

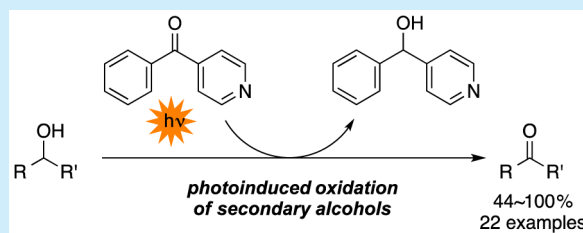
Photoinduced Oxidation of Secondary Alcohols Using 4-Benzoylpyridine as an Oxidant

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S Supporting Information

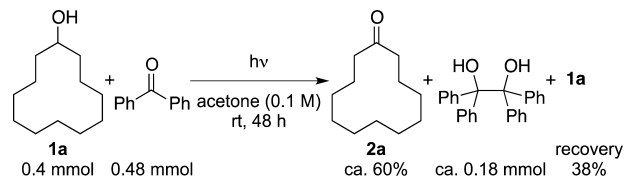
ABSTRACT: Photoinduced oxidation of secondary alcohols to ketones was achieved by utilizing an equimolar amount of 4-benzoylpyridine as an oxidant. This transformation proceeds at ambient temperature and exhibits high compatibility with polar functionalities including benzoyl, silyl, and methoxymethyl alcohol protecting groups as well as tosyloxy, bromo, sulfonyl, carbamate, ester, and carboxylic acid units. The present oxidation is solely promoted by the action of organic molecules without the aid of metallic reagents.



Oxidation is a fundamental transformation for functional group interconversions in synthetic organic chemistry.¹ Alcohol oxidation is especially important for preparation of carbonyl compounds, which serve as versatile synthetic intermediates due to their diverse reactivities.^{1,2} Despite a myriad of precedents and recent advancements in alcohol oxidation strategies, examples of photochemically induced alcohol oxidations at synthetically useful levels have still been mainly limited to benzyl alcohols.³ In the course of our studies on methodology development involving functionalizations of C–H bonds by the action of photoexcited benzophenone (Ph₂CO),⁴ the photoinduced benzopinacol synthesis⁵ caught our attention. The product, benzopinacol, is derived via reductive dimerization of Ph₂CO, and the reaction is usually carried out in *i*-PrOH. Thus, we anticipated this transformation could be applied for alcohol oxidation. The first report on the photoinduced benzopinacol synthesis appeared more than a century ago,^{5a} although its application to alcohol oxidation has been rarely investigated in the field of synthetic organic chemistry. If such oxidative transformation is realized, we can provide a new metal-free protocol for alcohol oxidation in which two different organic molecules participate in the redox process under photoirradiation conditions. We herein report a photochemically induced oxidation of secondary alcohols using 4-benzoylpyridine as an oxidant under mild conditions.

To develop a photoinduced alcohol oxidation, we initially investigated the fate of the alcohol that reduces Ph₂CO during the benzopinacol synthesis. We irradiated an acetone solution of cyclododecanol **1a** (0.4 mmol) and Ph₂CO (0.48 mmol) using a Hg lamp as shown in Scheme 1. As expected, formation of cyclododecanone **2a** (ca. 60% NMR yield) and benzopinacol (ca. 0.18 mmol) was observed. This result clearly demonstrated that Ph₂CO acted as an excellent oxidant for the photoinduced alcohol oxidation. However, two molecules of Ph₂CO were required to oxidize one molecule of alcohol.

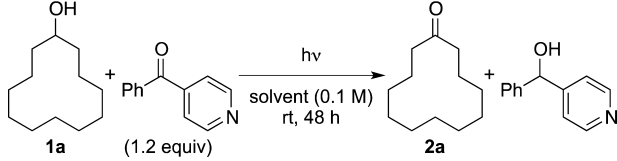
Scheme 1. Photoinduced Reaction between Cyclododecanol and Benzophenone



Having a promising result in hand of photochemically induced alcohol oxidation using an aryl ketone as an oxidant, we then searched for a better oxidant while optimizing reaction conditions (Table 1). Screening of aryl ketones revealed the oxidation of **1a** (0.5 mmol) with 4-benzoylpyridine (4-BzPy, 0.6 mmol) proceeded smoothly to give **2a** in 78% isolated yield with phenyl(pyridyl)methanol as a byproduct (0.49 mmol, entry 1).⁶ Accordingly, employment of 4-BzPy reduced the required amount of the oxidant to an amount equimolar to the starting alcohol. 2-Benzoyl- and 3-benzoylpyridine were less effective (entries 2 and 3),⁷ and neither an oxygen nor argon atmosphere improved the product yield (entries 4 and 5). Among the solvents examined, the oxidation was operative in a variety of solvents, including aprotic acetone, MeCN, CH₂Cl₂, PhCF₃, benzene, and AcOEt, as well as protic *t*-BuOH (entries 1 and 6–11). We selected acetone as the solvent in this study from the viewpoint of easy availability and cost.

With the optimized reaction conditions in hand, we examined oxidation of two androsterone stereoisomers (Scheme 2).⁸ Both *epi*-androsterone **1b** and androsterone **1b'** were readily converted to diketone **2b** in more than 90% yields.

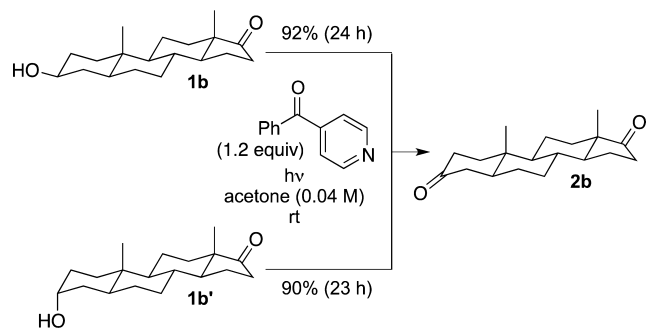
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Table 1. Optimization of Reaction Conditions^a


entry	conditions	solvent	yield, % ^b
1	air	acetone	80 (78) ^{c,d}
2	air, 2-benzoylpyridine ^c	acetone	trace ^f
3	air, 3-benzoylpyridine ^g	acetone	<66 ^h
4	O ₂	acetone	72
5	Ar	acetone	72
6	air	MeCN	77 ⁱ
7	air	CH ₂ Cl ₂	74 ⁱ
8	air	PhCF ₃	89 (83) ^c
9	air	benzene	80 ⁱ
10	air	AcOEt	76 ⁱ
11	air	<i>t</i> -BuOH	74 ⁱ

^aConditions: cyclododecanol **1a** (0.5 mmol, 1 equiv), 4-benzoylpyridine (0.6 mmol, 1.2 equiv), solvent (5 mL, 0.1 M), photoirradiation using a medium-pressure Hg lamp at rt for 48 h. ^bYield was calculated based on NMR analysis of the crude mixture unless otherwise noted. ^cIsolated yield is shown in parentheses. ^d¹H NMR analysis revealed ca. 0.49 mmol of phenyl(pyridyl)methanol was formed after the reaction. ^e2-Benzoylpyridine was employed instead of 4-benzoylpyridine. ^fAlcohol **1a** was recovered in ca. 97% NMR yield. ^g3-Benzoylpyridine was employed instead of 4-benzoylpyridine. ^hAlcohol **1a** was recovered in ca. 34% NMR yield. ⁱAlcohol **1a** was recovered in ca. 3–20% NMR yields.

Scheme 2. Oxidation of Androsterones



No apparent reactivity difference between these two stereoisomeric alcohols was observed.

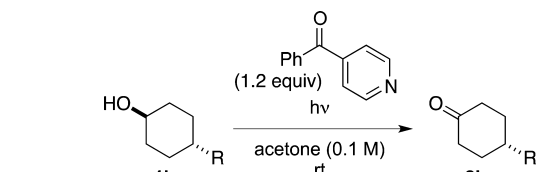
We next carried out the oxidation of androstanediol derivatives to clarify compatibilities of alcohol protecting groups under the same reaction conditions (Table 2). The benzoyl (**1c**), *tert*-butyldiphenylsilyl (**1d**), and methoxymethyl (**1e**) groups were retained, and chemoselective oxidation of the hydroxy group furnished the corresponding products **2c–e** in 70–76% yields (entries 1–3).⁹ In addition to cyclohexanols (**1c–e**), cyclopentanol (**1f**) was readily oxidized to give the ketone **2f** in 80% yield (entry 4). The diol **1g** was fully oxidized to diketone **2b** when more than 2 equiv of 4-BzPy were employed (44%, entry 5).

We then explored the generality of the photoinduced oxidation by using diversely functionalized cyclohexanol derivatives as substrates (Table 3). The compounds bearing tosyloxy (**1h**), bromo (**1i**), and sulfonyl functionalities (**1j**) were converted to the corresponding ketones **2h–j** in 66–77%

Table 2. Oxidation of Androstanediol Derivatives^a

entry	h	yield, % ^b
1	1c : R = Bz	2c 76
2 ^c	1d : R = TBDPS	2d 70
3	1e : R = MOM	2e 70
4 ^d	1f	2f 80
5 ^e	1g	2b 44

^aConditions: alcohol **1c–g** (1 equiv), 4-benzoylpyridine (1.2 equiv), acetone (0.04 M), photoirradiation using a medium-pressure Hg lamp at rt. ^bIsolated yield. ^cThe reaction was conducted in acetone (0.1 M). ^dThe reaction was conducted under Ar atmosphere. ^eDiol **1g** (1 equiv) was treated with 2.4 equiv of 4-benzoylpyridine.

Table 3. Oxidation of Cyclohexanol Derivatives^a


entry	R	1	time, h	yield, % ^b
1	R = CH ₂ OTs	1h	19	71 (2h)
2	R = CH ₂ Br	1i	24	77 (2i)
3	R = CH ₂ SO ₂ C ₆ H ₄ (<i>p</i> -OMe)	1j	48	66 (2j)
4 ^c	R = NHBoc	1k	24	56 (2k)
5	R = CO ₂ Et	1l	16	98 (2l)
6	R = CO ₂ H	1m	48	79 (2m)
7	(+)-neomenthol	1n	48	65 (2n)

^aConditions: alcohol **1h–n** (1 equiv), 4-benzoylpyridine (1.2 equiv), acetone (0.1 M), photoirradiation using a medium-pressure Hg lamp at rt. ^bIsolated yield. ^cLED lamp (365 nm) was used for irradiation.

yields (entries 1–3). The oxidation of the Boc-protected amine **1k** furnished the product **2k** in 56% yield (entry 4).¹⁰ The ester functionality (**1l**) was completely inert, and near-quantitative formation of the keto ester **2l** was observed (entry 5). The present photochemical oxidation was compatible with protic

conditions, and thus the carboxylic acid **1m** could be employed as a substrate for preparation of the keto acid **2m** (entry 6). Neomenthol **1n**, a sterically more hindered secondary alcohol with an isopropyl substituent at the vicinal position, was oxidized to menthone **2n** in 65% yield (entry 7).

We further investigated the applicability of the newly developed method for oxidation of acyclic alcohols (Table 4).

Table 4. Oxidation of Acyclic Aliphatic and Benzylic Alcohols^a

entry	h	yield, % ^b
1	48	82
2 1p : R, R' = <i>p</i> -MeO	8	2p 94
3 1q : R, R' = H	18	2q 100
4 1r : R, R' = <i>p</i> -Cl	32	2r 99
5 1s : R = <i>p</i> -MeO, R' = H	23	2s 94
6	22	
7	48	
8	12	

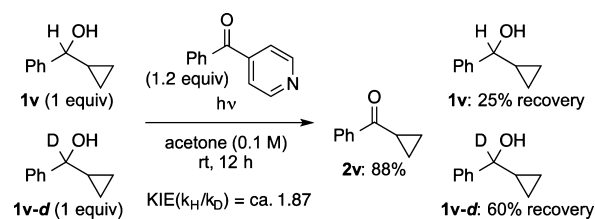
^aConditions: alcohol **1o–v** (1 equiv), 4-benzoylpyridine (1.2 equiv), acetone (0.1 M), photoirradiation using a medium-pressure Hg lamp at rt. ^bIsolated yield. ^cAlcohol **1u** was recovered in 88% NMR yield.

The photoinduced oxidation of the secondary aliphatic alcohol **1o** gave rise to 5-nonanone **2o** in 82% yield (entry 1).¹¹ The diphenylmethanol derivatives **1p–s** provided corresponding products **2p–s** in more than 94% yields (entries 2–5). Retardation of the oxidation was generally observed as the electron density on the aromatic ring of the starting alcohols decreased (entries 2–4). The unsymmetrical diarylmethanol was successfully oxidized to the corresponding ketone as well (entry 5). The oxidation of phenylethanol **1t** proceeded smoothly to afford acetophenone **2t** (entry 6). On the other hand, the attachment of the strongly electron-withdrawing CF₃ unit (**1u**) inhibited the formation of the ketone **2u** (entry 7). To obtain insight into the reaction mechanism, we conducted the oxidation of cyclopropyl(phenyl)methanol **1v** (entry 8). The reaction resulted in the formation of cyclopropyl phenyl ketone **2v** in 98% yield without opening the cyclopropane ring.

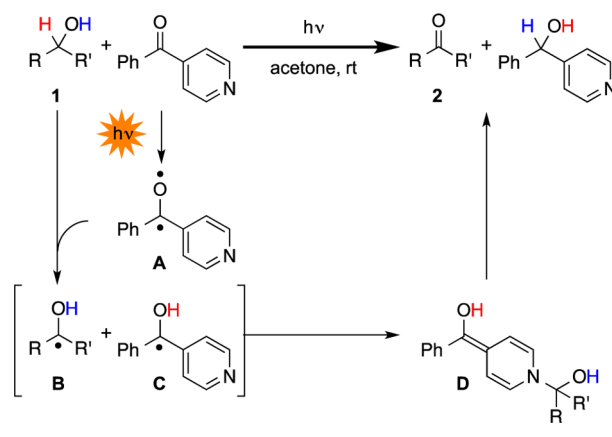
We further treated a mixture of the alcohol **1v** and its deuterated analogue **1v-d** under the oxidation conditions to obtain kinetic information on the transformation (Scheme 3). A kinetic isotope effect (KIE) was observed judging from the recovered alcohols **1v** and **1v-d**.¹² This outcome implied that cleavage of the C–H bond adjacent to the hydroxy group of the alcohol was the rate-determining step.

Consequently, we proposed a tentative reaction mechanism as illustrated in Scheme 4. The reaction starts with hydrogen abstraction of the starting alcohol **1** by photoexcited 4-BzPy

Scheme 3. Kinetic Isotope Effect of the Photochemical Alcohol Oxidation



Scheme 4. Proposed Reaction Mechanism for Photoinduced Alcohol Oxidation



A.¹³ Two ketyl radicals **B** and **C** are then transiently formed. This hydrogen abstraction step is supposed to be the rate-determining step based on the observed KIE. This observation accounts for the low reactivity of the CF₃-substituted alcohol **1u** having an electron-deficient C–H bond that is not readily cleaved by the electrophilic oxyl radical of **A**.¹⁴ Once ketyl radicals **B** and **C** are formed, facile radical coupling takes place to generate the hemiacetal-type intermediate **D**.^{7b,15} The use of 4-BzPy instead of Ph₂CO enables the rapid formation of the intermediate **D** as mentioned by the Görner^{7b} and Phillips¹⁵ groups and inhibits the pinacol-type homocoupling of the ketyl radical **C**.^{16,17} This is why the requisite amount of oxidant can be reduced to equimolar to the starting alcohol. Proton transfer and liberation of phenyl(pyridyl)methanol furnishes ketone **2** as the product.

In conclusion, we have developed a photoinduced oxidation of secondary alcohols by applying 4-benzoylpyridine (4-BzPy) as the sole oxidant. The amount of required oxidant was successfully reduced to an amount equimolar to the starting alcohol by the employment of 4-BzPy. This is in marked contrast to the case of Ph₂CO, which requires two molecules to oxidize one molecule of alcohol. Mechanistic investigations suggested the present oxidation proceeded via the facile formation of hemiacetal-type intermediate **D** and cleavage of the C–H bond adjacent to the hydroxy group of the alcohol was the rate-determining step. The present transformation proceeds at ambient temperature and shows high tolerance to a variety of polar functionalities including benzoyl, silyl, and methoxymethyl alcohol protecting groups as well as tosyloxy, bromo, sulfonyl, carbamate, ester, and carboxylic acid units. Because of the mildness of the reaction conditions, the present method should provide a unique tool for alcohol oxidation without the aid of metallic reagents.

■ ASSOCIATED CONTENT

■ Supporting Information

General experimental procedure and characterization of relevant compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01550.

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Notes

The authors declare no competing financial interest.

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- (8) The reactions were conducted in 0.04 M acetone solution because of the low solubility of the starting materials.
- (9) The photoinduced oxidation of benzylated androstane diol resulted in a complex mixture of products probably due to the sensitivity of the benzyl ether moiety under the present oxidation conditions.
- (10) The reaction using an LED lamp (365 nm, a KEYENCE UV-400 with UV-50A or UV-50H) gave a higher yield of the product **2k**. Under irradiation of a Hg lamp, the derived keto amide **2k** seems to be gradually decomposed.
- (11) Oxidation of the primary alcohol, 1-nonanol, was very sluggish, and a significant amount of the alcohol recovery was observed. Oxidation of 4-(hydroxymethyl)cyclohexanol resulted in a complex mixture of multiple unidentified products, and thus chemoselective clean oxidation to 4-(hydroxymethyl)cyclohexanone failed at the present stage.
- (12) The value of KIE (K_H/K_D) was calculated based on the consumed starting materials **1v** and **1v-d** since both of them provided the same product **2v**.
- (13) The C–H bond of alcohol **1** should be preferentially cleaved over the O–H bond due to the difference of bond dissociation energy (BDE). The BDE of Me₂CHOH is 94.8 kcal/mol, and that of Me₂CHOH is 105.7 kcal/mol; see: Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CPC Press: Boca Raton, FL, 2007; pp 71 and 257.
- (14) As a referee pointed out, two hydrogen transfers from the starting alcohol **1** to the photoexcited ketone **A** could be taking place in a nearly concerted fashion based on the low KIE as well as the no cyclopropane ring opening. Indeed, we observed formation of ca. 20% deuterated phenyl(pyridyl)methanol (PhPyCDOH) after the oxidation of ca. 76% deuterated cyclododecanol (cyclo-C₁₂H₂₃OD) with 4-BzPy. Further investigations are needed to obtain more detailed information on the reaction mechanism.
- (15) Formation of the intermediate **D** is reported by the photochemical reaction between 4-benzoylpyridine and 2-propanol; see: Du, Y.; Xue, J.; Ma, C.; Kwok, W. M.; Phillips, D. L. *J. Raman Spectrosc.* **2008**, *39*, 503.
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