, we demonstrated that the site selectivity, yield, and functional-group tolerance of this method are far higher than those of previously reported chlorination reactions of C(sp^3)–H bonds, especially when applied to the late-stage chlorination of complex molecules. The process we report is highly practical and occurs on the benchtop under mild reaction conditions with readily-available materials to deliver high purity alkyl chlorides. Additional studies on the mechanism and origin of site-selectivity of this chlorination reaction and the related azidation reaction are ongoing in our laboratory, as is the expansion of this reaction manifold to achieve the introduction of other valuable functional groups into complex small molecules, natural products, and active pharmaceutical ingredients.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · chlorination · halogenation · late-stage functionalization · radical reactions

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