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Surgical Cleavage of Unstrained C(sp^3)-C(sp^3) Bonds in General Alcohols for Heteroaryl C-H Alkylation and Acylation

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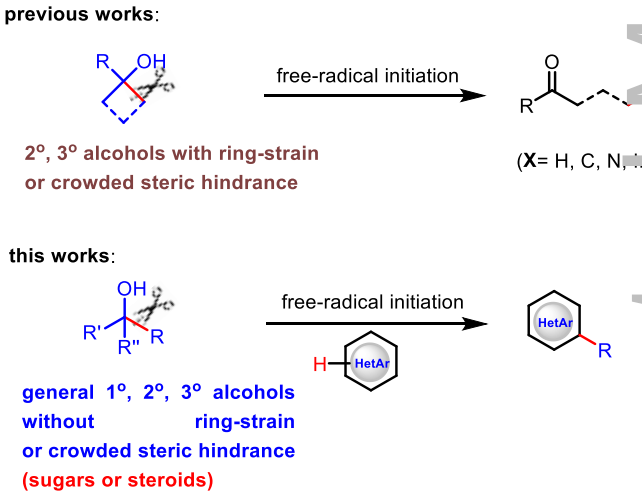
Abstract. We reported herein a predictable and surgical cleavage of carbon-carbon bond in alcohols. A wide range of 1°, 2° and 3° alcohols including sugars and steroids without ring strain or steric hindrance were all compatible with this system. Also it offered a green and practical strategy for generation of alkyl/acyl radicals using alcohols as the sources. Besides, the features of visible-light-initiation, catalyst and metal free, excellent selectivity and mild conditions make it valuable and attractive.

Keywords: Free-Radical; C-C Bond Cleavage; Alcohols; Sugars; C-H Alkylation; C-H Acylation

Introduction

The development of highly efficient strategy for selective carbon-carbon (C-C) bond cleavage could have profound impacts on synthetic organic chemistry, petroleum cracking and biomass conversion.[1,2] Among those established methods, the C-C bond breaking occurs via alcohols represents one of the most successful modes. In general, there are three fashions in the cleavage of a C-C bond adjacent to the hydroxyl group. The first mode is the cationic fragmentation such as the retro-Prins-type reaction and the well-known pinacol rearrangement etc. The second type is the anionic fragmentation such as the Eschenmoser fragmentation. And the last one is the *β*-scission of an alkoxy radical derived from an alcohol.[3] Recently, advances in the alkoxy-radical driven C-C bond fragmentation have been made by Chiba,[4] Zhu, [5] Chen,[6] and others.[7] These effective systems provide novel and attractive strategies for synthetic organic chemistry. However, most of these systems are limited in 2° and 3° alcohols either with ring-strain or crowded steric hindrance (Scheme 1). The *β*-C-C bond fragmentation of the alkoxy radical from unstrained alcohols especially 1° alcohols remains a great challenge. To the best of our knowledge, only three primary alcohols were reported to undergo *β*-scission of the corresponding alkoxy radical very recently.[8] Furthermore, selective radical fragmentation of the C-C bond adjacent to primary hydroxyl group in sugars has never been reported so far. Herein we wish to report a general and highly selective cleavage of the unstrained C(sp^3)-C(sp^3) bond in 1°, 2° and 3° alcohols for heteroaryl C-H alkylation and acylation (Scheme 1).



Scheme 1. Alcohol C-C bond cleavage via β-scission of alkoxy radical.

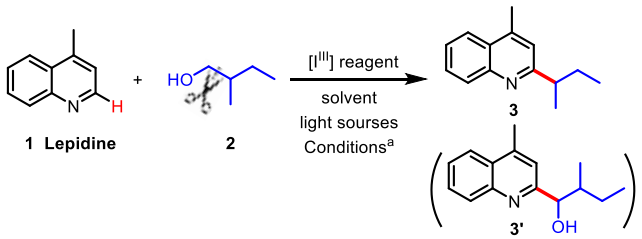
Results and Discussion

Selective cleavage of unstrained C(sp^3)-C(sp^3) bond in 2-Me-butanol for lepidine C-H alkylation.

In the 70s and 80s of the last century, the pioneering studies on photo-irradiation-induced C-C cleavage in alcohols via alkoxy radicals had been revealed by Suginome and Suárez et al.[9] However, these systems were suffered from excess heavy

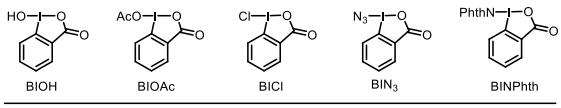
metals, limited substrate scope and relative low efficiency. Inspired by these studies and the hypervalent iodine mediated radical processes,[10] we began to question whether the combination of illumination with hypervalent iodine chemistry could be applied to break the unstrained C(sp^3)-C(sp^3) bonds in challenging 1° alcohols. If it works, general alcohols could be used as greener and safer alkyl radical sources than traditional reagents such as haloalkane and alkylmetallic reagents etc. Initially, a Minisci-type reaction[11] of lepidine **1** and 2-Me-butanol **2** in the presence of hypervalent iodine under photo-irradiation was examined (Table 1). However, 2 equiv. of (diacetoxyiodo)benzene (PIDA) exhibited no reactivity (entry 1). Oxygen atoms in the primary alcohols have lower electron density compared with those in the reported cyclic alcohols and tertiary alcohols, thus an array of hypervalent iodine reagents were screened (entries 2-12). As analyzed above, we were delighted to find that the desired product **3** was obtained in 95% yield when 2.0 equiv. of [bis(trifluoroacetoxy)iodo]benzene (PIFA) with more deficient electron instead of PIDA was applied (entry 2). This result prompted us to evaluate the effect of different substituents of hypervalent iodine (III) reagents on the yield of alkylation products. Other aryliodine bis(trifluoroacetate) also gave product **3** in moderate to excellent yield, which showed that the electronegativity and the position of the substituent on the phenyl have little effect on the reaction efficiency (entry 3 to entry 8). $I(OCOCF_3)_3$ or $C_4F_9I(OCOCF_3)_2$ could not promote C-C bond cleavage of 2-Me-butanol under the irradiation of blue light (entry 9 entry 10). In contrast to acyclic hypervalent iodine reagents, cyclic hypervalent iodine reagents such as hydroxybenziodoxole BIOH, acetoxybenziodoxole BIOAc and chloroxybenziodoxole BICl exhibited no reactivity (entries 11). Interestingly, when Zhdankin reagent BIN_3 was used, main product **3'** was produced via hydrogen atom transfer process of 2-Me-butanol (entries 12). Reducing amount of PIFA obviously dropped yield of the reaction (entries 13). Increasing reaction concentration led to an increased yield of by-products **3'** (entries 14 and entries 15). The strategy via in situ generation of PIFA using a catalytic amount of iodobenzene with oxone did not work (entries 16). Then different solvents such as DMF, DMSO, THF and acetone were evaluated to be less efficient than DCM (entries 17). Furthermore the light source had a remarkable impact on this reaction (entries 18-20). Irradiation of black light (UV 365 nm, 24 W) with higher energy gave comparable results (entries 18). However, with white light (CFL, 24 W), the yield was significantly reduced (entries 19). No reaction occurred in darkness (entries 20). Finally we found that the reaction could complete in 2 hours (entry 21) and be easily scaled up to gram level without decreasing efficiency (See SI).

Table 1. Surgical cleavage of unstrained C(sp^3)-C(sp^3) bond in 2-Me-butanol for lepidine C-H alkylation.



entry	reagent (equiv), reaction time, temp	solvent	3 %	3' %
1	**2** (5), PIDA (2.0), 12 h, 20 °C	DCM	0	0
2	**2** (5), PIFA (2.0), 12 h, 20 °C	DCM	95 (89)[b]	0
3	**2** (5), *p*-Me-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	70	0
4	**2** (5), *p*-F-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	65	0
5	**2** (5), *p*-Br-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	78	0
6	**2** (5), *p*-Cl-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	68	0
7	**2** (5), *o*-Cl-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	61	0
8	**2** (5), *m*-Cl-PhI(OCOCF$_3$)$_2$, 12 h, 20 °C	DCM	80	0
9	**2** (5), I(OCOCF$_3$)$_3$ (2.0), 12 h, 20 °C	DCM	0	0
10	**2** (5), $C_4F_9I(OCOCF_3)_2$ (2.0), 12 h, 20 °C	DCM	0	0
11	**2** (5), cyclic [I^{III}] reagents[c] (2.0), 12 h, 20 °C	DCM	0	0
12	**2** (5), BIN_3(2.0), 12 h, 20 °C	DCM	4	18
13	**2** (5), PIFA (1.5), 12 h, 20 °C	DCM	56	0
14	**2** (5), PIFA (1.5), 12 h, 20 °C	DCM (0.5)	43	15
15	**2** (5), PIFA (1.5), 12 h, 20 °C	DCM (0.3)	21	20
16	**2** (5), PhI (0.2), Oxone (0.3), CF_3COOH (0.3), 12 h, 20 °C	DCM	0	0
17	**2** (5), PIFA (1.5), 12 h, 20 °C	solvent[d]	<10	0
18	**2** (5), PIFA (2.0), 12 h, 20 °C, UV (365 nm, 24 W)	DCM	93	
19	**2** (5), PIFA (2.0), 12 h, 20 °C, CFL (White, 24 W)	DCM	44	0
20	**2** (5), PIFA (2.0), 12 h, 20 °C, in darkness	DCM	0	0
21	**2** (5), PIFA (2.0), 2 h, 20 °C	DCM	93 (85)[b]	0

Cyclic [I^{III}] reagent[c]:



[a] Yields are based on ^{1}H-NMR analysis of reaction mixture on a 0.1 mmol scale at a 0.2 M concentration unless specified otherwise using ACS grade solvents under an air atmosphere. Source of light: 24 W blue LEDs. [b] Isolated yield. [c] Cyclic hypervalent iodine [I^{III}] reagents were used. [d] Other solvents such as DMF, DMSO, acetone and THF were used.

Substrate Scope and Selectivity.

Selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in alcohols for lepidine C-H alkylation and acylation. With the optimized conditions in hand, we then explored the scope of this system. As shown in Scheme 2, a wide range of 1°, 2° and 3° alcohols without ring strain or steric hindrance were all compatible with this reaction. Initially a series of cyclic and acyclic 1° alcohols were examined (**4**-**17**). The cleavage of the C(sp^3)-C(sp^3) bond in alcohols

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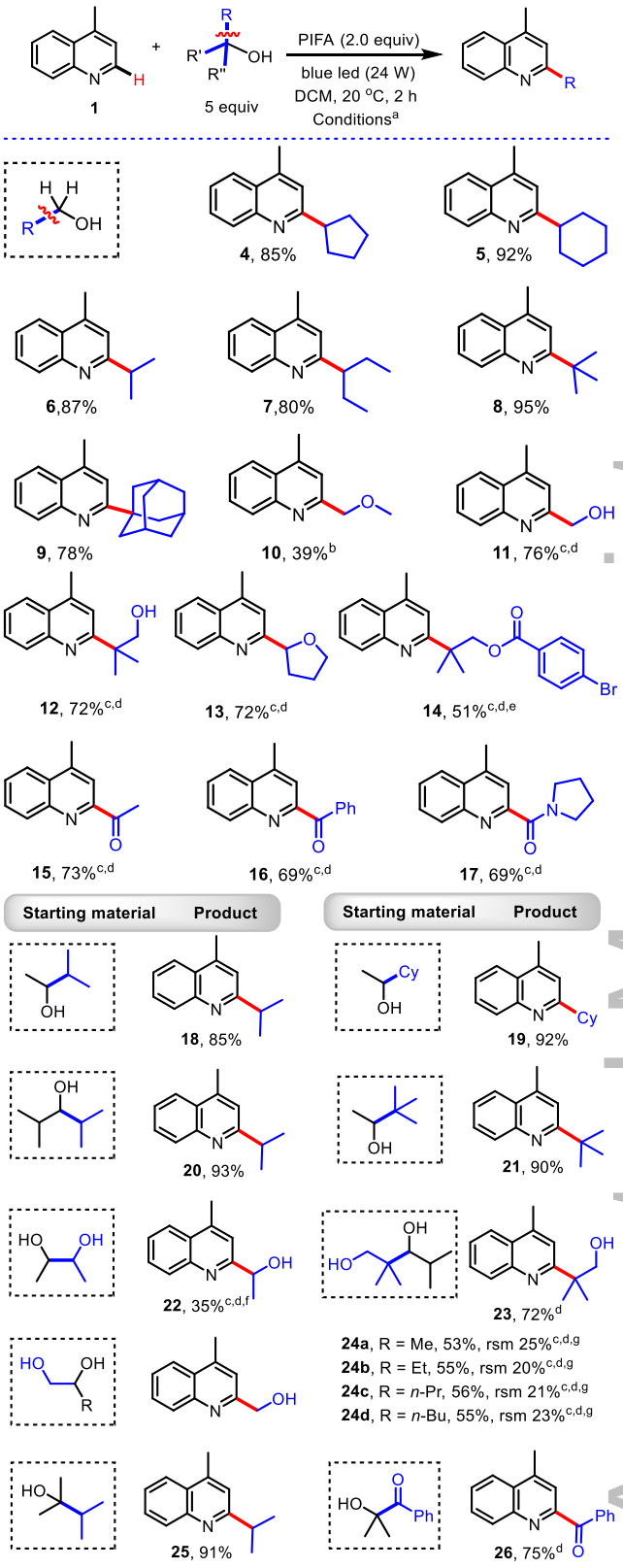
underwent smoothly and the corresponding alkylated Lepidine were obtained in high to quantitative yields (**4**-**9**). In addition, alcohols with diverse functional groups, such as unprotected hydroxyl, ether, ester, ketone and even amide were also screened (**10**-**17**). At the beginning, the reactions failed to conduct by using these substrates under standard conditions. But the problems were solved soon by replacing the solvent dichloromethane (DCM) with glycol dimethyl ether (GDE). The possible reason is the strong coordination between hypervalent iodine and alcohols bearing more than one heteroatoms, which makes it difficult to produce alkoxy radical. The *O*-atoms in ether solvents might preferentially coordinate with the *I*-atom, and hence prevent the strong coordination between alcohols and PIFA. By using GDE as the solvent, functionalized alcohols were also effective substrates. It's noteworthy that unprotected diols were amenable to this system (**11 and 12**). Especially it could achieve the *β*-hydroxyl alkylation of heteroarene (**12**), which cannot be reached in the previous Minisci-type reactions.[11] Besides, the unstrained C(sp^3)-C(sp^3) bonds in α-hydroxy ketones and α-hydroxy amides could also cleave to produce corresponding acyl radicals and amide radicals, and subsequently achieve lepidine C2-H acylation and amidation reactions (**15**-**17**). Then we examined various secondary and tertiary alcohols (**18**-**26**). Under the optimal reaction conditions, they all can afford the expected alkylated and/or acylated heteroarenes via the selective C-C bond cleavage. The diol compounds could also react smoothly (**22**-**24**). Interestingly, when a diol with a primary and a secondary hydroxyl groups was used as a substrate, the secondary hydroxyl group preferentially reacted with PIFA to give the corresponding alkylated lepidine (**23** and **24**). This selectivity might be due to the nucleophilicity of the *O*-atoms. Furthermore, another attractive selectivity is the C-C bond cleavage. It can be seen from **23** and **24** that the *β*-fragmentation of the C-C bond occurred where a more stable alkyl radical would form. For example, it was not an isopropyl but a quaternary carbon that alkylated to heteroarene because the 3° C-centered radical is stable than the 2° one. Also the desired products were isolated in excellent yields with tertiary alcohols (**25** and **26**).

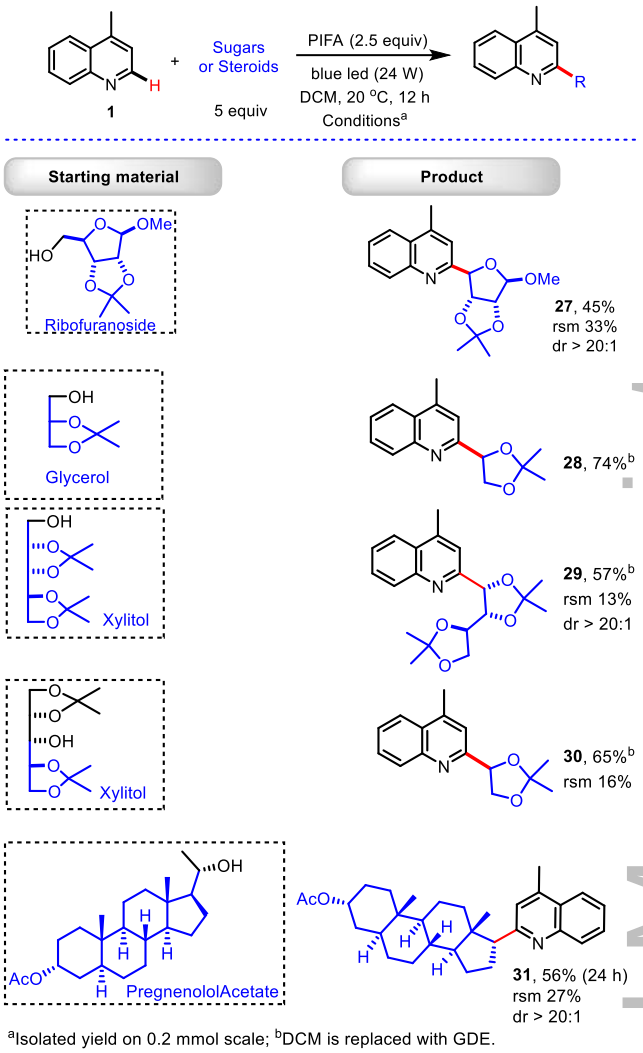


[a]Isolated yield on 0.2 mmol scale; [b]Side product **10'** was formed in 44% isolated yield, see SI; [c]DCM is replaced with GDE; [d]t = 12 h, PIFA = 2.5 equiv; [e]About 20% of aldehyde and acid byproduct from the corresponding alcohol was formed; [f]Ketone by further oxidation of the product **22** was formed in 40% isolated yield, see SI; [g]Aldehyde by further oxidation of the product **24** was formed in <10% isolated yield, see SI. *rsm is the short for of recovery starting material

Scheme 2. C-H alkylation of lepidine by selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in alcohols.

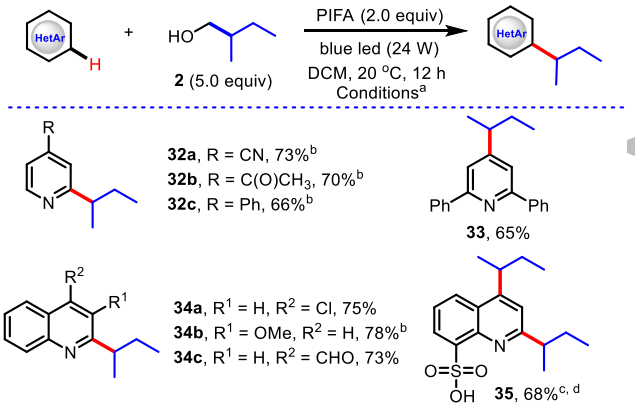
Selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in sugars and steroids for heteroaryl C-H alkylation and acylation. The selective C-C bond cleavage via *β*-fragmentation of alkoxy radical has been successfully applied in skeletal modification of sugars and steroids derivatives.[3, 9, 10] However, most of these systems were limited in breaking the C-C bond (C1-C2) adjacent to the secondary hydroxyl group. To the best of our knowledge, the selective C-C bond cleavage via *β*-scission of the primary alkoxy radical in sugars has not been realized before. Based on the results of Scheme 2, we began to apply this strategy in sugars and steroids (Scheme 3). Fortunately, for the first time, we successfully incorporated a series of cyclic and/or linear sugars and steroids into heteroarenes via primary alkoxy radical-promoted selective cleavage of unstrained C(sp^3)-C(sp^3) bond. As shown in Scheme 3, both cyclic sugar Ribofuranoside (**27**) and linear sugars such as Glycerol (**28**) and Xylitol (**29** and **30**) were compatible with this system. It is worth noting that only one configurational isomer was observed in these reactions. This unique selectivity should be due to the stereo-electronic effect (anomeric effect). The hyperconjugation effect between electrons in SOMO and *p*-orbital of the vicinal *O*-atom makes the radical addition occurred at the axial direction. Interestingly, this protocol can realize selective C-C bond cleavage in one same sugar molecule (**29** and **30**). For example, (2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)methanol and bis(2,2-dimethyl-1,3-dioxolan-4-yl)methanol gave the corresponding products **29** and **30** respectively in good yields. In addition, steroid Pregnenolol acetate was also evaluated to be effective substrate, which reacted with lepidine to afford the expected product in 56% yield (**31**). Thus this method provided a new strategy for skeletal modification of sugars and steroids compounds.

Selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in 2-Me-butanol for heteroaryl C-H alkylation. Next, a variety of heteroarenes were tested. As depicted in Scheme 4, alkylation of pyridines and quinolines heteroarenes selectively took place at C2 and/or C4 positions, while isoquinoline solely preferred the C1 position (see **32-36**). In general, the electronic effect of substituents in heteroarenes had little impact on the reaction (**34b** vs **34c**). Other heteroarenes, such as quinoxaline, phthalazine, quinazoline, benzoquinoline and phenanthridine, were also proved to be suitable substrates (see **36-41**). Various functional groups including unprotected hydroxyl or phenolic hydroxyl, ether, benzoate or acetate, halogen, sulfonic acid, amide, sulfonamide and even olefins were tolerated. This Minisci C–H alkylation can also be successfully applied to functionalize complex natural products and drug molecules (**42-46**). For instance, fenazaquin, quinoxyfen, fasudil and quinine can be selectively alkylated at the specific position of the heteroaryl ring in good yield under standard reaction conditions (**42-45**). *N*,*N*-dibenzoyl-famciclovir resulted in monoalkylation and dialkylation in excellent yield (**46**).



[a]Isolated yield on 0.2 mmol scale; [b]DCM is replaced with GDE.
*rsm is the short for of recovery starting material.

Scheme 3. C-H alkylation of lepidine by selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in sugars or steroids.



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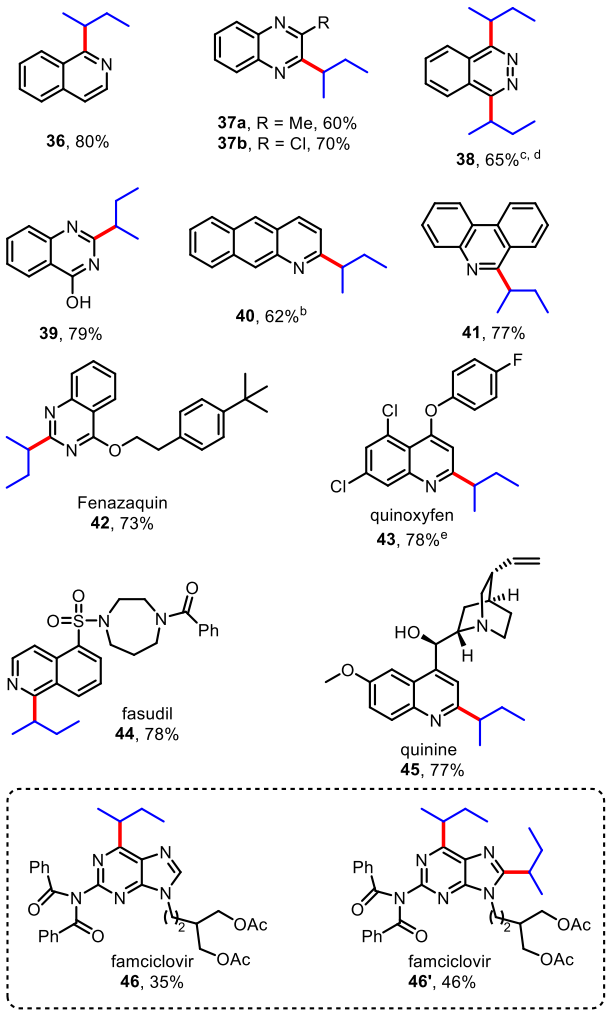


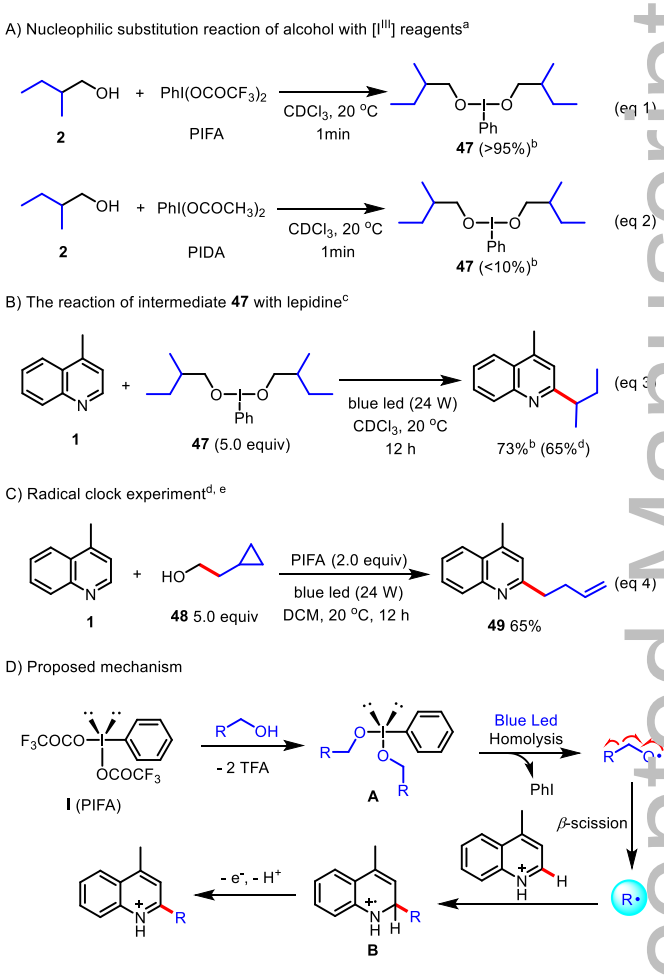
[a]Isolated yield on 0.2 mmol scale; [b]Dialkylated product was formed <10%; [c]t = 24 h, PIFA = 2.5 equiv; [d]Monoalkylated product was formed <10%; [e]5 equiv. of glycol dimethyl ether (GDE).

Scheme 4. Substrate scope of heteroarenes.

Mechanistic Studies.[12]

As demonstrated in Scheme 5, a set of experiments were designed to study the mechanism in details. Initially, mixing **2** with PIFA in $CDCl_3$ immediately led to a metastable intermediate **47**, which was speculated by crude ^{1}H-NMR and ^{13}C-NMR (eq 1). However, reaction of PIDA and alcohol **2** could not yield intermediate **47** (eq 2) (see the SI). These results could explain the fact that PIDA exhibited no reactivity in the cleavage of C(sp^3)-C(sp^3) bond in alcohol (entry 1, Table 1). Subsequently reaction of intermediate **47** with lepidine smoothly gave the expected product **3** in 73% yields (eq 3). Then a radical clock experiment was conducted (eq 4). The PIFA promoted reaction of lepidine with 2-cyclopropylethan-1-ol (**48**) afforded the ring-opening product **49** in 65% yield and 2-formyl lepidine **49'** in 10% (see the SI), which clearly supported a free-radical pathway involving β-scission of alkoxyl radical.

Finally, based on the results of control experiments and the previous literatures,[3, 9-11] a plausible mechanism was proposed (Scheme 5D). Firstly, nucleophilic substitution reaction of PIFA with alcohol produced intermediate **A**. Then photo-irradiated homolysis of **A** afforded an alkoxy radical by liberating PhI. Subsequently, the alkoxy radical underwent a β-fragmentation to give an alkyl radical and formaldehyde. Next addition of alkyl radical to a protonated heteroarene generated a radical cation **B**, which then conducted single electron oxidation followed by deprotonation to yield the final product. The by-products such as iodobenzene and aldehydes or ketones were isolated and/or detected.



Scheme 5. Mechanistic Studies.

Conclusion

In summary, we have developed a visible-light-induced highly selective cleavage of unstrained C(sp^3)-C(sp^3) bonds in general alcohols, especially for challenging primary alcohols. Through this strategy, a wide range of 1°, 2° and 3° alcohols including sugars and steroids without ring strain or steric hindrance can be utilized as more sustainable and safer alkyl radical precursors than traditional ones. As depicted in this work, an efficient heteroaryl C-H alkylation and/or acylation could be achieved by

a Minisci-type reaction of heterocycles with alcohols. Besides, the features of metal and photo-catalyst free, scalability and compatibility of diverse functional groups make it very attractive to synthetic organic chemistry. Most importantly, this protocol can be used to break a given C-C bond selectively even in sugars and complex natural products, which would have great potential for application in biomass conversions. Future studies on exploring catalytic hypervalent iodine systems are ongoing in our lab.

Experimental Section

Lepidine **1** (28.6 mg, 0.2 mmol, 1.0 equiv) and 2-methylbutanol **2** (88.0 mg, 1.0 mmol, 5.0 equiv) were first dispersed in 1 mL DCM. PIFA (171.6 mg, 0.4 mmol, 2.0 equiv) was then added. The reaction was irradiated with 24 W blue LEDs and kept at rt under fan cooling for 2 h. After the reaction completion monitored by TLC, the mixture was quenched by addition of saturated $NaHCO_3$ until pH>8 and then extracted with DCM (3 x 2 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (eluted with hexane/acetone (v/v 20:1)) to give the desired product (isolated yield 85%).

Acknowledgements

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[12] For the details about mechanistic studies, see the Supporting Information.

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FULL PAPER

Surgical Cleavage of Unstrained C(sp^3)-C(sp^3) Bonds in General Alcohols for Heteroaryl C-H Alkylation and Acylation

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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