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ARTICLE

Visible light-Promoted Ring-Opening Functionalization of Unstrained Cycloalkanols via Inert C-C Bond Scission

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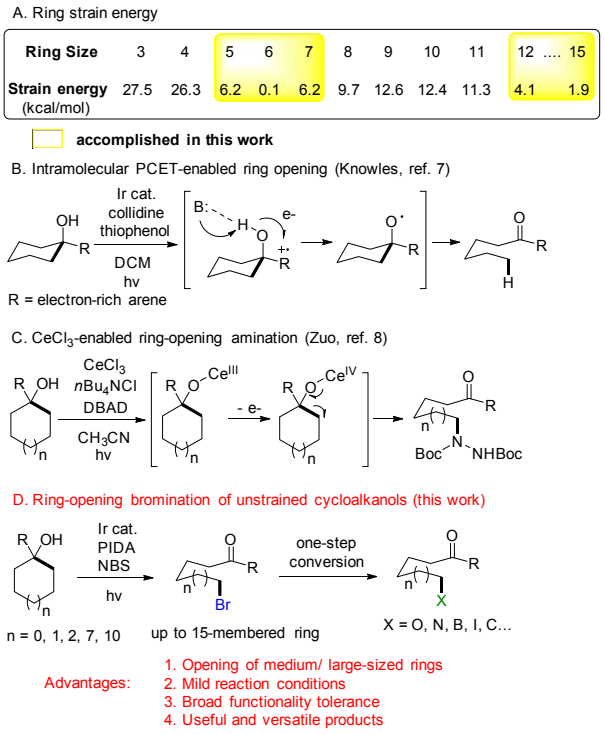
Described herein is a novel, useful, visible light-promoted ring-opening functionalization of unstrained cycloalkanols. Upon scission of the inert cyclic C-C σ-bond, a set of medium- and large-sized rings are readily brominated under mild reaction conditions to afford the corresponding distal bromo-substituted alkyl ketones that are hard to make otherwise. The products are versatile building blocks, which are easily converted to other valuable molecules in one-step operation. The protocol is also applicable to the unprecedented ring-opening cyanation and alkynylation of unstrained cycloalkanols.

Introduction

C-C bond activation is always a challenging issue in synthetic chemistry. Over the past few decades, this area has received great attention relying on the cleavage of cyclic C-C bonds.[1] The strained cycloalkanols such as cyclopropanols and cyclobutanols have emerged as privileged precursors for the preparation of β- and γ-substituted ketones through the radical-mediated ring-opening functionalization. [2,3] Recently, we have consecutively reported the ring-opening functionalization of cyclobutanols to construct various chemical bonds, e.g., C-F, C-Cl, C-N, C-S, C-C, etc., based on the silver or manganese catalysis.[4] However, the opening of unstrained rings (in particular, 5-7 and 12-15 membered rings) are always confronted with a formidable challenge. It is mainly attributed to the significantly decreased ring-strain energy (Scheme 1A).[5] During our research, it was also found that the intramolecular dehydration took place in competition with ring-opening pathway to suppress reaction outcome. Therefore, an efficient catalytic protocol should be sought for the ring opening of unstrained cycloalkanols.

Photoredox catalysis has proven to be a powerful tool for the mild generation of alkyloxy radical that triggers the subsequent ring-opening reactions or other transformations.[6] Recently, Knowles et al. applied the intramolecular proton-coupled electron transfer (PCET) to the photocatalytic ring opening of unstrained cycloalkanols.[7] In this remarkable



Scheme 1 Ring-opening functionalization of unstrained cycloalkanols.

progress, however, the electron-rich tertiary alcohols were required to generate the arene radical cation, a key intermediate for the intramolecular PCET process. It somewhat limited the practicality of protocol (Scheme 1B). Later, Zuo et al. disclosed an elegant photocatalytic ring-opening amination of unstrained cycloalkanols by cerium chloride complex (Scheme 1C).[8] Beyond that, other types of ring-opening

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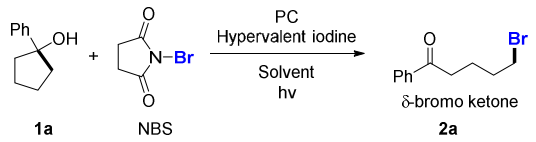
Table 1 Reaction parameters survey[a]



1a NBS 2a

PC 1: $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$; **PC 3**: *fac*-$Ir(ppy)_3$;
PC 2: $[Ir(ppy)_2(dtbbpy)]PF_6$; **PC 4**: $Ru(bpy)_3Cl_2 \cdot 6H_2O$

Entry	Solvent (v/v 20/1)	Photoredox catalyst	Hypervalent iodine	Yield (%)[b]
1	DCM/H_2O	PC 1	PIDA	22
2	DCE/H_2O	PC 1	PIDA	21
3	$CHCl_3$/H_2O	PC 1	PIDA	15
4	CCl_4/H_2O	PC 1	PIDA	74
5	DMF/H_2O	PC 1	PIDA	0
6	DMSO/H_2O	PC 1	PIDA	0
7	acetone/H_2O	PC 1	PIDA	<5
8	toluene/H_2O	PC 1	PIDA	<5
9	$PhCF_3$/H_2O	PC 1	PIDA	68
10	CH_3CN/H_2O	PC 1	PIDA	35
11	THF/H_2O	PC 1	PIDA	0
12	MeOH/H_2O	PC 1	PIDA	0
13	CCl_4/H_2O	PC 2	PIDA	76
14	CCl_4/H_2O	PC 3	PIDA	59
15	CCl_4/H_2O	PC 4	PIDA	24
16	CCl_4/H_2O	PC 2	BI-OH	70
17	CCl_4/H_2O	PC 2	IBX	55
18	CCl_4/H_2O	PC 2	DMP	65
19[c]	CCl_4/H_2O	PC 2	PIDA	70
20	CCl_4	PC 2	PIDA	<5
21	CCl_4/H_2O	PC 2	-	53
22	CCl_4/H_2O	-	PIDA	45
23	CCl_4/H_2O	-	-	0
24[d]	CCl_4/H_2O	PC 2	PIDA	0
25	$PhCF_3$/H_2O	PC 2	PIDA	78

[a]**1a** (0.2 mmol), NBS (0.3 mmol, 1.5 equiv.), hypervalent iodine (0.4 mmol, 2.0 equiv.), and PC (0.006 mmol, 3 mol %) in mixed solvents (2.0 mL/ 0.1 mL) at rt, 14 W blue LEDs irradiation. [b]Yields of isolated products. [c]CCl_4/H_2O (2.0 mL/ 0.2 mL). [d]In dark.

functionalization of unstrained cycloalkanols are still anticipated.

Alkyl bromides are versatile building blocks in synthetic chemistry, which can be easily converted to other valuable molecules through nucleophilic substitution or cross couplings. We considered that the ring-opening bromination of unstrained cycloalkanols would give rise to the distally bromo-substituted alkyl ketones which are synthetically valuable but hard to make otherwise. Herein, we provide support for this hypothesis (Scheme 1D). A set of medium- and large-sized rings are readily brominated through the mild cleavage of inert cyclic C-C σ-bond with the assistance of visible-light irradiation. The newly formed C-Br bonds can function as the privileged precursors for many other useful chemical bonds. Moreover, the protocol is also applicable to the unprecedented ring-opening cyanation and alkynylation of unstrained cycloalkanols.

Results and discussion

At the outset, we implemented the reaction parameters survey with the less strained 1-phenylcyclopentanol **1a** as model substrate and NBS as bromine source (Table 1). It was found that the use of biphasic solvents was crucial to the reaction. In the presence of photoredox catalyst (PC) and hypervalent iodine reagent, the ring-opening bromination readily proceeded under visible-light irradiation, affording the desired δ-bromo alkyl ketone **2a**. A brief evaluation of solvents indicated that CCl_4/H_2O delivered the best yield (entry 4), while the use of $PhCF_3/H_2O$ also resulted in the comparable yield (entry 9). The yield was slightly improved to 76% by using PC 2 instead of PC 1 (entry 13). Other than PIDA, hypervalent iodine reagents such as BI-OH, IBX, and DMP were also suitable to the reaction, but leading to lower yields (entries 16-18). The amount of H_2O was important to the reaction outcome. Raising the volume of H_2O in biphasic solvents decreased the yield (entry 19), whereas using anhydrous CCl_4 only led to trace amounts of product **2a** (entry 20). Both PC and PIDA were not indispensable; removing either one could still afforded the product in modest yields (entries 21 and 22). It might suggested that the overall ring-opening process was appeared as an overlying outcome of two different pathways. The reaction did not proceed in the absence of both PC and PIDA or in dark (entries 23 and 24). Finally, the yield of **2a** was further improved to 78% with the use of $PhCF_3/H_2O$ as the mixed solvent (entry 25).

With the optimized reaction conditions in hand, we set about investigating the generality of protocol (Scheme 2). Firstly, a variety of cyclopentanols were tested. Generally, electron-deficient aryl substituents were preferred in the reaction, leading to the δ-bromo alkyl ketones in synthetically useful yields. Halides (**2b**-**2d**), in particular bromide (**2d**), were well tolerated, providing a platform for the late-stage product manipulation. Positional change (*para*-, *meta*-, and *ortho*-) of substituents did not impede the transformation (**2g**-**2i**). Although the highly electron-rich aryl such as anisole was not suitable due to the electrophilic bromination of aryl, it could be overcame by mounting an additional electron-withdrawing group (**2h**). This method also allowed for the preparation of secondary bromide (**2j**). The ring opening of unsymmetric cycloalkanols proceeded in a regioselective manner. However, the synthesis of tertiary bromide was failed under the current reaction conditions. The scope of cyclohexanols was investigated more extensively than cyclopentanols. Besides the functional groups already examined, other groups such as cyano (**2q** and **2t**) and ester (**2z**) were also compatible to the reaction conditions. In addition to the aryl-substituted cyclohexanols, the alkyl-substituted cyclohexanols were apt to furnish the elusive distal-bromo dialkyl ketones (**2w** and **2x**). Various substituents could be incorporated to the alkyl chain by using the functionalized cycloalkanol precursors (**2y**-**2ab**). In the presence of excess NBS, the threefold bromination took place on the toluene-substituted cycloalkanol to give product **2ac** which was brominated at both benzylic and distal positions. The reaction with the cyclohexanol derived from

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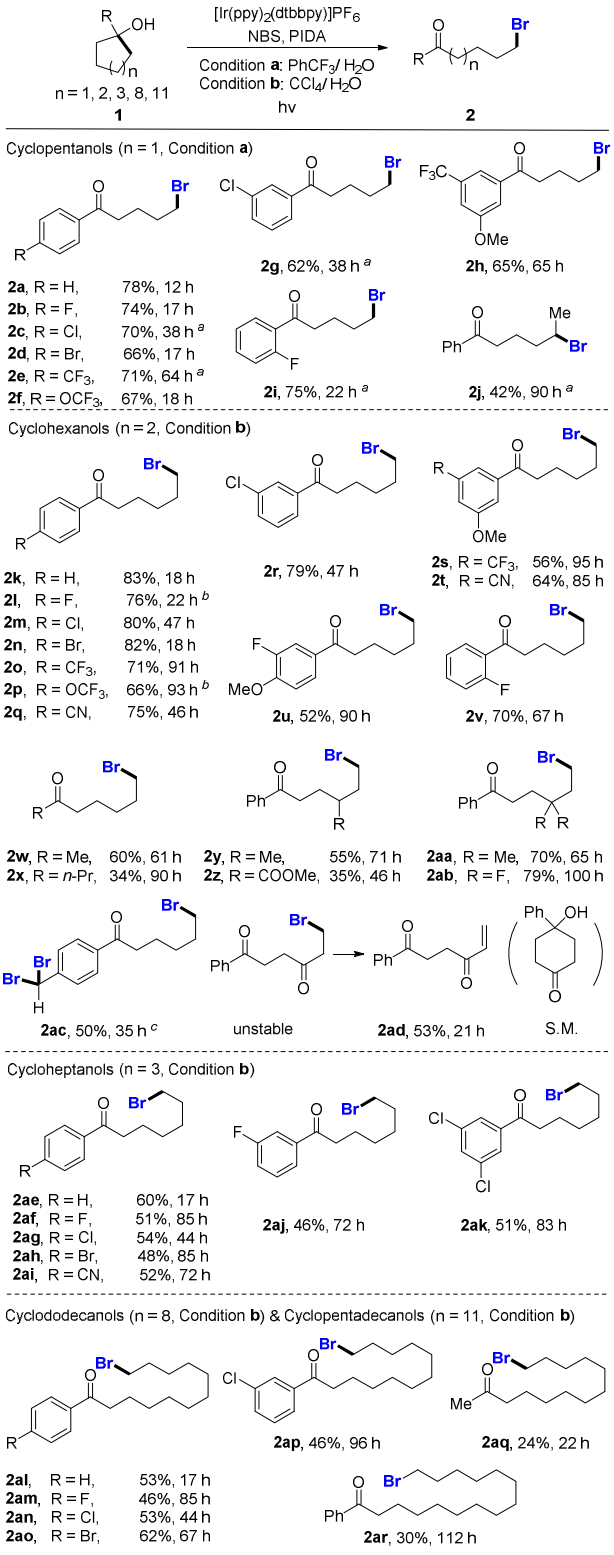
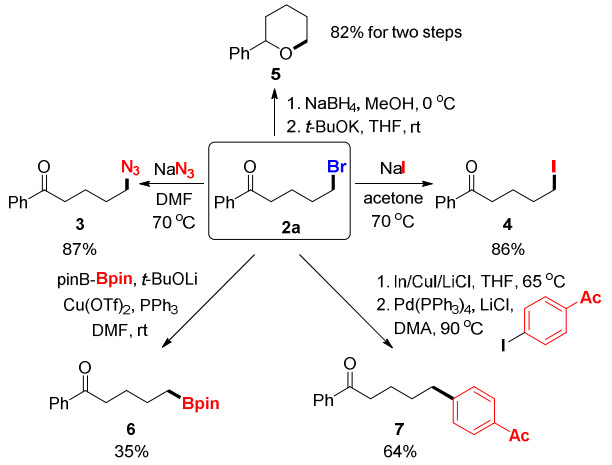


Scheme 2 Scope of unstrained cycloalkanols.

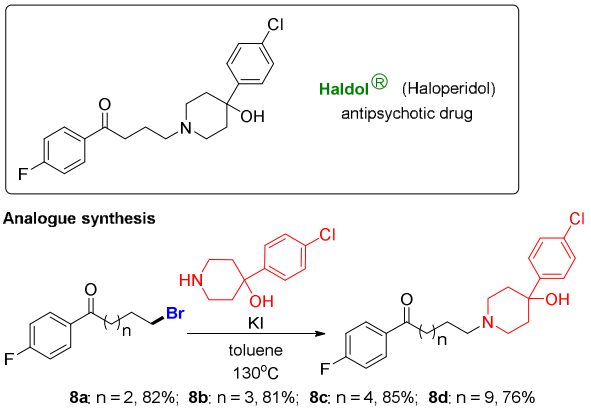
Reaction conditions: **1** (0.2 mmol), NBS (0.3 mmol, 1.5 equiv.), PIDA (0.4 mmol, 2.0 equiv.), and PC (0.006 mmol, 3 mol %) in mixed solvents (2.0 mL/ 0.1 mL) at rt, 14 W blue LEDs irradiation. Yields of isolated products are given. [a]With Condition **b**. [b][Ir(dF(CF3)ppy)2(dtbbpy)]PF6 as PC. [c]NBS (0.8 mmol, 4.0 equiv.).



Scheme 3 Transformation of products to other useful molecules.

1,4-cyclohexandione afforded the unsaturated 1,4-diketone via dehydrobromination (**2ad**). Likewise, the ring-opening bromination of cycloheptanols bearing various functional groups also readily proceeded, affording the corresponding distal-bromo alkyl ketones in useful yields (**2ae**-**2ak**). Unfortunately, the ring opening of eight- and ten-membered cycloalkanols failed, leading to complex mixtures. The reason is unclear so far. Remarkably, the opening of large-sized rings such as cyclododecanols and cyclopentadecanols occurred efficiently, yielding a variety of distally brominated alkyl ketones that are hard to make otherwise (**2al**-**2ar**).

To manifest the utility of protocol, the products were converted to other valuable molecules via nucleophilic substitution or cross-coupling in one or two steps (Scheme 3). Firstly, the bromide in **2a** was easily replaced by azide and iodide, forming new C-N_3 and C-I bonds in good yields (**3** and **4**).[9] Then, the ketone in **2a** was reduced to alcohol that intramolecularly attacked the alkyl bromide, leading to tetrahydropyran **5** in two steps with high yield.[10] Alternatively, the C-Br bond was readily converted to C-B and C-C bonds via transition-metal catalyzed cross-coupling reactions, affording synthetically useful building blocks or molecules (**6** and **7**).[11]



Scheme 4 Production of haloperidol analogues.

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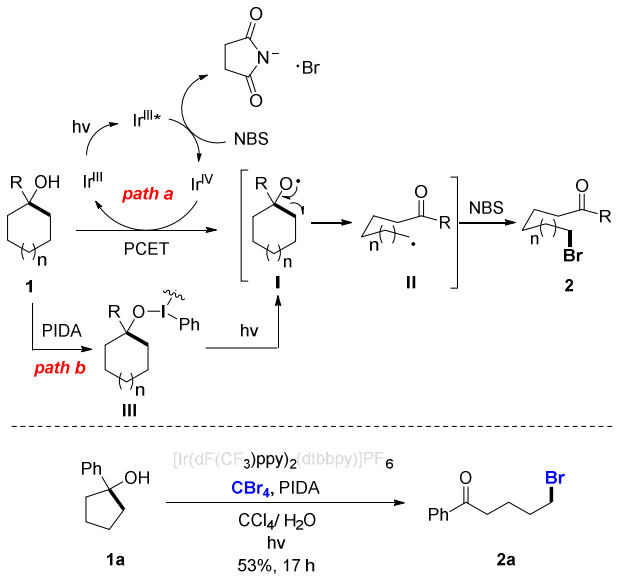
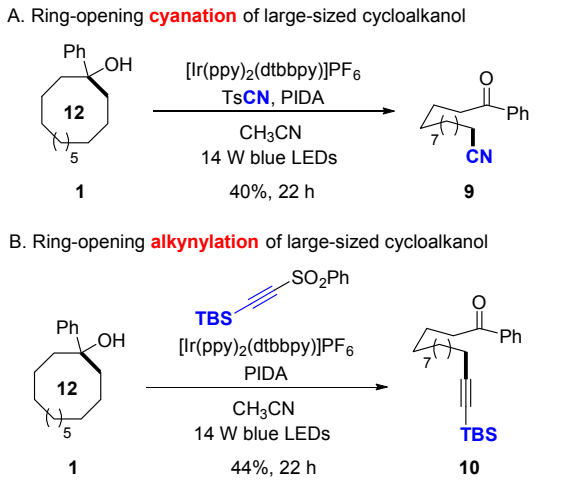


Scheme 5 Plausible pathways of ring-opening bromination.



Scheme 6 Ring-opening cyanation and alkynylation of unstrained cycloalkanols.

Haloperidol is a marketed antipsychotic drug extensively used to treat schizophrenia and Tourette's syndrome. After gaining a portfolio of distal-bromo alkyl bromides as precursors, we accomplished the preparation of haloperidol analogues in high yields (**8a**-**8d**, Scheme 4).[12] The test for their biological activities is now ongoing.

According to the experimental results, the plausible mechanism is depicted (Scheme 5, top). Although the detailed process for the generation of cycloalkoxy radical **I** is not fully understood, the radical **I** might be delivered via two pathways. Firstly, Stern-Volmer studies disclose that the excited state of Ir^{III} catalyst **PC 2** could be oxidatively quenched by NBS to generate the Ir^{IV} complex (see the Supporting Information). However, the oxidation potential of this Ir^{IV} complex ($E_{1/2}^{IV/III}$ = 1.21 V in MeCN vs. SCE) is unable to oxidize cycloalkanol **1** ($E_{p/2}$ > 2.0 V in MeCN vs. SCE) to alkoxy radicals **I** via SET process (for the cyclic voltammetry studies, see the Supporting Information). Thus, we postulate an intramolecular proton-coupled electron transfer (PCET) process for the generation of alkoxy radical **I** in the presence of an Ir^{IV} complex and weak base such as succinimide anion (path a).[13] Alternatively, homolysis of the O-I bond *in situ* formed by the reaction of cycloalkanol **1** with PIDA might also lead to the alkoxy radical **I** (path b).[14] In either way, the visible-light irradiation is indispensable. The subsequent β-C scission of **I** leads to the ring-opened alkyl radical **II**, which is intercepted by NBS to give the final product **2**. Notably, CBr_4 is also a competent bromine source in lieu of NBS to afford the same brominated product, suggesting the formation of intermediate **II** during the reaction (Scheme 5, bottom).

This protocol is also applicable to the challenging ring-opening cyanation and alkynylation of unstrained cycloalkanols.[15] Under the similar reaction conditions, 1-phenyl cyclododecanol was readily converted to the distally cyano- or alkynyl-substituted alkyl ketones in synthetically useful yields (**9** and **10**), providing a non-trivial approach to construct the remote C-C bonds (Scheme 6).

Conclusions

We have described a novel and efficient visible light-enabled ring-opening functionalization of unstrained cycloalkanols via the mild cleavage of cyclic C-C σ-bonds. A variety of cyclopentanols, cyclohexanols, cycloheptanols, cyclododecanols, and cyclopentadecanols are readily proceeded to furnish the distally brominated alkyl ketones that often function as the precursors of complex molecules in organic and medicinal synthesis. As shown above, this method provides the important feedstocks for the production of haloperidol analogues. The newly formed C-Br bonds in products are easily transformed into other valuable chemical bonds, thus illustrating the utility of method. The protocol is also applicable to the elusive ring-opening cyanation and alkynylation of unstrained cycloalkanols, providing an unusual strategy for construction of the remote C-C bonds.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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‡ Dedicated to Professor Takahiko Akiyama on the occasion of his 60th birthday.

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15 The ring-opening cyanation and alkynylation of cyclobutanols have been reported in ref. 3g, 3l, and 4i. However, the reaction with unstrained medium- or large-sized cycloalkanols remains unknown.

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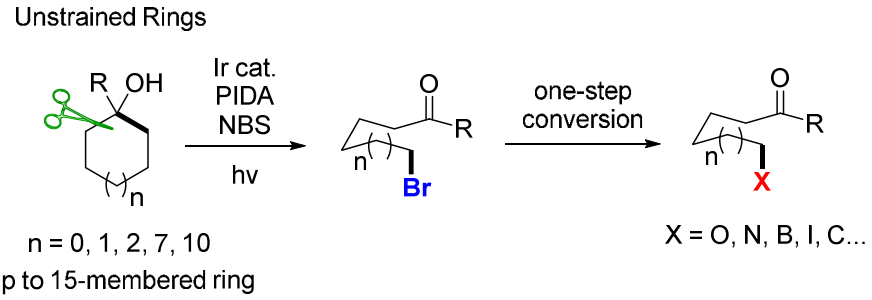

Reported herein is a novel, useful, visible light-promoted ring-opening functionalization of unstrained cycloalkanols.