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Transition-Metal Free Chemoselective Hydroxylation and Hydroxylation−Deuteration of Heterobenzylic Methylenes

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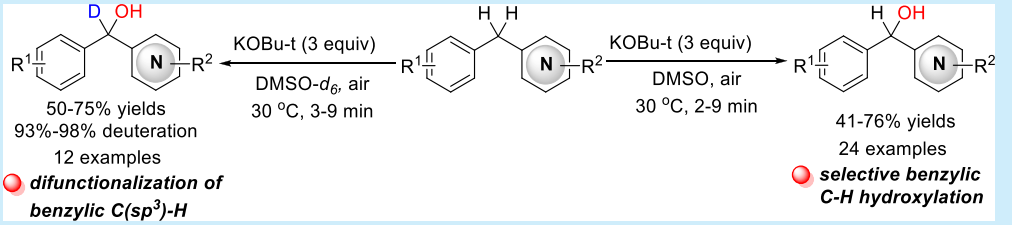

ABSTRACT: We developed an approach for direct selective hydroxylation of heterobenzylic methylenes to secondary alcohols avoiding overoxidation to ketones by using a KOBu-t/DMSO/air system. Most reactions could reach completion in several minutes to give hydroxylated products in 41−76% yields. Using DMSO-d_6, this protocol resulted in difunctionalization of heterobenzylic methylenes to afford α-deuterated secondary alcohols (>93% incorporation). By employing this method, active pharmaceutical ingredients carbinoxamine and doxylamine were synthesized in two steps in moderate yields.

The direct selective oxyfunctionalization of the benzylic C(sp^3)−H bond to the formation of alcohols (lowest oxidation state in contrast to corresponding ketones, aldehydes, and carboxylic acids) is still challenging and limited.[1] To date, only a few examples of selective oxidation to hydroxylated products employing enzymatic catalysis,[2] bionic catalysis,[3] and core−shell catalysis[4] have been reported. Very recently, Sekar[5] and Ritter[6] reported new strategies by the direct synthesis of protected hydroxy groups such as the acetyl (Ac) or methanesulfonyl (Ms) group, to minimize overoxidation to the corresponding ketones (Scheme 1a,b). However, the direct aerobic chemoselective oxidation of (hetero)benzylic C(sp^3)−H bonds to secondary alcohols remains a significant challenge. There are two major reasons.[5] (1) Most of the aerobic oxidation procedures follow a radical pathway, whereby the readily formed (hetero)benzylic radical intermediate immediately reacts with molecular oxygen to form a peroxo intermediate, which is then transformed into a carbonyl group (aldehyde/ketone) by the elimination of H_2O. In addition, the reduction of O_2 to H_2O is highly exothermic, giving a thermodynamic driving force for aerobic oxidation. (2) If some alcohols are obtained by cleavage of the O−O bonds, they will be further oxidized to carbonyl groups, because of the higher reactivity of alcohols compared to that of the substrates in the presence of radical species. Therefore, it is very necessary to develop a practical methodology to oxidize (hetero)benzylic methylenes to secondary alcohols directly with ambient air as the terminal oxidant.[7]

Aryl(pyridin-2-yl)methanols have been widely used for the synthesis of active pharmaceutical ingredients (APIs) such as bepotastine, carbinoxamine, and doxylamine, which are effective

Scheme 1. Selective Hydroxylation of Heterobenzylic C(sp^3)−H Bonds

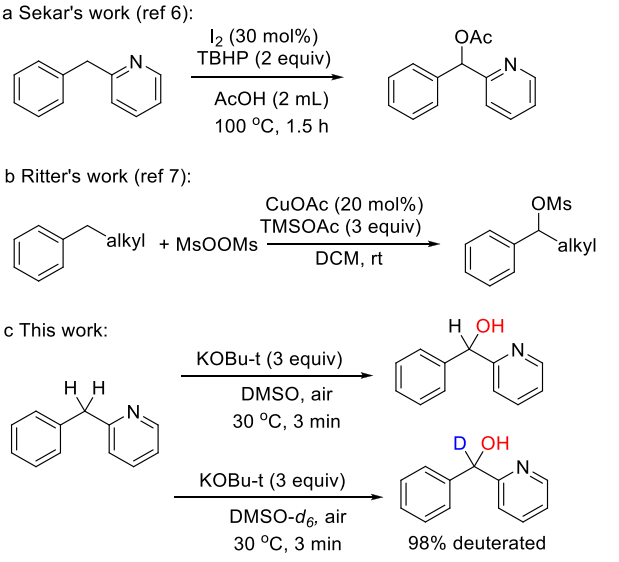

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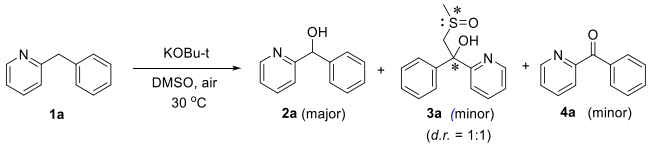
Table 1. Optimization of Reaction Conditions[a]



entry	base	t (min)	solvent	yield (%)[b] 2a	3a	4a
1[c]	KOBu-t	4	DMSO	59	15	7
2[d]	KOBu-t	15	DMSO	45	9	31
3[e]	KOBu-t	30	DMSO	25	13	40
4	KOBu-t	3	DMSO	71	10	trace
5[f]	KOBu-t	3	DMSO	72	8	trace
6	KOBu-t	30	DMSO	42	37	trace
7[g]	KOBu-t	30	DMSO	trace	78	trace
8	KOBu-t	60	DMF	trace	–	86
9	KOBu-t	60	toluene	no reaction	–	–
10	KOBu-t	60	MeCN	18	–	27
11	KOBu-t	4	tetramethylene sulfoxide	41	–	14
12	LiOBu-t	30	DMSO	trace	trace	trace
13	NaOBu-t	30	DMSO	24	7	15
14	KOH	60	DMSO	42	trace	36
15	DBU	60	DMSO	no reaction	–	–
16	DABCO	60	DMSO	no reaction	–	–

[a]Unless specified, to a solution of a base (1.5 mmol) in 2 mL of anhydrous DMSO was added dropwise 2-benzylpyridine **1a** (0.5 mmol) in 1 mL of anhydrous DMSO (0.5 mol/L) in 1 min, and the reaction mixture under ambient air was stirred at 30 °C until **1a** was consumed, as monitored by TLC. [b]Isolated yield. [c]With 2 equiv of KOBu-t. [d]With 1 equiv of KOBu-t. [e]With 0.5 equiv of KOBu-t. [f]With 4 equiv of KOBu-t. [g]The reaction was carried out at 60 °C.

antagonists of the histamine 1 (H1) receptor in the treatment of allergic rhinitis, chronic urticaria, and skin diseases.[8]

Traditionally, aryl(pyridin-2-yl)methanols have been synthesized via a two-step process: oxidation of benzylpyridines to benzoylpyridines followed by monohydrogenation.[9] It is highly desirable to develop direct conversion of heterobenzylic C(sp^3)−H to corresponding alcohols. Herein, to continue our study of functionalization of azaarenes[10] and aerobic C−O formation reactions,[11] we report our studies of a chemoselective transition-metal free aerobic hydroxyfunctionalization of heterobenzylic C(sp^3)−H bonds to synthesize secondary alcohols by using air as the sole oxidant with high chemoselectivities and moderate to excellent yields. Moreover, deuterated secondary alcohols can be obtained via "one-pot" site-specific hydroxylation−deuteration of heterobenzylic methylenes by using DMSO-d_6 as the solvent (Scheme 1c).

We commenced our studies by investigating the model reaction of 2-benzylpyridine **1a** (0.5 mmol in 1 mL of DMSO) in a solution of a base (1.0 mmol) in DMSO (2 mL) (Table 1). According to the independent reports of Maes[12] and Gao,[13] a small amount of phenyl(pyridin-2-yl)methanol **2a** was formed as only the byproduct in the oxidation of 2-benzylpyridine to form phenyl(pyridin-2-yl)methanone. In contrast, in the presence of 2 equiv of KOBu-t for 4 min at 30 °C, **2a** was obtained in 59% yield with 15% DMSO-linked byproduct **3a** and 7% ketone byproduct **4a** (Table 1, entry 1). Encouraged by this result, we then varied the reaction conditions to optimize the yield of **2a**. Decreasing the amount of KOBu-t led to the increasing yields of byproducts (entries 2 and 3). Increasing the amount of KOBu-t favored the formation of **2a** with <10% **3a** and a trace amount of **4a** (entries 4 and 5, respectively), and 3 equiv was found to be necessary (entry 4, 71% yield). Moreover, the results showed that a prolonged reaction time led to a lower yield (entry 6). The reaction at 60 °C gave only product **3a** in 78% yield (entry 7). In addition, solvent screening revealed that only trace amounts of products were obtained in DMF, toluene, or CH_3CN, whereas tetramethylene sulfoxide afforded **2a** in a lower yield (entry 11, 41% yield). These results revealed that the sulfoxide moiety was important and DMSO was the most suitable solvent for this reaction. In addition, LiOBu-t, NaOBu-t, KOH, and organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were shown to be less efficient (entries 12−16, respectively).

After optimizing the reaction conditions, we then examined the process using a variety of substrates. As shown in Scheme 2, all of the tested substrates produced the hydroxylated products **2** within 2−9 min in moderate to good isolated yields with minor byproducts **3**. The reaction could well tolerate electron-withdrawing groups (EWGs) such as F and Cl (**2b** and **2c**, 58% and 60% yields, respectively), an electron-donating group (EDG) (Me, **2d**, 62% yield), and an electron-neutral group (vinyl group, **2e**, 53% yield) on the *para* position of the benzene rings. A *meta*-Me-substituted benzene ring also provided the desired product **2f** in 61% yield. Interestingly, more sterical substrates, involving *o*-Me and *o*-Br substitution of the benzene ring, afforded the corresponding alcohols in good yields (71% for **2g** and 68% for **2h**). Other aromatic substrates, including 2-naphthalene, 1-naphthalene, and thiophene, also resulted in smooth reactions, affording **2i**−**2k**, respectively, in good yields. In addition, the substrates with a pyridine ring bearing -Me, -OMe, and -Cl groups were also shown to be compatible with this process (**2l**−**2o**). Similarly, the pyridines bearing a C-3 furnished the corresponding alcohols with higher yields (**2l**−**2n**). Besides 2-benzylpyridine derivatives, 4-benzylpyridine substrates also provided the desired products (**2p**−**2s**) in moderate to good yields. Furthermore, other azaarenes,

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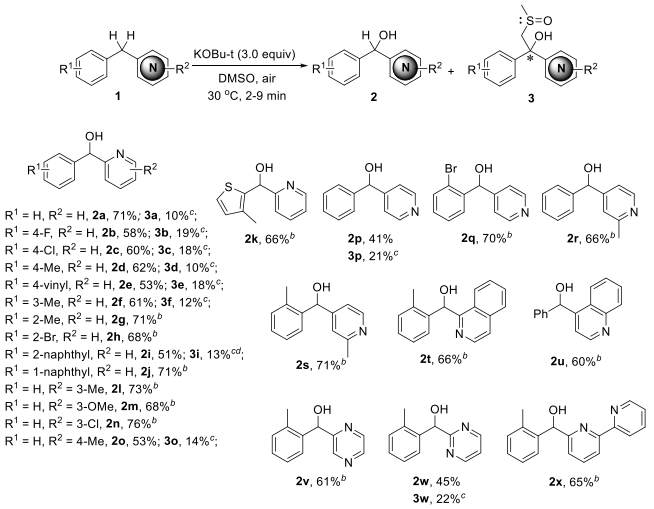
Scheme 2. Hydroxylation Reactions of Heterobenzylic C(sp^3)−H Bonds[a]



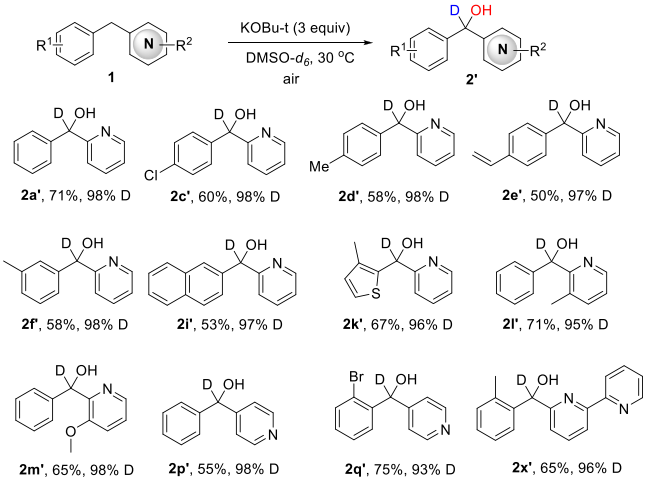
[a]Reaction conditions: To a solution of KOBu-t (1.5 mmol) in 2 mL of anhydrous DMSO was added dropwise substrate **1** (0.5 mmol) in 1 mL of anhydrous DMSO (0.5 mol/L) in 1 min, and the solution was stirred at 30 °C under ambient air. Isolated yield of **2**. [b]The yield of **3** (<10%) was based on the ^{1}H NMR analysis of the crude mixture. [c]Isolated yield of **3**. The characterization data are reported in the Supporting Information. [d]The isolated yield of **4i** (11%) is reported in the Supporting Information.

including isoquinoline, quinoline, pyrazine, and pyrimidine, were also tested as substrates for this hydroxylation reaction. Gratifyingly, the expected products were formed in moderate yields (**2t**−**2w**). Moreover, the LC-MS study for characterization of the corresponding byproducts was performed by employing **1t** as the substrate. The mass peaks for **2t** and **3t** could be detected (see Figure S11). It is noteworthy that a new tridentate ligand based on 2,2′-bipyridine was synthesized by this novel methodology in 65% yield (**2x**).

The synthesis of α-deuterated alcohols is an important research area in organic chemistry due to their significance in pharmaceuticals.[14] Traditional methods for the synthesis of α-deuterated alcohols include the reduction of carbonyl compounds with deuterated reducing agents such as $LiAlD_4$ and $NaBD_4$,[15] or transition-metal-catalyzed H/D exchange.[16] We now report that a practical "one-pot" difunctionalization (hydroxylation−deuteration) of 2-benzylpyridine derivatives gives α-deuterated aryl(pyridin-2-yl)methanol **2′** by using DMSO-d_6 as the solvent, which has the advantages of being inexpensive, readily available, and highly safe (for optimization of reaction conditions, see Table S1). Various benzylpyridine derivatives **1** afforded the desired deuterated aryl(pyridinyl)-methanols **2′** with 93−98% benzylic deuteration after aqueous workup and without any sacrifice of yield (Scheme 3). Besides, the reactions also gave the deuterated DMSO-linked byproducts **3′** similarly (10% isolated yield for **3a′**).

On the contrary, Sekar[8c] and Maes[8d] have independently reported iron-catalyzed C−H hydroxylation to form N-heterocycle-containing triarylmethanols or (alkyl)(aryl)-azinylmethanols from the corresponding substrates. However, these reactions normally require high temperatures or long reaction times. To overcome these difficulties, we now report an extension of our KOBu-t-promoted hydroxylation of heterobenzylic C(sp^3)−H bonds for the synthesis of N-heterocyclic

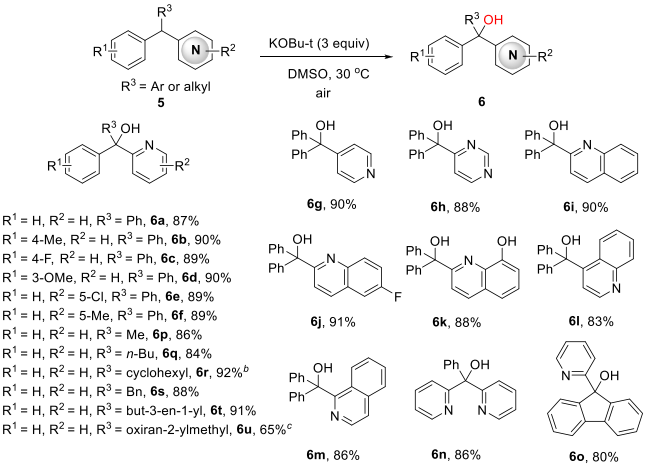
Scheme 3. Difunctionalization of Heterobenzylic C(sp^3)−H Bonds[a]



[a]Reaction conditions: To a solution of KOBu-t (0.9 mmol) in 1.5 mL of anhydrous DMSO-d_6 was added dropwise **1** (0.3 mmol) in 0.5 mL of anhydrous DMSO-d_6 (0.6 mol/L) in 1 min, and the mixture was stirred at 30 °C under ambient air. Isolated yield.

trisubstituted methanols[17] as potential API intermediates. Indeed, when aryl- or alkyl-substituted benzylpyridines **5** were submitted to the optimized reaction, tertiary alcohols **6** were successfully obtained in satisfactory yields (Scheme 4). For

Scheme 4. Hydroxylation Reactions of Heterobenzylic C(sp^3)−H Bonds[a]



[a]Reaction conditions: To a solution of KOBu-t (1.5 mmol) in 2 mL of anhydrous DMSO was added dropwise **5** (0.5 mmol) in 1 mL of anhydrous DMSO (0.5 mol/L), and the mixture was stirred for 0.5−2 h at 30 °C under ambient air. Isolated yield. [b]The reaction was carried out under O_2 for 20 h. [c]The reaction mixture was stirred for 10 h under ambient air.

example, 2-benzhydrylpyridine **5a** led to the desired product **6a** in an excellent yield. Furthermore, both EWGs and EDGs on the derivatives were formed in excellent yields (89−91%). It is important to note that the reaction of 2-(9*H*-fluoren-9-yl)pyridine **5o** also proceeded smoothly. Moreover, a range of alkyl-substituted tertiary alcohols **6**, such as Me (**6p**, 86%), Bu (**6q**, 84%), cyclohexyl (**6r**, 92%), and Bn (**6s**, 88%), were also obtained in high yields. Substrates containing diverse function-

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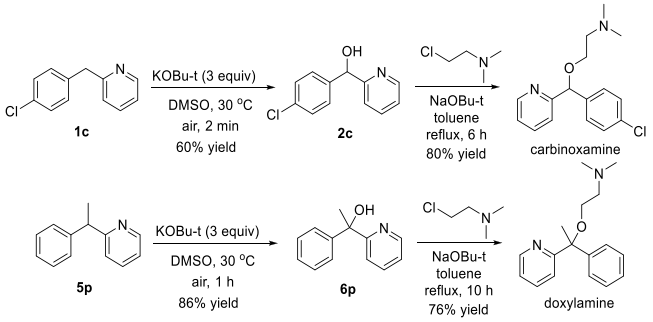
Org. Lett. XXXX, XXX, XXX−XXX

alities such as a terminal olefin or an epoxide group were also investigated, to afford **6t** and **6u** successfully in 91% and 65% yields, respectively.

To test the practicality of this methodology, a gram-scale reaction using substrate **5p** was carried out (see page S38 of the Supporting Information). The product **6p** was obtained with a comparable yield (1.00 g, 84% yield). By employing this novel strategy, API carbinoxamine was synthesized from 2-(4-chlorobenzyl)pyridine in two steps by selective hydroxylation and O-alkylation in 48% overall yield. Similarly, another API, doxylamine, was obtained from 2-(1-phenylethyl)pyridine in a 65% overall yield (Scheme 5).

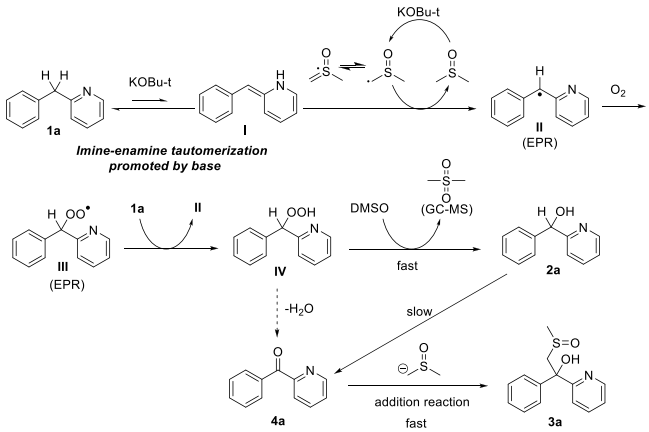
Scheme 5. Application for the Synthesis of APIs Carbinoxamine and Doxylamine



To understand the mechanism of this chemoselective hydroxylation reaction, we performed several control experiments and in situ spectroscopic investigations. First, the reaction of **1a** was carried out under a N_2 atmosphere. Not surprisingly, hydroxylated product **2a** was not obtained and most of the **1a** was recovered, indicating the necessity of molecular oxygen for this reaction. Upon addition of 5 equiv of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) to the reaction mixture under a N_2 atmosphere, the corresponding TEMPO coupling product **7a** was isolated in 85% yield (see Figure S6). This implies that the reaction proceeds via the heterobenzylic radical intermediate. Moreover, it was gratifying to find that the radical species could be trapped by ethene-1,1-diyldibenzene to give radical addition product **8a** (see Figure S7). To capture the reaction intermediate, the deuteration experiment was carried out by using 1 equiv of KOBu-t as a base and DMSO-d_6 as the solvent. After 3.5 min, α-deuterated aryl(pyridin-2-yl)methanol **2a′** and dideuterated 2-benzylpyridine **1a′** were separated in 47% and 37% yields, respectively (see Figure S8). When diphenylmethane was tested in this reaction, no desired product was observed and most of the diphenylmethane was recycled (88% recycled with 44.5% deuterated) under the same condition (see Figure S8). This indicated that a N-containing heterocycle was necessary for this reaction. Furthermore, under the standard reaction condition, **1a′** could react smoothly to give **2a′**. Additionally, deuterated **2a′** could not be formed by employing **2a** as the substrate (see Figure S8). These results indicated that the deuteration of substrates was much faster than the hydroxylation process. Under the standard condition, byproduct **3a** could be obtained in 85% yield from ketone **4a** in 5 min (see Figure S9). Furthermore, EPR and GC-MS investigations were also performed to better understand the reaction mechanism with **5p** as the substrate. When KOBu-t and DMSO were tested, no EPR signal was observed (see Figure S10a). However, the EPR spectrum of a mixture of **5p**, KOBu-t, and DMSO displayed a resonance characteristic of an organic radical (see Figure S10b). Moreover, when 2 equiv of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was added, the superoxide free radical signal appeared (see Figure S10c). In addition, (methylsulfonyl)-methane was detected in the GC-MS analysis. This result reveals that DMSO is the reductant, being oxidized in accepting one oxygen atom in the reaction.

On the basis of the results presented above, a possible reaction mechanism is proposed in Scheme 6. Initially, intermediate **I**

Scheme 6. Proposed Mechanism of Selective Hydroxylation



facilitates formation of an enamine tautomer that is more susceptible to aerobic oxygenation.[18] Then **I** is induced by a DMSO free radical in the presence of KOBu-t to form radical **II** (detected by EPR).[19] Radical **II** reacts with molecular oxygen to give intermediate **III** (detected by EPR), which abstracts a hydrogen atom from **1a** to afford radical **II** and hydroperoxide **IV**.[20] Finally, **2a** is formed by reduction of **IV** with DMSO instead of the typical dehydration to give ketone **4a**. DMSO is oxidized to dimethyl sulfone [detected by GC-MS (see Figure S12)].[4,21] Ketone **4a** is generated from **2a** via dioxygen oxidation. Another byproduct **3a** is formed by nucleophilic addition reaction between ketone **4a** and DMSO anion. The formation of **2a** from **1a** and the formation of **3a** from **4a** are rapid reactions, and the formation of ketone **4a** from alcohol **2a** is slower.

In summary, using a KOBu-t/DMSO/air system, we have developed the first example of a transition-metal free direct hydroxylation of benzylpyridine derivatives to their corresponding secondary alcohols, with high chemoselectivity, in moderate to good yields. In addition, by employing DMSO-d_6 as the solvent, site-selective hydroxylation−deuteration of heterobenzylic methylenes has been demonstrated to be a very efficient difunctionalization strategy to afford α-deuterated secondary alcohols with >93% deuteration. Mechanistic studies indicate that the hydroxylation reaction proceeds via a radical pathway. By employing this novel strategy, two APIs, carbinoxamine and doxylamine, were synthesized in a practical two-step sequence in moderate yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03108.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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