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Transition-Metal- and Light-Free Directed Amination of Remote Unactivated C(sp^3)−H Bonds of Alcohols

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Supporting Information

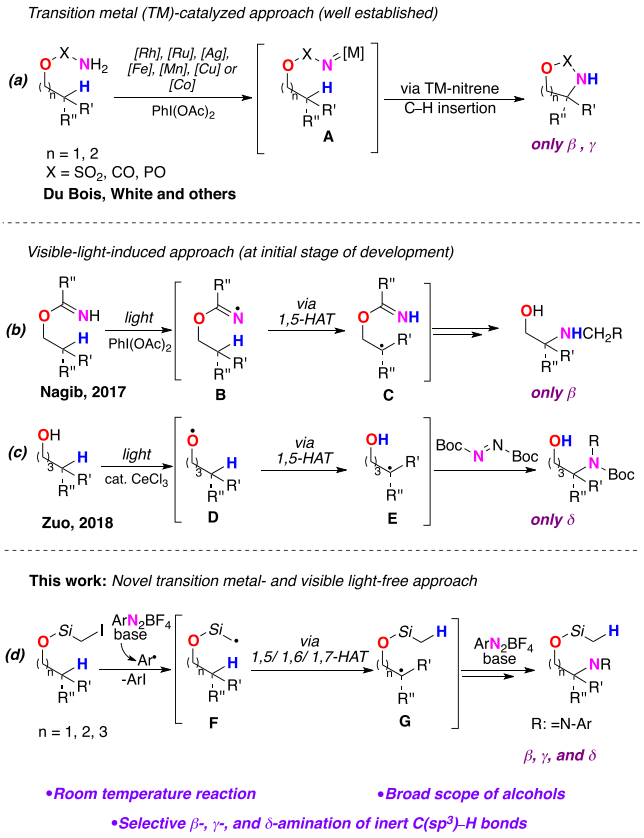
ABSTRACT: Due to the great value of amino alcohols, new methods for their synthesis are in high demand. Abundant aliphatic alcohols represent the ideal feedstock for the method development toward this important motif. To date, transition-metal-catalyzed approaches for the directed remote amination of alcohols have been well established. Yet, they have certain disadvantages such as the use of expensive catalysts and limited scope. Very recently, transition-metal-free visible-light-induced radical approaches have emerged as new powerful tools for directed remote amination of alcohols. Relying on 1,5-HAT reactivity, these methods are limited to β- or δ-amination only. Herein, we report a novel transition-metal- and visible-light-free room-temperature radical approach for remote β-, γ-, and δ-C(sp^3)−N bond formation in aliphatic alcohols using mild basic conditions and readily available diazonium salt reagents.

A diverse range of natural products, pharmaceuticals, and catalyst designs feature amino alcohols as privileged motifs.[1] One of the most powerful strategies toward their synthesis is the directed site-selective C(sp^3)−H amination of aliphatic alcohols,[2] which are ubiquitous in complex molecules and are inexpensive and sustainable starting materials. The seminal strategy for directed amination of alcohols developed by Du Bois, White, and others relies on insertion of Rh-,[3] Ru-,[4] Ag-,[5] Fe-,[6] Mn-,[7] Cu-,[8] or Co[9]-based transition-metal-nitrene species **A** into distal unactivated C(sp^3)−H bonds[10] (Scheme 1, *a*). However, the innate metallacyclic intermediates restrict these metal-based methods to γ- and β-site functionalization. Recently, radical approaches for remote functionalization of alcohols[11] have gained broad attention due to the discoveries of new mild methods for generation of radicals and their versatile hydrogen atom transfer (HAT) reactivity.[12] To date, only two methods on remote site-selective C(sp^3)−H amination of alcohols have been developed relying on radical intermediates. In 2017, the Nagib group introduced an elegant metal-free visible-light-induced radical relay for synthesis of β-amino alcohols from their alcohol analogues (Scheme 1, *b*).[13]

This method utilizes a novel, easily installable/removable imidate-based chaperone capable of generating N-centered radical species **B**, which undergoes a 1,5-HAT process producing **C**. Subsequent 5-*endo*-trig radical cyclization of **3** and *in situ* hydrolysis delivers the amination products with exclusive β-selectivity. Later, the Zuo group developed another visible-light-induced protocol to access δ-amino alcohols (Scheme 1, *c*).[14] In this case, Ce-catalyzed generation of alkoxy radicals **D** directly from alcohols followed by 1,5-HAT and radical addition of **E** to di-*tert*-butyl azodiformate leads to δ-selective C−N bond formation. Overall, these radical approaches eliminated the necessity for use of expensive transition metal catalysts and conventional heating for remote C(sp^3)−H amination of alcohols.

However, due to the preference of heteroatom-centered radicals for 1,5-HAT,[12b] the scope of these radical transformations remains limited and γ-amination toward valuable 1,3-amino alcohols has not yet been achieved. Therefore, development of more general metal-free methods featuring

Scheme 1. Directed Remote C−H Amination of Alcohols



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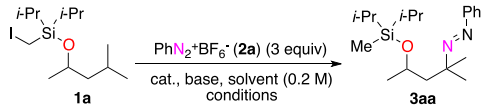
benign conditions is highly desired.[15] Herein, we report the first transition-metal- and visible-light-free room-temperature protocol for remote β-, γ-, and δ-C(sp^3)−N bond formation in aliphatic alcohols using mild basic conditions and readily available diazonium salts (Scheme 1, *d*). This method employs the ability of the latter to initiate radical reactions in the presence of bases or other reducing agents,[16] as well as to trap nucleophilic radical intermediates to form a new C−N bond.[17] Thus, previously unknown iodine atom abstraction from the silyl methyl iodide moiety of a tethered alcohol by an aryl radical, formed from the diazonium salt in the presence of base, leads to silyl methyl radical species **F**. This electrophilic radical,[18] due to electronic mismatch, is not predisposed to coupling with the diazonium reagent and instead undergoes a selective 1,6-, 1,5-, or 1,7-HAT process to produce transposed nucleophilic radical species **G** at the remote C(sp^3)−H site of the alcohol.[19] The latter would be ultimately trapped by excess diazonium salt, which is known to be a facile process ($k = 10^6$ M^{-1} s^{-1} for primary alkyl radicals; $k \geq 10^8$ M^{-1} s^{-1} for tertiary alkyl radicals),[17b] and reduced by base to produce β-, γ-, or δ-diazenylated alcohols, accordingly. Thus, the base plays a double duty by reducing both the diazonium cation and its radical adduct.

Continuing our previous work on visible-light-induced Pd-catalyzed remote functionalization of aliphatic alcohols with the employment of Si-based auxiliaries,[19a] we began our studies on remote amination by subjecting standard substrate **1a** to the reactions with different electrophilic reagents. It turned out that when substrate **1a** and diazonium salt **2a** were mixed in methanol under our blue light/Pd-based conditions, in 1 h the γ-diazenylated Si-protected alcohol **3aa** was obtained in 22% GC yield (Table 1, entry 1). *To our surprise, the control*

Table 1. Optimization Table



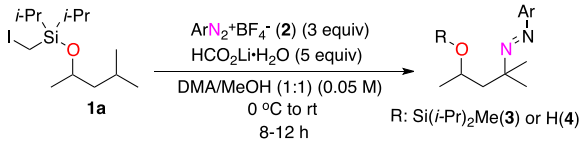
no.	cat.	base	solvent	cond	yield (3aa),[a] %
1[b]	[Pd][c]	Cs_2CO_3	MeOH	rt, 1 h	22
2	[Pd][c]	Cs_2CO_3	MeOH	rt, 1 h	20
3		Cs_2CO_3	MeOH	rt, 1 h	23
4			MeOH	rt, 1 h	0
5		Cs_2CO_3	DMA/MeOH	rt, 1 h	60
6		$HCO_2Li{\cdot}H_2O$	DMA/MeOH	rt, 30 min	64
7		***$HCO_2Li{\cdot}H_2O$***	***DMA/MeOH***[d]	***0 °C to rt, 2 h***	**76**

[a]0.1 mmol scale reaction; GC-MS yield (standard: pentadecane). [b]Reaction mixture was irradiated with visible light. [c]5 mol % $Pd(OAc)_2$/10 mol % Xantphos. [d]0.05 M concentration.

*experiments revealed that this reaction does not require employment of Pd catalyst or visible light to proceed with the same efficiency toward **3aa**!* (entries 2, 3). The control experiment proved the necessity of base for the success of this transformation (entry 4). Excited by the obtained results, we began optimizing this novel transition-metal- and visible-light-free base-promoted remote amination by screening different solvent systems (see SI for full optimization). We realized that poor solubility of nonpolar silyl ether **1a** in methanol was a key problem; therefore a cosolvent was required for better efficiency and reproducibility. The mixture of *N*,*N*-dimethylacetamide (DMA) and methanol (1:1) was found to be an optimal solvent system, producing **3aa** in 60% yield (entry 5). Testing different bases revealed that inexpensive and decently soluble in methanol $HCO_2Li{\cdot}H_2O$ was superior to other inorganic bases (entry 6). *Finally, using more diluted solution and decreasing the temperature to 0 °C allowed the reaction to deliver **3aa** in 76% GC yield after 2 h* (entry 7).

With the optimized conditions in hand, we investigated the scope of diazonium salts (Table 2). Both electron-rich (**2b**−**g**)

Table 2. Screening of Diazonium Salts



no.	Ar	yield of **3** or **4**, %
1	C_6H_5 (**2a**)	84%[a] (**3aa**), 68%[b] (**4aa**)
2	*p*-MeC_6H_4 (**2b**)	86%[a] (**3ba**), 81%[b] (**4ba**)
3	*o*-MeC_6H_4 (**2c**)	69%[b] (**4ca**)
4	*m*-MeC_6H_4 (**2d**)	83%[a] (**3da**)
5	*p*,*o*-diMeC_6H_3 (**2e**)	87%[a] (**3ea**)
6	*p*,*m*-diMeC_6H_3 (**2f**)	80%[a] (**3fa**)
7	*p*-$MeOC_6H_4$ (**2g**)	81%[a] (**3ga**), 64%[b] (**4ga**)
8	*p*-$CF_3C_6H_4$ (**2h**)	54%[b] (**4ha**)
9	*p*-CNC_6H_4 (**2i**)	52%[b] (**4ia**)
10	*m*-ClC_6H_4 (**2j**)	67%[a] (**3ja**)
11	*m*-FC_6H_4 (**2k**)	73%[a] (**3ka**)
12	*p*-ClC_6H_4 (**2l**)	76%[a] (**3la**)

[a]0.1 mmol scale reaction; NMR yield (standard: CH_2Br_2). [b]0.5 mmol scale reaction, followed by deprotection with aqueous HCl (5 equiv); isolated yield.

and electron-deficient (**2h**−**l**) diazonium salts were reactive toward remote diazenylation of **1a**, leading to the desired products **3** in good to excellent yields. We noticed that the yields were generally slightly higher in the case of more electron-rich diazonium salts. Interestingly, *ortho*-substitution at diazonium salts did not have much effect on the yield of this transformation (entries 3, 5).

The products possessing *p*-H (**4aa**), *p*-Me (**4ba**), *o*-Me (**4ca**), *p*-MeO (**4ga**), *p*-CF_3 (**4ha**), and *p*-CN (**4ia**) substituents were isolated as the γ-diazenylated alcohols **4** after *in situ* deprotection of silicon auxiliary in good yields. Based on these results, *p*-tolylN_2BF_4 (**2b**) was selected as the preferred diazenylating reagent for the remote amination of aliphatic alcohols.

The remote diazenylation of Si-tethered alcohols was found to be quite general (Scheme 2). In contrast to our recently developed Heck relay process,[19b] the product of premature coupling was never observed in this transformation, due to the electronic mismatch of the silyl methyl radical and diazonium cation.[18] First, using the optimized conditions and *p*-tolylN_2BF_4 (**2b**), the scope of γ-diazenylation was examined (Scheme 2, a). Similarly to the standard substrate **1a**, its symmetric analogue **1b** furnished the corresponding product **3b** in excellent yield. Substrates **1c** and **1d**, which possess competitive Hβ and Hδ sites of abstraction, reacted preferentially at the γ-C−H sites, producing **2c** and **2d** in high yields. This result is in agreement with the previously

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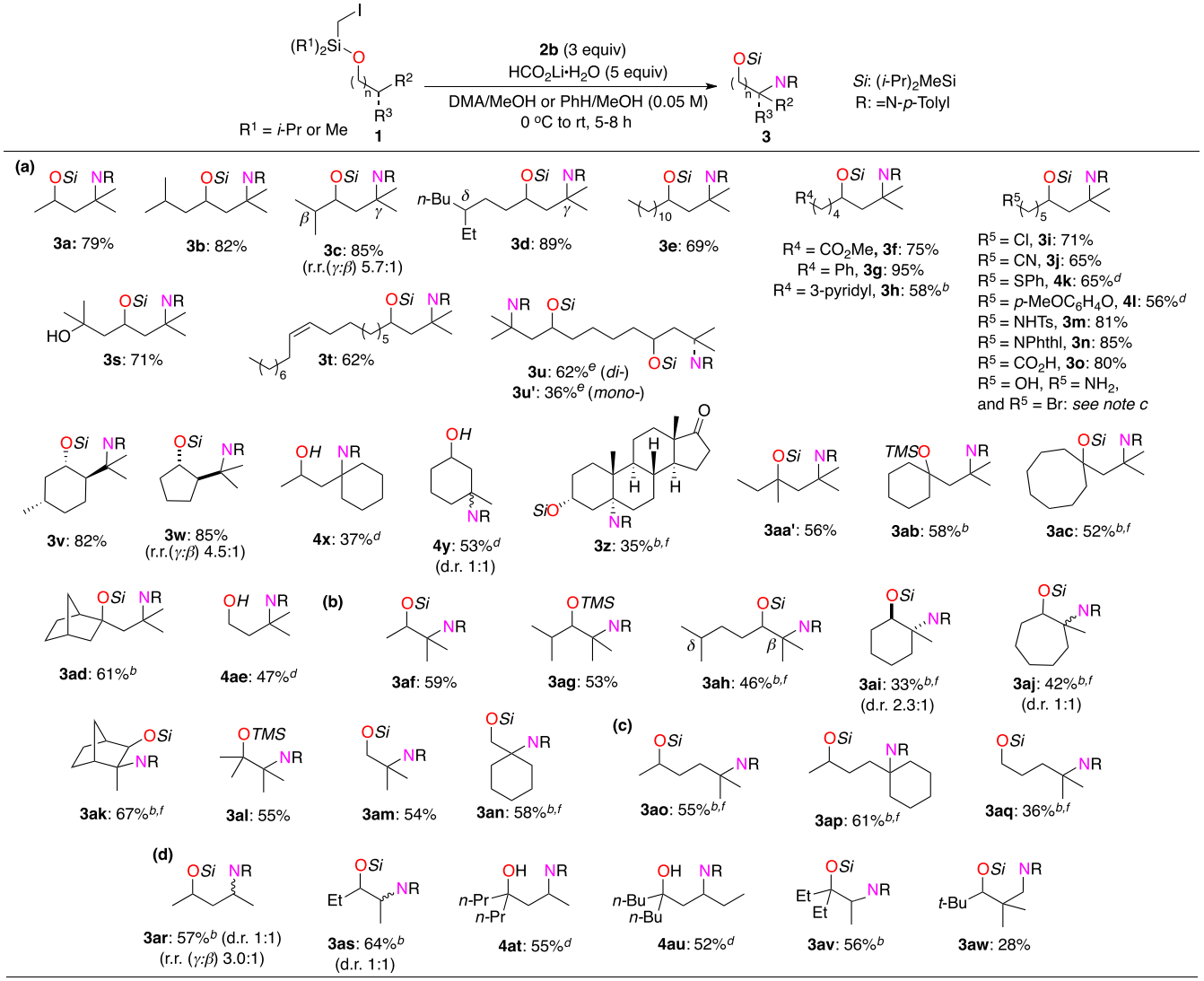
Scheme 2. Scope of Transition-Metal-Free Amination of Remote Unactivated C(sp^3)–H Sites of Aliphatic Alcohols:[a] (a) γ-Diazenylation; (b) β-Diazenylation; (c) δ-Diazenylation; (d) Diazenylation at Secondary and Primary C–H Sites



[a]0.3 or 0.4 mmol scale reactions. Isolated yield,%. [b]NMR yield,% (standard: CH_2Br_2). [c]When R^5 = OH (**3p**): 20% NMR yield; R^5 = NH_2 (**3q**): decomp; R^5 = Br (**3r**): decomp. [d]Products **3** were deprotected and isolated as free alcohols **4**. [e]Calculated yield, %. [f]Mixture of regio- or stereoisomers: NMR yield of major isomer is represented.

observed reactivity preference of the silicon tether toward 1,6-HAT over 1,5-HAT and 1,7-HAT for tertiary sites with similar bond dissociation energies.[19a] Alcohols possessing an unsubstituted long chain (**1e**) and –CO_2Me and –Ph-substituted chains (**1f**, **1g**, respectively) underwent γ-3° C–H diazenylation reaction in a highly efficient and regioselective manner. Moreover, functional groups such as *3-pyridyl- (**3h**), chloride- (**3i**), cyanide- (**3j**), phenylsulfide- (**4k**), p-metoxyphenoxide- (**4l**), N-tosylamide- (**3m**), N-phthalimide- (**3n**), carboxylic acid (**3o**), tertiary alcohol (**3s**), and alkene (**3t**) were all tolerated under these conditions* (see robustness screening in the SI).[20] However, trace or no product was observed with substrates possessing a primary alcohol, amine, or bromide moiety (**3p**, **3q**, and **3s**, respectively). Interestingly, this method afforded the double γ-diazenylation of diol **1u**: product **3u** was isolated together with the monodiazenylated adduct **3u′**. (–)-Menthol derivative **1v** was selectively diazenylated at the isopropyl group in 82% yield. Reaction of its five-membered analogue **1w** was less selective, giving a mixture of γ- and β-diazenylated alcohols **3w** in 85% yield (4.5:1 ratio). γ-Diazenylation of C–H bonds of cyclic alcohols **1x**–**1z**, even in the complex setting of androsterone **1z**, proceeded uneventfully, delivering products **3k**–**3m** in reasonable yields. Furthermore, cyclic (**1ab**–**ad**) and acyclic (**1aa′**) tertiary alcohols were also compatible, giving rise to products **3aa′**–**ad**. Primary alcohol **1ae** furnished the desired product **4ae** in 47% yield in the γ-diazenylation reaction followed by one-pot Si-auxiliary deprotection.

Next, we investigated the scope of the kinetically less favorable β-diazenylation (Scheme 2, b). To our delight, secondary alcohols **1af** and **1ag** reacted quite efficiently under slightly modified conditions (see SI for details), producing **3af** and **3ag** in 81% and 53% yields, respectively. Diazenylation of **1ah** possessing accessible β-3° C–H, γ-2° C–H, and δ-3° C–H sites preferably occurred at the β-position, thus supporting our earlier conclusion that, for this silicon tether, the 1,5-HAT is more favorable than the 1,7-HAT.[19a] In addition, γ- and δ-diazenylation products were also observed in this reaction as

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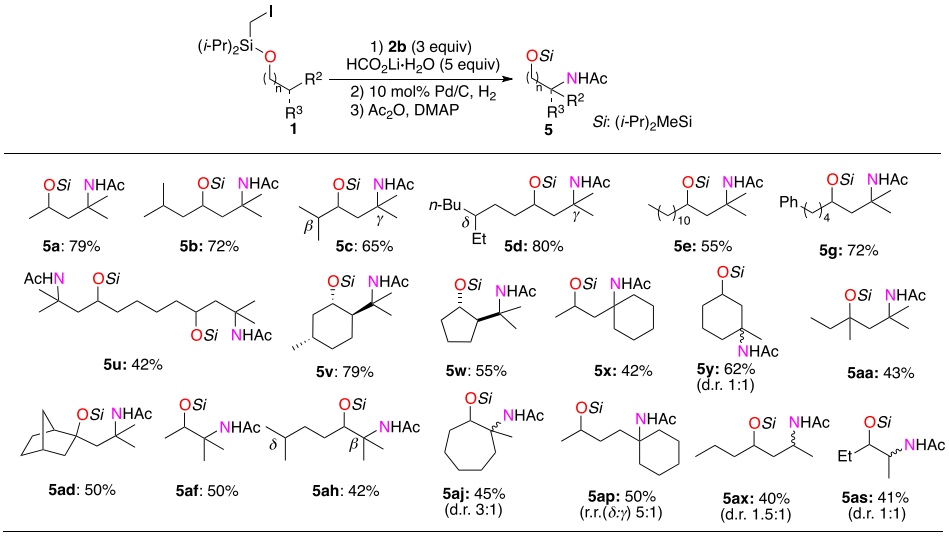
Scheme 3. Transformations of Diazenylated Alcohols: Hydrogenation toward Amino Alcohols[a]



[a]0.3−0.4 mmol scale reactions. Isolated yield, %.

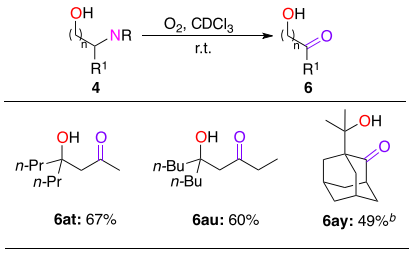
minor regioisomers. Cyclic (**1ai**, **1aj**) and bicyclic (**1ak**) alcohols underwent diazenylation reaction at the β-tertiary C−H sites, as well (products **3ai**, **3aj**, **3ak**). Moreover, this protocol was compatible with tertiary (**1al**) and primary alcohols (**1am**, **1an**), leading to the desired products **3al**, **3am**, and **3an**, respectively. Challenging δ-diazenylation was targeted as well (Scheme 2, c). Gratifyingly, reactions of secondary (**1ao**, **1ap**) and primary (**1aq**) alcohols led to the desired products as mixtures of δ- and γ-diazenylation products in good yields.

Finally, we applied this methodology for 2° C−H and even 1° C−H site functionalization (Scheme 2, d). *Both γ- and β-diazenylation reactions were accomplished for secondary (**1ar**, **1as**) and tertiary (**1at**, **1au**, **1av**) alcohols in good yields. Remarkably, this diazenylation protocol was also applicable for unactivated 1° C−H site functionalization, yielding primary diazene **3aw** in 28% yield!*

Lastly, we examined the synthetic utility of the obtained β-, γ-, and δ-diazenylated alcohols toward their highly valuable amino alcohol derivatives. Thus, the synthesized substrates were subjected to hydrogenation conditions[21] followed by acylation to access the corresponding protected amino alcohols **5** (Scheme 3). *To our delight, the diverse range of secondary and tertiary cyclic and acyclic 1,2- 1,3- and 1,4-amino alcohols were obtained in reasonable yields via a three-step procedure starting from Si-tethered alcohols **1**.* Moreover, it was found that secondary diazenes, which are prone to isomerize into hydrazones, could efficiently be oxidized in the presence of oxygen into the corresponding ketones.[22] Thus, this approach can be further used for the remote oxygenation of aliphatic alcohols[23] with secondary sites into γ-hydroxy ketones **6** (Scheme 4). This method potentially can be used to generate aldol equivalent products, which are difficult to access by other methods (**6ay**).

In summary, we have developed the first *classical-radical-initiator-, transition-metal- and visible-light-free*, auxiliary-enabled remote C−H functionalization protocol for selective γ-, β-, and δ-C(sp^3)−N bond formation in aliphatic alcohols. This method features mild radical conditions and employs readily available diazonium salts to serve a double duty as the I atom abstracting agent and a coupling partner. The reaction is promoted by a weak base, lithium formate, and does not require use of transition metals or radical initiators. The scope of obtained diazenylated alcohols is very broad, and their transformations toward amino alcohols and hydroxy ketones were accomplished with good efficiency. Overall, this is a highly accessible, inexpensive, and practical method for functionalization of remote β-, γ-, and δ-unactivated C−H sites of alcohols, expected to find broad applications in synthesis.

Scheme 4. Transformations of Diazenylated Alcohols: Oxygenation toward Hydroxy Ketones[a]



[a]0.2−0.4 mmol scale reactions. Isolated yield, %. [b]Compound synthesized via a semi-one-pot procedure from the corresponding Si-auxiliary protected alcohol **1ay**. Isolated yield over two steps, %.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04189.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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