Direct Site-selective Deoxygenation of Benzylalcohol Derivatives

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Abstract: We present here a simple yet efficient method for direct and site-selective deoxygenation of benzyl alcohol derivatives, including polyols, without requiring pre-activation. This reaction system, consisting of Hantzsch ester (HE), Cs_2CO_3, and a photocatalyst under photoirradiation, enables direct and site-selective deoxygenation. Mechanistic studies revealed that *in situ* reversible acylative activation of hydroxy groups plays a pivotal role in achieving the unique selectivity. This approach offers a general and practical strategy for selective transformation of polyols.

1. Introduction

Selective and efficient covalent bond cleavage is a fundamental strategy in synthetic chemistry, enabling streamlined access to valuable organic molecules.[1] Direct and selective deoxygenation[2] (C–O bond cleavage) has attracted significant attention due to the ubiquitous presence of alcohols and polyols in natural products, bulk chemicals, and synthetic intermediates.[3] Mesolystic cleavage of C–O bonds is one of the most useful strategies.[2b] Traditional methods for mesolytic cleavage of strong C–O bonds often require transformation into C–X bonds or pre-functionalization of hydroxy groups with one-electron reducing agents. For instance, the Barton-McCombie reaction relies on unstable thiocarbonyl intermediates and toxic trialkyltin reagents (Figure 1a).[4] A more practical alternative involves the deoxygenation of acylated alcohols, which are stable and readily accessible. However, the reductive removal of benzoyloxy groups requires the use of strong reductants, such as SmI_2,[5] and highly reducing electrodes[6] (Figure 1b, top), or UV irradiation,[7] due to their high reduction potential (benzoate ester: $E_{1/2}$ ~ −2.7 V vs. Fc^+/Fc)[5,8].

Recent advancements in photoredox catalysis[9] have revolutionized the field of deoxygenation and deoxygenative coupling reactions. Photoredox catalysts can generate single-electron donors under mild conditions, facilitating efficient reductive cleavage of strong C–O bonds while improving functional group tolerance and operational simplicity. In 2014, Reiser and co-workers reported a photoredox-catalyzed deoxygenation of secondary benzyl alcohols after activation by installing a 3,5-bis(trifluoromethyl)benzoyl group ($E_{1/2}$ = –1.73 V vs. SCE, *i.e.* $E_{1/2}$ ~ −2.1 V vs. Fc^+/Fc) (Figure 1b, middle).[10] More recently, Wickens and co-workers reported a deoxygenation of various alcohols after benzoyl activation. Utilizing carbon dioxide radical anions offers an efficient benzoyloxy group removal process without air or moisture sensitivity (Figure 1b, bottom).[11] A notable breakthrough was reported by Doyle, Rovis, and co-workers in 2018. They developed a method for direct deoxygenation of primary benzyl alcohols via in situ activation of hydroxy groups by phosphoranyl radicals.[12] This approach enabled voltage-independent C–O bond activation in primary benzylic alcohols without requiring pre-functionalization (Figure 1c).

Despite these advances, current deoxygenation strategies depend on *irreversible* activation of hydroxy groups, posing significant challenges for deoxygenation of polyols (Figure 1d). Site-selective deoxygenation of polyols often necessitates the selective introduction of activating groups, leading to additional protection and deprotection steps, which increase synthetic complexity.[13] Several studies have shown sequential site-selective deoxygenation via catalyst-controlled acylation of hydroxy groups,[14] enabling the synthesis of biologically important mono-deoxygenated polyols such as deoxy pyranosides, deoxy vancomycins, and deoxy erythromycins. However, a general method for direct and site-selective deoxygenation of unprotected polyols remains an unmet challenge.[15]

Herein, we report a direct and site-selective deoxygenation strategy for benzyl alcohol derivatives, including polyols (Figure 1e). We discovered that a simple reaction system comprising Hantzsch ester (HE), Cs_2CO_3, and 4DPAIPN under photoirradiation efficiently promotes direct and site-selective deoxygenation of benzyl alcohol derivatives. Mechanistic investigations revealed that *in situ* and *reversible* acylative activation of hydroxy groups plays a crucial role in enabling site-selective deoxygenation. We propose a general method for direct and site-selective alcohol deoxygenation without pre-functionalization, offering a new synthetic approach for direct and selective deoxygenative reactions.

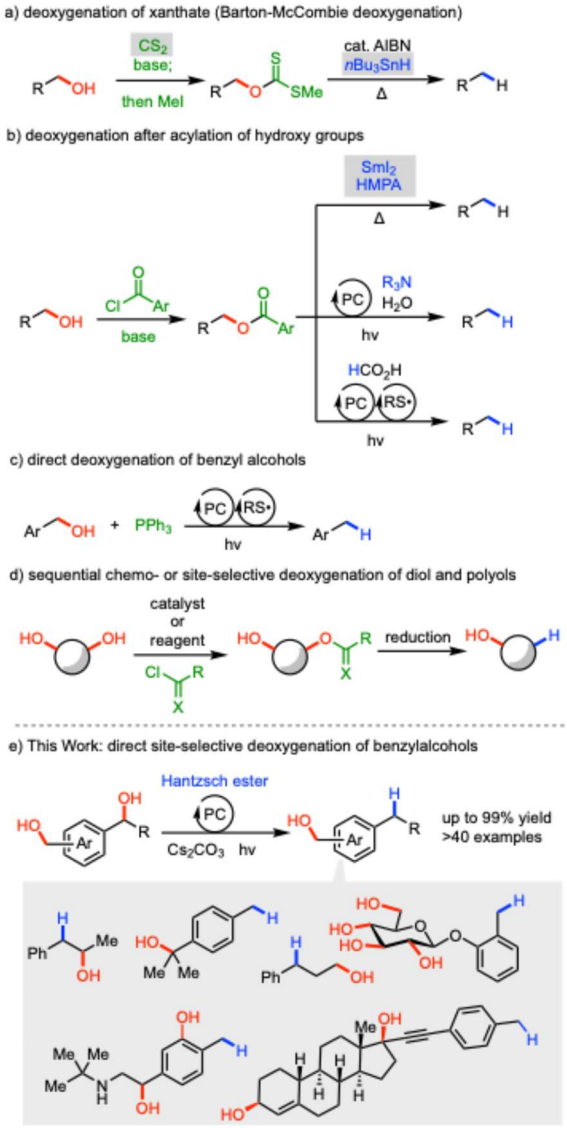
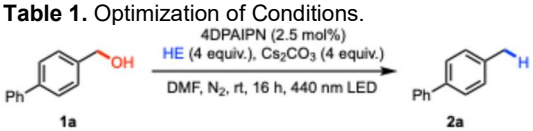


Figure 1. Deoxygenation reaction.

2. Results and Discussion

We initially considered using CO_2 as an environmentally friendly activating reagent for alcohols through *in situ* formation of carbonate acids.[16] During our screening for a CO_2-promoted deoxygenation protocol (For details, see Supporting Information.), we discovered that the combination of 4DPAIPN,[17] Hantzsch ester (HE),[18] and Cs_2CO_3 under photoirradiation effectively deoxygenates benzyl alcohol derivative **1a** (Table 1, Entry 1). Notably, the reaction proceeded even under an N_2 atmosphere, yielding the desired product **2a** in 81% yield (Table 1, Entry 2). To gain deeper insight into the reaction mechanism, we conducted several control experiments (Table 1). In the absence of 4DPAIPN, **2a** was still obtained in 37% yield (Entry 3), suggesting that both the anion radical of 4DPAIPN and the excited-state anion of HE can serve as single-electron donors[18,19] to facilitate C–O bond cleavage. Given the high reduction potential of photoactivated HE, it can act as a single-electron donor even in the absence of a photocatalyst. The results in entry 4 indicate that HE, Cs_2CO_3, and light are all essential to promote the reaction. The use of other photocatalysts resulted in lower conversion. (Entry 5). Substituting HE with *N*,*N*-diisopropylethylamine (DIPEA) still afforded **2a**, albeit in much lower yields (Entry 6). The use of a stronger base (*t*BuOK) or a weaker base ($CsHCO_3$) led to diminished yields (Entries 7 and 8). During reaction optimization, we found that ester **3a**, derived from Hantzsch ester, activates alcohol **1a** via intermediate **4a** formation through transesterification (discussed in detail later). Thus, to further enhance the yield, we introduced the less hindered ester **3b** as an additive, achieving the quantitative formation of **2a** (For details, see Supporting Information.).

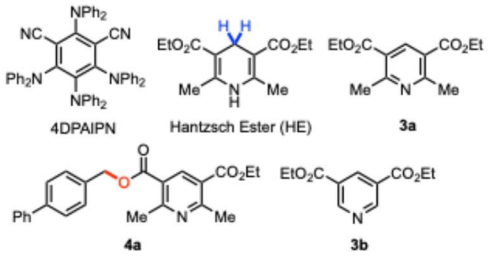
Table 1. Optimization of Conditions.



1a **2a**

Entry	Variations	Yield [%][a]
1	under CO2 (1 atm)	51
2	none	86 (81)
3	w/o 4DPAIPN	37
4	w/o HE, Cs_2CO_3, or light	<5
5	3DPA2FBN, 5CzBN, or Ir(ppy)$_3$ instead of 4DPAIPN	11–37
6	DIPEA instead of HE	16
7	^{t}BuOK instead of Cs_2CO_3	27
8	$CsHCO_3$ instead of Cs_2CO_3	<5
9	w/ ester **3b** (4 equiv.)	>99 (99)

a) Yield was determined by ^{1}H NMR spectroscopy (isolated yield).



4DPAIPN Hantzsch Ester (HE) **3a**

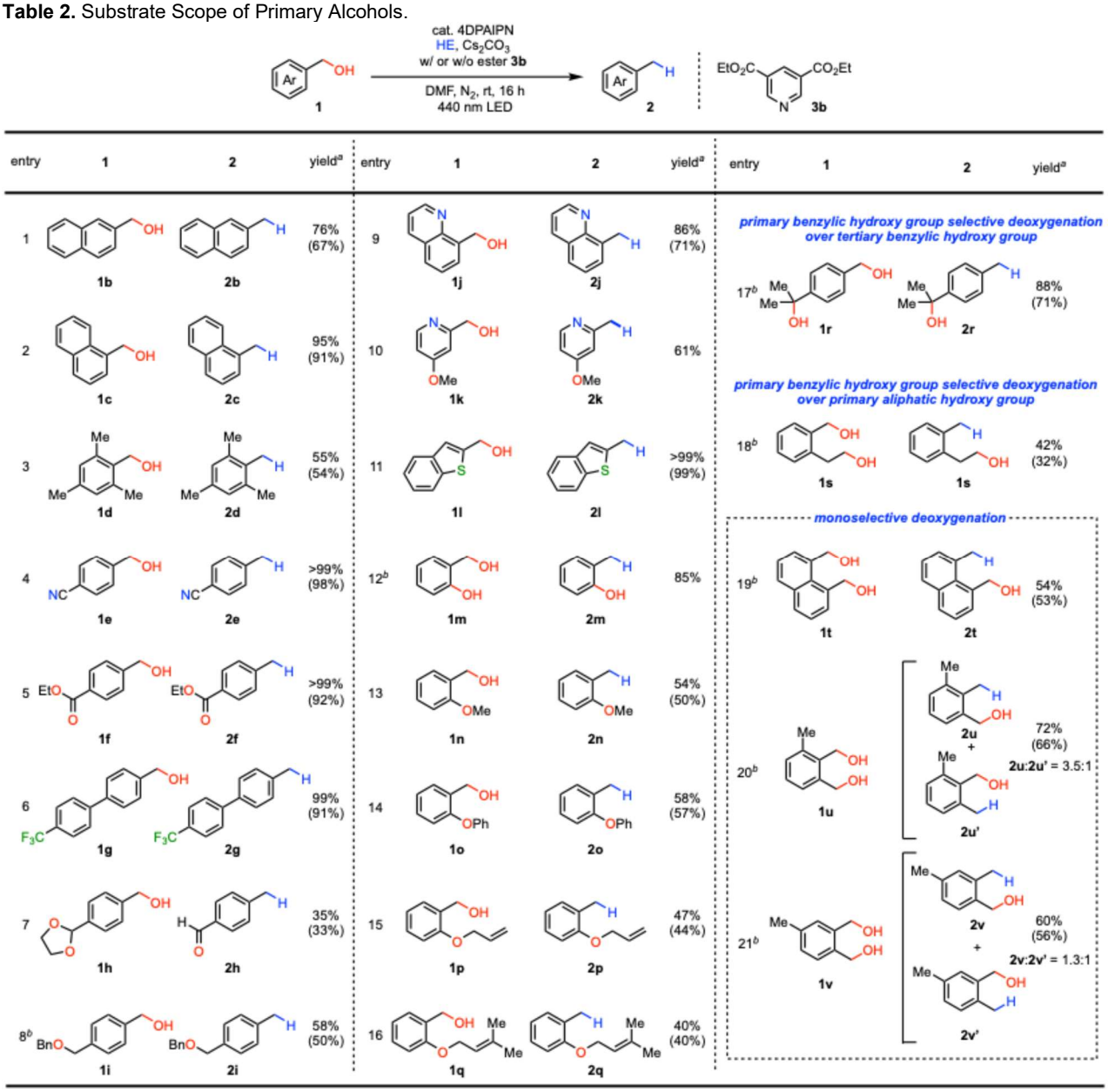
4a **3b**

We next explored the substrate scope of primary benzyl alcohols (Table 2). Both 2-naphthalenemethanol (**1b**) and 1-naphthalenemethanol (**1c**) underwent smooth conversion to the corresponding methylnaphthalenes (**2b** and **2c**) (Entries 1 and 2). The reaction was also applicable to sterically hindered mesitylmethanol (**1d**), yielding the deoxygenated product **2d** in 55% yield (Entry 3). Notably, the deoxygenation reaction was compatible with several functional groups (Entries 4–8). Benzyl alcohol derivatives containing nitrile (**1e**), ester (**1f**), and trifluoromethyl (**1g**) groups were quantitatively converted to their corresponding deoxygenated products (**2e**–**2g**). The acetal moiety in **1h** remained intact under the reaction conditions, and the product **2h** was obtained after acetal deprotection to facilitate the isolation. Mono-benzyl-protected 1,4-benzenedimethanol (**1i**), which possesses three benzylic C–O bonds, selectively yielded **2i**, highlighting the crucial role of a free hydroxy group in promoting deoxygenation.

Both electron-deficient and electron-rich heterocyclic alcohols (**1j**–**1l**) were compatible with the reaction, affording the

corresponding products in good to excellent yields (Entries 9–11). Various cresol derivatives (**1m**–**1q**) also underwent successful deoxygenation (Entries 12–16). Among them, unprotected *ortho*-cresol (**1m**) exhibited higher reactivity even in the absence of **3b** than its alkyl-substituted congeners (**1n**–**1q**). Allyl-substituted substrates (**1p** and **1q**) did not afford any cyclized products. We then examined the reaction with diols (**1s**–**1v**). In the case with diols, the reaction without ester **3b** generally gave better results and showed unique selectivity. Benzyl alcohol **1r**, which contains both primary and tertiary benzylic alcohol moieties, selectively produced the mono-deoxygenated product **2r** (Entry 17). The sterically crowded tertiary benzylic alcohol moieties are intact in the reaction conditions. In contrast, benzyl alcohol **1s**, with a less hindered primary aliphatic alcohol moiety, selectively yielded the mono-deoxygenated product **2s** (Entry 18). Moreover, diols with two benzylic primary alcohol moieties, such as 1,8-dihydroxynaphthalene (**1t**) and 1,2-phenylenedimethanol derivatives (**1u** and **1v**), consistently yielded mono-deoxygenated products without forming double-deoxygenated products (Entries 19–21).

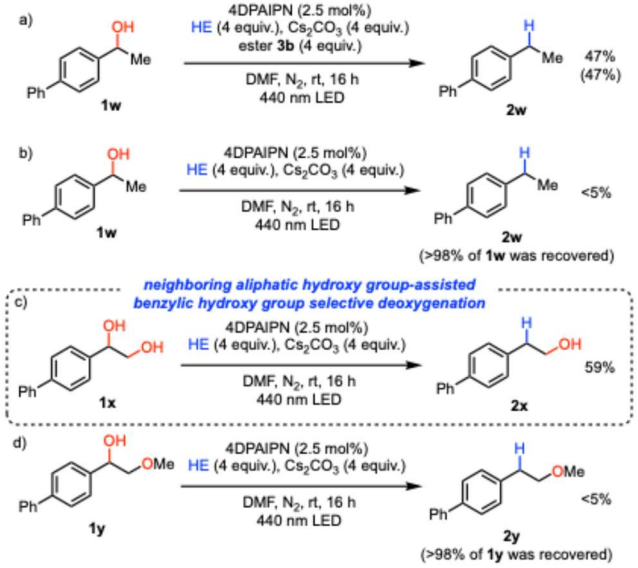
Table 2. Substrate Scope of Primary Alcohols.



[a] NMR yield (isolated yield). [b] The reaction was performed without ester **3b**.

The substrate scope of secondary alcohols also showed unique reactivity trends (Scheme 1). In the presence of ester **3b**, deoxygenation of secondary benzyl alcohol **1w** proceeded, yielding **2w** in moderate yield (Scheme 1a). The use of ester **3b** was essential for promoting the deoxygenation of **1w**; **1w** remained unreacted in the absence of ester **3** (Scheme 1b). However, secondary benzyl alcohols featuring a 1,2-diol structure, such as **1x**, unexpectedly underwent smooth mono-deoxygenation to yield **2x** even in the absence of ester **3b** (Scheme 1c), without deoxygenation of the primary aliphatic

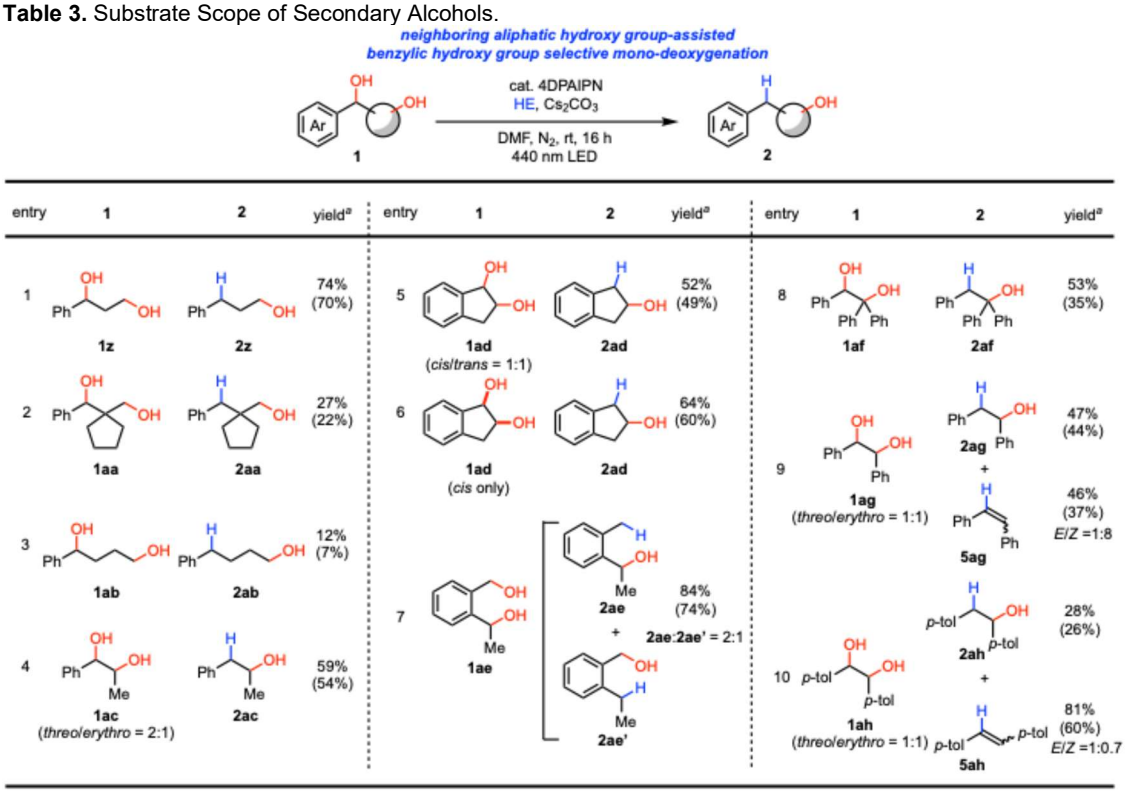
alcohol moiety. In contrast, the methoxy-substituted substrate **1y** remained unreacted (Scheme 1d), highlighting the critical role of a neighboring hydroxy group in facilitating the deoxygenation.



Scheme 1. Initial investigation for deoxygenation of secondary benzyl alcohols.

These observations prompted further investigation into the scope of secondary alcohols with a diol moiety. To evaluate the effect of chain length between two hydroxy groups, we examined several 1,3-diols and a 1,4-diol (Entries 1–3). The 1,3-diol **1z** proved to be a good substrate, yielding the mono-deoxygenated product **2z** in high yield, whereas sterically crowded 1,3-diol **1aa** and 1,4-diol **1ab** exhibited lower reactivity. Deoxygenation of 1-phenylpropane-1,2-diol (**1ac**, *threo*:*erythro* = 2:1), as well as indane-1,2-diol (**1ad**), resulted in the formation of mono-deoxygenated products **2ac** and **2ad** in good yield (Entries 4–6). Diols with two benzylic primary alcohol moieties (**1ae**–**1ah**) consistently yielded mono-deoxygenated products (Entries 7–10). The formation of stilbene derivatives **5ag** and **5ah** is likely to be due to E1cb reaction of the hydroxy group. The preferential formation of the less stable *Z*-isomer of **5ag** can be attributed to photo-mediated isomerization of the corresponding *E*-isomers.

Table 3. Substrate Scope of Secondary Alcohols.

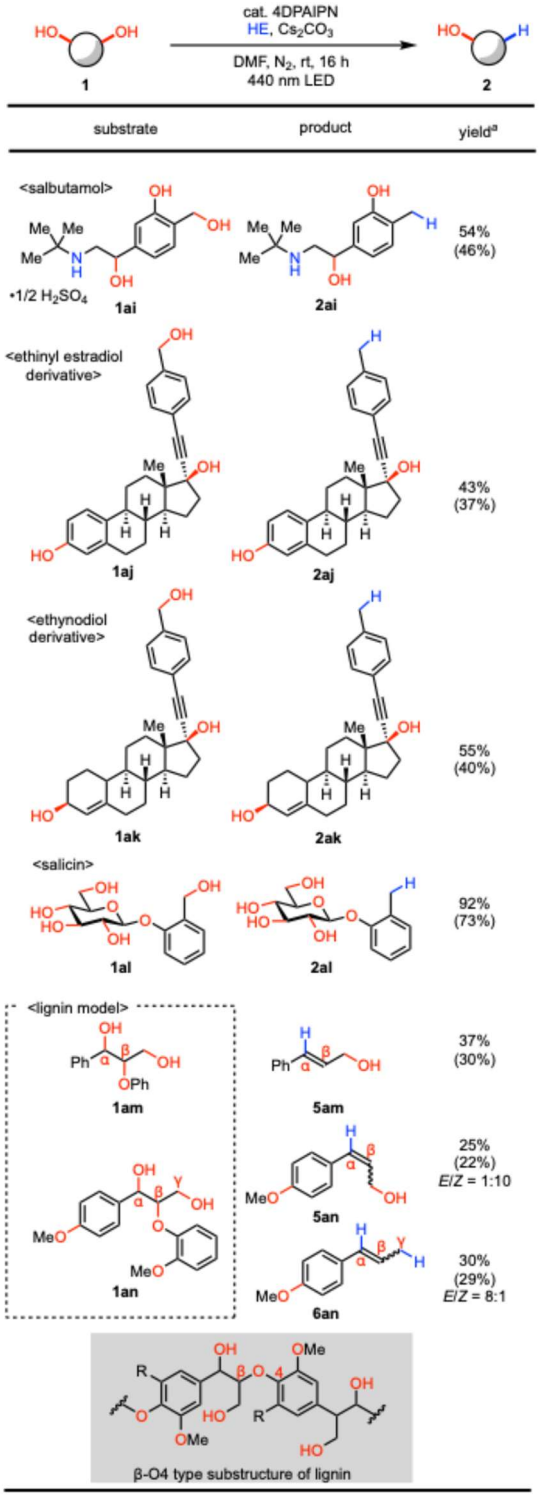


[a] NMR yield (isolated yield).

Investigation of the substrate scope of the reaction revealed several unique selectivity trends: 1) preferential deoxygenation of primary benzylic alcohols over sterically hindered secondary and tertiary benzylic alcohols, 2) selective deoxygenation of benzylic alcohols over aliphatic alcohols, 3) monoselective deoxygenation of diols containing two benzylic alcohol moieties, and 4) neighboring hydroxy group-facilitated deoxygenation. Leveraging this unique selectivity, we applied the reaction to polyols, for which the achievement of selective deoxygenation is likely to be challenging (Table 4). The reaction of salbutamol (**1ai**), which contains two benzylic alcohol moieties and a secondary amine,

selectively yielded the primary deoxygenated product (**2ai**). Additionally, estrogen derivatives **1aj** and **1ak** afforded products **2aj** and **2ak** in 43% and 55% yields, respectively, despite the presence of a tertiary propargylic alcohol or a secondary allylic alcohol moiety. Unprotected glycosides, salicin (**1al**), underwent selective mono-deoxygenation at the benzylic position, affording the desired product **2al** in high yields. To further explore the utility of the deoxygenation, we investigated its application to lignin model compounds. Lignin, the second most abundant natural polymer after cellulose, remains largely underutilized,[20] Despite its potential as a renewable feedstock, industrial lignin is predominantly burned for energy rather than converted into valuable chemicals. Its degradation is particularly challenging due to its intricate structure, high chemical stability, and absence of highly efficient enzymatic pathways. Given that the β-O-4 substructure constitutes approximately 45–60% of lignin linkages and that selective C–O bond cleavage can yield valuable aromatic compounds, significant research efforts have been devoted to the degradation of β-O-4 model compounds over the past decade.[21] However, photochemical lignin fragmentation typically requires pre-oxidation of the benzylic alcohol moiety (α-C–O bond),[22] reducing the overall efficiency. Under our reaction conditions, however, lignin model compounds **1am** and **1an** underwent direct α- and β-C–O bond cleavage, yielding the corresponding cinnamyl alcohol derivatives **5am** and **5an**, as well as the styrene derivative **6an**, where α-, β-, and γ-C–O bonds were cleaved in a single step. These results highlight the efficiency of this methodology for lignin model degradation via one-step multiple C–O bond cleavage.

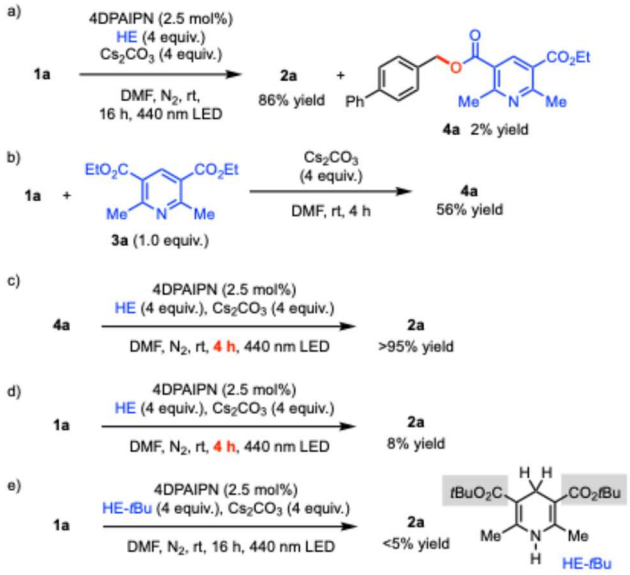
Table 4. Site-selective deoxygenation of polyols.



[a] NMR yield (isolated yield).

To elucidate the reaction mechanism, we conducted several mechanistic studies (Scheme 2). As previously mentioned, in the reaction with primary alcohol **1a**, careful analysis of the crude mixture revealed the formation of a small amount of **4a** (Scheme 2a). In the presence of Cs_2CO_3, transesterification between **1a** and **3a** proceeded efficiently at room temperature, yielding **4a** (Scheme 2b). The importance of **4a** in the deoxygenation reaction was evaluated. Under the deoxygenation conditions, **4a** quantitatively yielded the deoxygenated product **2a** within four

hours (Scheme 2c), whereas alcohol **1a** afforded only 8% yield of **2a** in four hours (Scheme 2d). This stark contrast underscores the critical role of transesterification in activating the alcohols. Further supporting this conclusion, the reaction using sterically demanding Hantzsch *tert*-butyl ester (HE-*t*Bu) resulted in no reaction, with **1a** being fully recovered (Scheme 2e). This is consistent with the observed acceleration upon adding ester **3b** (Table 1, entry 9); the more sterically accessible ester **3b** would be a more efficient activator of the alcohols. Collectively, these results highlight the essential role of acylated intermediate **4** in facilitating the deoxygenation reaction.



Scheme 2. Elucidating the importance of the transesterification in deoxygenation.

We then conducted cyclic voltammetry (CV) measurements for **1a**, **4a**, and 4DPAIPN in DMF (Figure 2a). The CV analysis of alcohol **1a** exhibited a reversible wave with $E_{1/2}$ = −3.49 V vs. Fc^+/Fc in DMF, likely corresponding to the reduction of the aromatic moiety ($E_{1/2}$(benzene) ~ −3.42 V vs. SCE). Meanwhile, CV analysis of **4a** gave three peaks: an *irreversible* reduction peak at $E_{p/2}$ = −2.40 V[23] along with reversible waves at $E_{1/2}$ = −2.94 and 3.25 V (vs. Fc^+/Fc in DMF). The irreversible peak indicates rapid chemical transformation of the generated radical anion of **4a**. CV analysis of **4a** in the presence of Cs_2CO_3 also gave similar results (For details, see Supporting Information.). The reduction potential of 4DPAIPN ($E_{1/2}$ = −2.11 V in DMF) was also determined, indicating that the reduction of **4a** by the radical anion of 4DPAIPN would be slightly endothermic by 6.7 kcal/mol.

To gain deeper insights into the radical anion of **4a**, we performed density functional group (DFT) calculations at the UM06-2x/6-311+G(d,p)(scrf=DMF)//UM06-2x/6-31+G(d) level (Figure 2b). According to the DFT calculations, a stable conformer of the radical anion of **4a** (**4a-1c**$^{\bullet-}$) exhibited high Mulliken spin density at the pyridine C2 and C6 positions. Furthermore, the oxygen atom of the ester moiety showed a larger negative Mulliken charge (−0.499) than that of the nitrogen atom of the pyridine moiety. Based on these results, the resonance structure shown in Figure 2b makes the greatest contribution to the resonance hybrid of radical anion **4a-1c**$^{\bullet-}$. After a conformational change from **4a-c1**$^{\bullet-}$ to **4a-c2**$^{\bullet-}$, which exhibits almost the same spin densities and Mulliken charges as those of **4a-c1**$^{\bullet-}$, mesolytic cleavage of **4a-c2**$^{\bullet-}$ occurs to form radical intermediate **X** with a small activation barrier of 10.5 kcal/mol at 298 K. This mesolytic cleavage process is thermodynamically favorable by −19.4 kcal/mol at 298 K.

Based on the experimental and computational findings, we propose a possible reaction mechanism illustrated in Figure 2c. Initially, Hantzsch ester undergoes gradual oxidation to generate ester **3a**. In the presence of Cs_2CO_3, transesterification between ester **3a** and alcohol **1** leads to formation of the acylated alcohol intermediate **4**. Upon photoirradiation, the excited state of the 4DPAIPN ($E_{1/2}$(*PC/$^{\bullet-}$PC) = +1.10 V vs SCE in MeCN)[17] is reduced by Hantzsch ester (HE),[18] generating the radical anion of 4DPAIPN (PC$^{\bullet-}$), along with the radical cation of Hantzsch ester (HE$^{\bullet+}$). A subsequent single-electron transfer (SET) from PC$^{\bullet-}$ to **4** produces the radical anion **4**$^{\bullet-}$. Although CV analysis suggests that this SET process is endothermic, the ensuing mesolytic cleavage of **4**$^{\bullet-}$ is highly exothermic and proceeds rapidly, yielding radical **X** and carboxylate **Y**.[23] According to the results of Table 1, entry 3 (a control experiment without 4DPAIPN), the excited state of Hantzsch ester anion can also reduce **4** to generate **4**$^{\bullet-}$. The resulting radical **X** abstracts a hydrogen atom from HE$^{\bullet+}$, affording the deoxygenated product **2** and regenerate **3a**, which is reused as an acylating reagent. Overall, the lower reduction potential of acylated intermediate **4** relative to alcohol **1**, as well as the facile mesolytic cleavage of radical anion **4**$^{\bullet-}$, underscores the crucial role of acylation by **3a** in enabling direct deoxygenation. The reaction exploits Hantzsch ester not only as a two-electron donor but also as an efficient promotor of mesolytic cleavage of acyloxy C–O bonds.

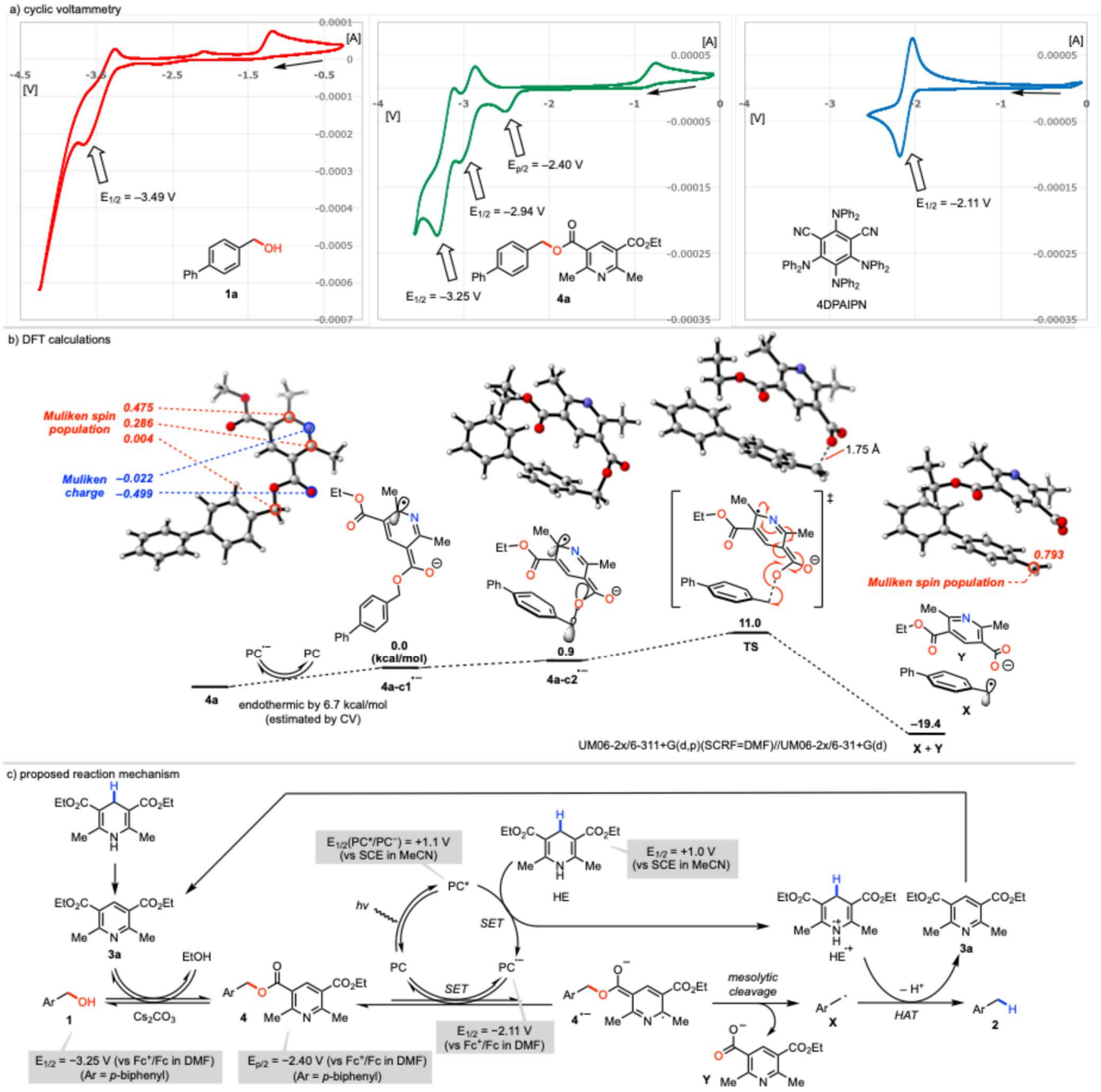


Figure 2. Mechanistic studies and proposed reaction mechanism.

Finally, we performed several reactions to elucidate the rationale behind the observed unique selectivities. We firstly examined the preferential cleavage of primary benzylic C–O bonds over secondary and tertiary benzylic C–O bonds (*i.e.*, the reactions of **1r**, **1ai**, **1aj**, **1ak**). As demonstrated in Figure 3a, transesterification between ester **3a** and **1a** (a primary benzylic alcohol) proceeds significantly faster than that with **1w** (a secondary benzylic alcohol). This suggests that the steric differences among benzylic alcohols dictate the faster transesterification of primary benzylic alcohols, leading to their preferential activation and deoxygenation over secondary and tertiary counterparts. In contrast, the selective deoxygenation of benzylic alcohols over aliphatic alcohols follows a different mechanistic rationale, primarily governed by both the reversibility of transesterification and the rate of mesolytic cleavage of the C–O bonds (Figure 3, b–d). Transesterification of **1z** with ester **3a** exclusively afforded the primary acylated product **4z**, without forming benzylic acylated product **4z'** (Figure 3b). However, under the deoxygenation conditions, **4z** selectively yielded the benzylic- deoxygenated product **2z** (Figure 3c). These results suggest the following mechanistic pathway. Initially, the sterically less hindered primary aliphatic hydroxy group of **1z** undergoes acylation by **3a**, forming intermediate **4z**. While **4z** is also prone to single-electron reduction, the subsequent mesolytic cleavage of $\mathbf{4z}^{\bullet-}$ is slow due to the instability of the resulting primary aliphatic radical **Y**, as supported by DFT calculations (For details, see Supporting Information.). Consequently, the radical anion $\mathbf{4z}^{\bullet-}$ reverts to **4z**, which is consistent with the CV measurement of **3a** (ethyl ester) showing *reversible* reduction wave peaks $E_{1/2} = -2.51$

V vs. Fc^+/Fc in DMF, in contrast to the irreversible peaks observed for **4a** (benzyl-type ester). Instead, a reversible acyl migration generates intermediate **4z'** *in situ*, which is more susceptible to C–O bond cleavage, leading to the formation of secondary benzylic radical **2z**. This mechanistic model explains not only the selective deoxygenation of benzylic hydroxy groups over aliphatic hydroxy groups but also the acceleration observed in cases involving neighboring hydroxy groups (*i.e.*, the reactions of **1s**, **1x**, **1z**, **1aa**, **1ab**, **1ac**, **1ad**, **1ae**, **1al**, **1am**, and **1an**). Moreover, the high yield observed for substrate **1z** (1,3-diol) than **1ab** (1,4-diol) is likely due to the formation of a favorable six-membered transition state during the acyl migration. In contrast, acyl migration of **1ab** requires a less favorable seven-membered transition state, resulting in a lower yield of **2ab**. Next, we investigated the rationale for the observed mono-selective deoxygenation of diols containing two benzylic hydroxy groups (*i.e.*, **1t**, **1u**, **1v**, **1ae**, **1af**, **1ag**, and **1ah**). To determine whether the rate of transesterification is a key factor, we evaluated the transesterification rates of **1t** and **2t** (Figure 3e). A stoichiometric reaction of **1t**, **2t**, and **3a** in the presence of Cs_2CO_3 preferentially yielded **4t'**, indicating that the rate of transesterification is not the primary determinant of mono-selectivity. Instead, the rate of mesolytic cleavage appears to be the key factor. Several reports have indicated that protonation of a radical anion facilitates mesolytic cleavage of benzoate esters.[10,11] Based on this, we propose that intramolecular hydrogen bonding between the enolate anion and the adjacent hydroxy group facilitates mesolytic cleavage, thereby contributing to the observed mono-selective deoxygenation (Figure 3f). Totally, the unique selectivity of the reaction arises from the difference between the reaction rate of the reversible acylative activation and the irreversible mesolytic cleavage.

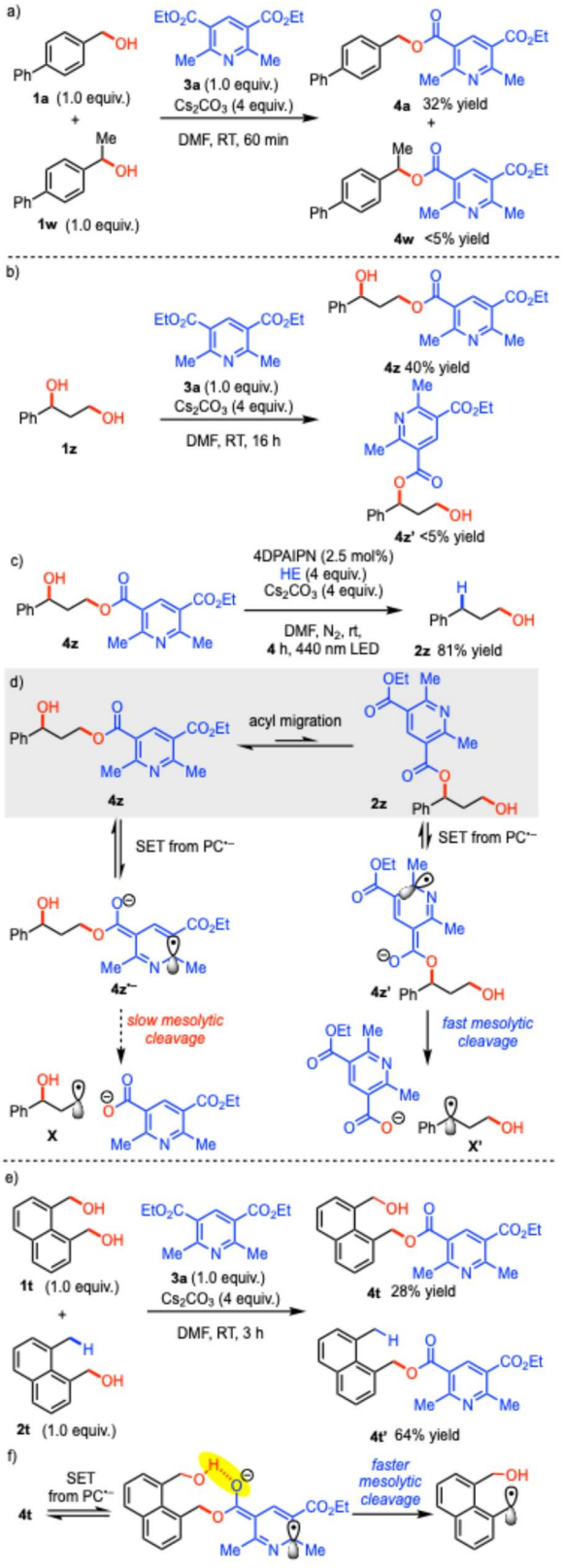


Figure 3. Mechanistic studies for elucidating the rationale for the observed selectivity.

3. Conclusion

We have developed a simple and efficient reaction system comprising Hantzsch ester (HE), Cs_2CO_3, and 4DPAIPN under photoirradiation, enabling direct and site-selective deoxygenation of benzyl alcohol derivatives without pre-functionalization. Mechanistic studies revealed that *in situ* acylative activation of hydroxy groups by ester **3a**, derived from Hantzsch ester, is crucial for facilitating deoxygenation. The unique site selectivity arises from the interplay between the reversible acylative activation rate and the irreversible mesolytic cleavage. This work highlights the utility of an *in situ* reversible activation strategy in advancing direct and site-selective deoxygenation strategies.

Supporting Information

The data that support the findings of this study are available in the Supporting Information of this article.

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Keywords: Deoxygenation, Site-selectivity, Photocatalysis, Transesterification, Polyols

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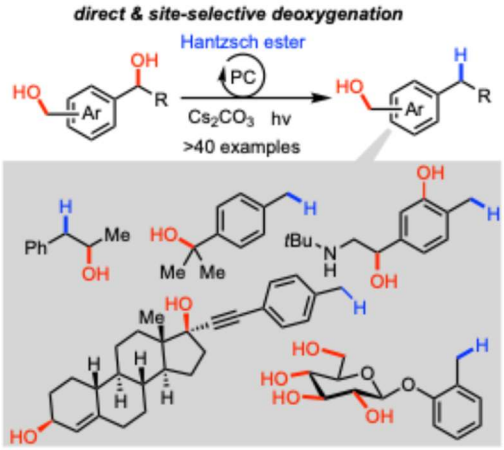

A simple photoredox system comprising Hantzsch ester, Cs_2CO_3, and 4DPAIPN that enables direct and site-selective deoxygenation of benzyl alcohol derivatives is described. Mechanistic studies revealed that in situ reversible acylative activation of hydroxy groups plays a pivotal role in achieving the unique selectivity, highlighting the importance of reversible activation strategies in selective molecular transformations.

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