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Visible Light Mediated Reductive Cleavage of C−O Bonds Accessing α-Substituted Aryl Ketones

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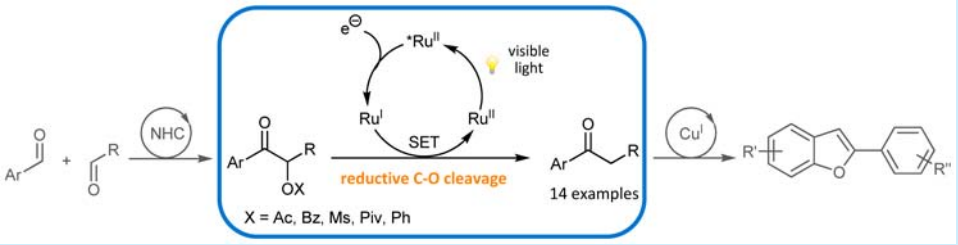
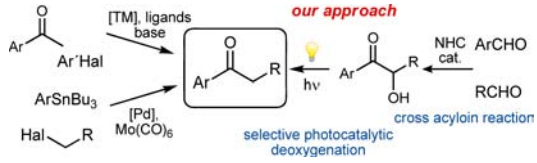
Supporting Information



ABSTRACT: C−O σ-bonds in multifaceted benzoin derivatives can be effectively cleaved as acetates using catalytic amounts of $[Ru(bpy)_3]Cl_2$ as photoredox catalyst in combination with Hantzsch ester and triethylamine as a sacrificial electron donor. This mild and operationally simple method is applicable to a great variety of substrates. Homo- and cross-benzoins, which are easily accessed by NHC (*N*-heterocyclic carbene) catalysis, with both electron-withdrawing and electron-donating substituents, including aryl halogenides, can be employed. The deoxygenated counterparts are isolated in good to excellent yields. These broadly accessible, α-substituted (nonsymmetric) aryl ketones are versatilely applicable for further transformations as illustrated by the syntheses of 2-arylbenzofurans.

α-Aryl ketones, including 1,2-diarylethanones, are not only common pharmacophores, being also present in a large number of biologically active natural products,[1] but also often serve as valuable building blocks for the synthesis of a great variety of important heterocycles, such as indoles, oxazoles, pyrazoles, imidazoles, and isoflavones. Consequently, the selective preparation of these compounds has attracted considerable interest. Although several synthetic methods are available, transition-metal-catalyzed α-arylations of enolates (employing Pd, Ni, Cu, etc.) are most effective[2] but also suffer from some drawbacks, such as expensive ligands, catalysts, and starting material or rather harsh reaction conditions. Hence, alternative, operationally simple synthetic strategies employing readily available, inexpensive starting materials would be welcomed by synthetic chemists.

Building on the recent successful developments in selective NHC cross acyloin and benzoin reactions,[3] we questioned whether these products (stemming from simple aldehydes) would be attractive precursors for accessing α-aryl ketones.



Key to this strategy would be a broadly applicable, mild, and selective deoxygenation protocol, preferably mediated by visible light as an abundant and nontoxic reagent. Herein, we report the successful realization of this goal.

C−O bonds are prominent structural elements in the abundant families of natural products including sugars and biopolymeric lignins. Hence, their activation is of increasing interest in the rapidly growing field of research dealing with alternative sustainable resources.[4] Attracted by the great inherent synthetic potential of activating such strong C−O bonds, many different protocols have been dedicated to their challenging reductive cleavage. However, dating back to Kiliani's first deoxygenation report,[5] most of the protocols still suffer from the use of superstoichiometric amounts of hazardous chemicals and/or rather harsh reaction conditions. Apart from continuous improvements[6] and newer methods,[7−10] such as, e.g., the use of superelectron donors,[7] the radical Barton−McCombie reaction[11] is arguably the most widely applied deoxygenation protocol. Numerous recent modifications have been published meeting the concerns of employing highly toxic stannanes or altering the original, required xanthate activating group.[12] Despite the advances realized, most methods depend on hydroxyl derivatization, lowering the atom-economy of the process due the stoichiometric formation of (complex) by-products, and only a few methods are *catalytic*.

Recently, harsh UV-irradiative activation[13] has been complemented by visible light photocatalysis.[14] Beside the

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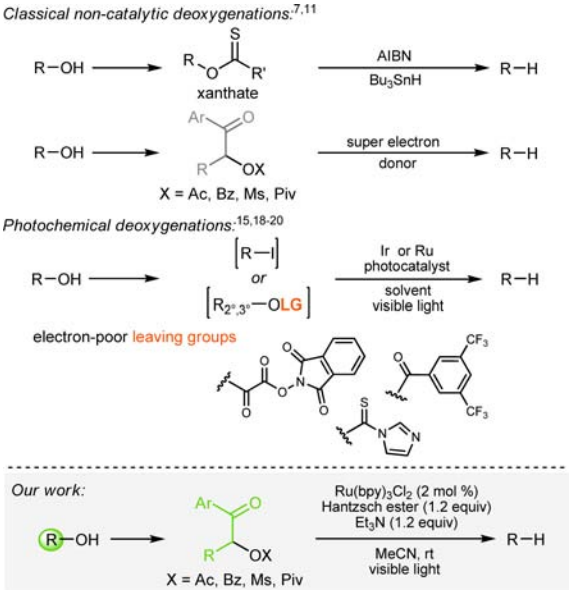
combination of a Garegg−Samuelsson reaction followed by a photoreductive dehalogenation in a batch to flow process,[15] which hence does not include the direct activation of a C−O bond, Stephenson and co-workers also published a method for a photoredox Ir-promoted deoxygenation,[16] focusing on the limited set of lignin model substrates in fragmenting weakened β-O-4 linkages and concurrently generating stabilized phenolates.[17] Tertiary alcohols can be cleaved as *N*-phthalimidoyl oxalates[18] while a broader set of substrates can be accessed with either *O*-thiocarbamates[19] or 3,5-bis(trifluoromethyl)-benzoates[20] as auxiliary activation groups.

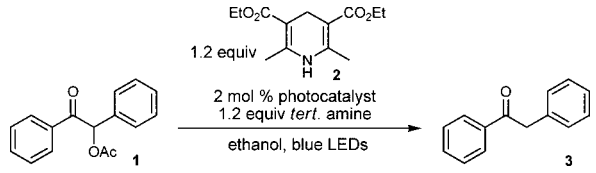


Our primary goal was to find an efficient and concomitantly very mild method for the photocatalytic cleavage of C−O bonds that would tolerate the presence of substituents susceptible to reduction (e.g., aryl bromides and iodides),[21] which can easily be cleaved off under published deoxygenation conditions employing Ir-based photocatalysts[16,19,20] and which maybe also be problematic for classical Pd-catalyzed approaches to α-aryl ketones.[2] As the direct cleavage of free hydroxyl groups seemed not to be promising we aimed at conditions that could be combined with the use of simple, well-known, and inexpensive activation groups for the alcohol functional group to render this method more attractive and easily applicable in synthesis.

With respect to providing an alternative pathway to α-aryl ketones as outlined above and their potential further applications for the synthesis of interesting 2-arylbenzofurans from 2-bromoaryl ketones,[22] we started our investigation by evaluating the reaction of benzoins. We first explored the proposed activation of the C−O bond in the context of simple *O*-acetylated benzoin **1** as our test substrate.

For the initial examination of a range of common photocatalysts and tertiary amines as reductive quencher (Table 1) ethanol was the solvent of choice due to solubility issues. Here, $Ru(bpy)_3^{2+}$ (entry 4) outperformed the other catalysts: the use of more reductive iridium salts (entries 1, 2) afforded the deoxygenated product in a low-yielding reaction together with many side products. Moreover, with eosin Y[23] (entry 3) full conversion could not be achieved even after 12 h (yield 30%). Our continued survey revealed that a combination of $Ru(bpy)_3^{2+}$, triethylamine, and Hantzsch ester **2** as an additive in acetonitrile was superior (entry 6). Test reactions without Hantzsch ester

Table 1. Optimization Reactions[a]



entry	catalyst	tertiary amine	time (h)	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	Bu_3N	12	49
2	Ir(ppy)$_2$(dtb-bpy)PF_6	Bu_3N	2.5	35
3[c,d]	eosin Y (λ_{max} = 539 nm)	Bu_3N	12	30
4	$Ru(bpy)_3Cl_2$	Bu_3N	1	81
5	$Ru(bpy)_3Cl_2$	Et_3N	1	86
6[e]	$Ru(bpy)_3Cl_2$	Et_3N	1	88
7[e,f]	$Ru(bpy)_3Cl_2$	Et_3N	1	2
8[e]	$Ru(bpy)_3Cl_2$		1	64
9[e,f]	$Ru(bpy)_3Cl_2$		96	0
10[e]		Et_3N	96	53
11[e,g]	$Ru(bpy)_3Cl_2$	Et_3N	96	0

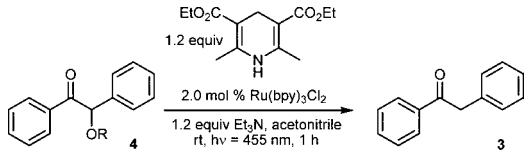
[a]Conditions: *O*-acetylbenzoin **1** (0.5 mmol), photocatalyst (2 mol %), Hantzsch ester (**2**, 1.2 equiv), *tert*-amine (1.2 equiv), ethanol (3 mL). [b]Yield of isolated product. [c]Irradiation with green LEDs. [d]No full conversion. [e]Using acetonitrile as a solvent. [f]Reaction performed without Hantzsch ester. [g]Reaction performed in the dark.

(entries 7 and 9) demonstrated its role as hydrogen donor, but it may also act as reductive quencher (Table 1, entry 8). Further control experiments to evaluate the influence of each component on the process proved the necessity of all reaction partners but also revealed, albeit with a strongly increased reaction time (up to 96 h), an alternative pathway without the presence of a photocatalyst (entry 10) yielding 53% yield of deoxybenzoin **3**. A possible reason for this observation may be a photoinduced electron transfer (PET) between the Hantzsch ester and the carbonyl group of the benzoin.[24]

A dark reaction was not observed during 96 h, confirming the requirement of a light source (entry 11).

The generality of this reaction with respect to other common leaving groups apart from acetate is summarized in Table 2.[17] Although a direct cleavage of the free hydroxyl or methoxy group could not be achieved under our best conditions (entries 1 and 2), derivatizing the alcohol function with more electron-

Table 2. Scope of Different Leaving Groups[a]



entry	substrate	R	product	yield[b] (%)
1	**4a**	H	3	0
2	**4b**	Me	3	0
3	**1**	Ac	3	88
4	**4c**	Ms	3	57
5	**4d**	Piv	3	94
6	**4e**	Bz	3	75
7	**4f**	Ph	3	84

[a]Conditions: *O*-protected benzoin **4** (0.5 mmol), $Ru(bpy)_3Cl_2$ (2 mol %), Hantzsch ester (1.2 equiv), Et_3N (1.2 equiv), MeCN (3 mL). [b]Yield of isolated product.

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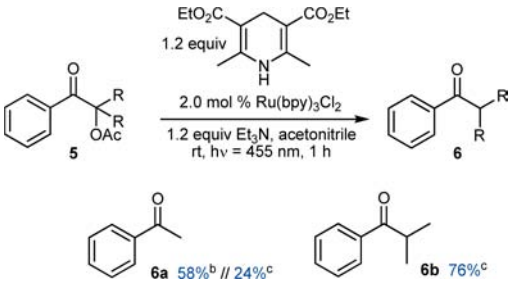
withdrawing groups (**4c**–**g**) (better leaving groups) facilitates the C–O cleavage, affording the deoxybenzoin **3** in good to excellent yields.

To explore the substrate scope further, we examined different *acyloin* derivatives under our established best conditions (Scheme 1). For product **6a** we only achieved moderate yields,

Scheme 1. Acyloin Derivatives



[a]Conditions: *O*-acetylacyloin **5** (0.5 mmol), $Ru(bpy)_3Cl_2$ (2 mol %), Hantzsch ester (1.2 equiv), Et_3N (1.2 equiv), MeCN (3 mL). [b]Volatile product: yield determined by GC/FID using mesitylene as internal standard. [c]Yield of isolated product.

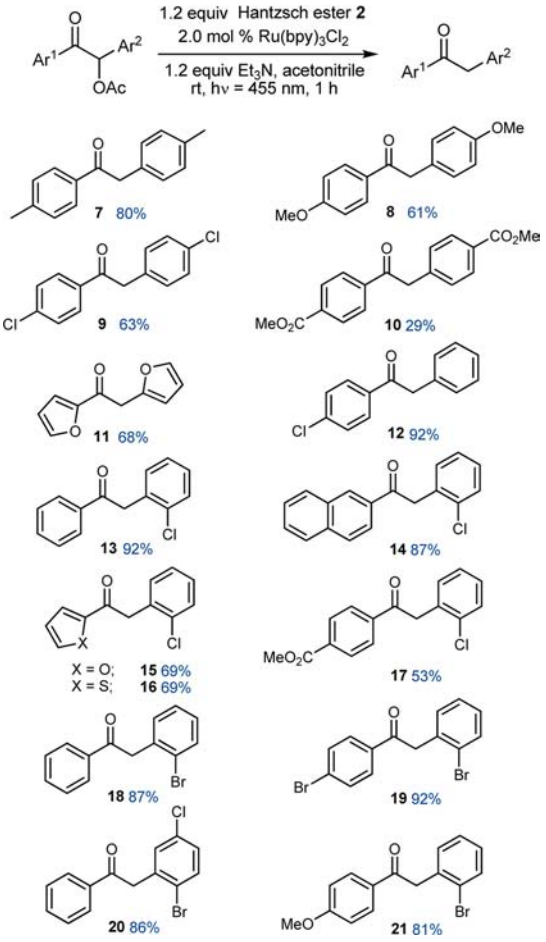
probably caused by the less stable primary radical intermediate. By contrast, deoxygenation of the tertiary alcohol afforded **6b** in good yields of 76%. Notably, our conditions are mild enough for selective deoxygenation of acyloin **5b**, avoiding reported base-promoted aldol-type cyclization side products, facilitated by the Thorpe–Ingold effect.[7]

Having identified optimal reaction conditions, we aimed to define the substrate scope of a variety of different of homo- and cross-benzoins with diverse substituents (Scheme 2). All homobenzoin substrates afforded the corresponding 1,2-diarylethanones (**7**–**9**, **11**) in good to excellent yields (up to 92%) with the exception of the ester-substituted compound **10**. Here, nonproductive electron transfer between the photocatalyst and the aryl ester group might interrupt the desired cleavage reaction.[26] Despite this, benzoin derivatives substituted with electron-withdrawing (**9**, **12**–**17**, and **20**) and electron-donating (**8** and **11**) substituents, including mixed cross combinations (**15** and **21**) as well as heteroaromatic substrates (**11**, **15**, and **16**), are competent substrates allowing the corresponding aryl ketones to be obtained in good to high yields (60–87%).

Most importantly, our conditions proved to be highly selective for the projected C–O bond cleavage. In contrast to other reported Ir-based photocatalytic deoxygenation protocols,[16,19,20] where C_{Ar}–Hal bonds (especially Ar–I) are prone to be reductively cleaved,[21] our method allows the employment of bromo-substituted substrates (**18**–**21**) and hence enables the introduction of versatile, functional handles for further transformations.[27] In this context, we could employ our *o*-bromo-substituted 1,2-diarylethanones for the synthesis of functionalized 2-arylbenzofurans.[28] In a Cu-catalyzed reaction, we obtained the cyclized products **22**–**25** in high yields using a protocol of Chen[29] (Scheme 3).

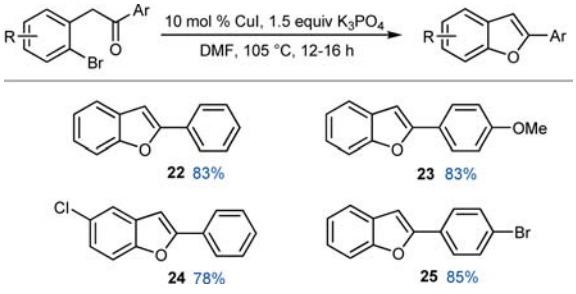
The proposed catalytic cycle for the photoreductive C–O bond cleavage is outlined in Scheme 4. Following the reductive quenching of photoexcited $Ru(bpy)_3^{2+*}$ with the tertiary amine [or the Hantzsch ester (HE) radical] as reductive quencher, a single electron transfer (SET) reduction of the carbonyl group[30] using the transiently formed Ru(I) species occurs and concurrently regenerates the photocatalyst. The generated

Scheme 2. Benzoin Derivatives



[a]Conditions: *O*-acetylbenzoin (0.5 mmol), $Ru(bpy)_3Cl_2$ (2 mol %), Hantzsch ester (1.2 equiv), Et_3N (1.2 equiv), MeCN (3 mL). [b]Yield of isolated product.

Scheme 3. Synthesis of 2-Arylbenzofurans



[a]Conditions according to Chen.[29]

ketyl radical anion then undergoes mesolytic cleavage of the C_α–O bond by elimination of the acylate and with concomitant formation of the α-carbonyl radical intermediate. Direct hydrogen transfer from Hantzsch esters to the radical species generates the deoxygenated aryl ketone.

In summary, we have developed a mild and effective photocatalytic method for the deoxygenation of simple *O*-acetyl benzoin and acyloin derivatives. In contrast to previously described methods, ours does not require activated substrates. Notably, the protocol's functional group tolerance is excellent and allows the use of aryl halogen substrates. We could further

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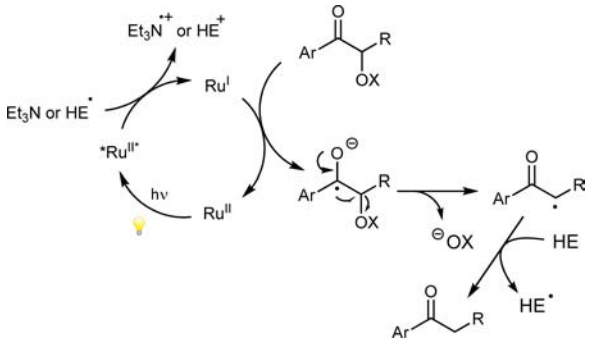
Scheme 4. Proposed Mechanism



demonstrate the convenient application of these versatile α-aryl ketone building blocks for the synthesis of arylbenzofurans.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02378.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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