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Metal-Free Solvent/Base-Switchable Divergent Synthesis of Multisubstituted Dihydrofurans

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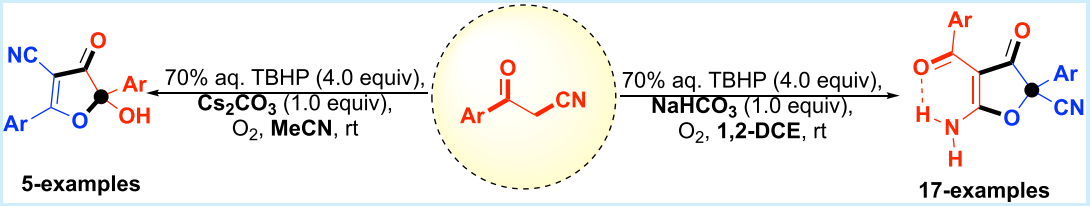

ABSTRACT: A general protocol for the synthesis of multisubstituted 2,3-dihydrofuran-2-carbonitriles and 4,5-dihydrofuran-3-carbonitriles was demonstrated under a metal-free regime with the same oxidant, TBHP. By simply switching the reaction solvent and base, the reaction proceeds via two pathways. An unexpected −CN group migration rearrangement and hydroxylation have occurred in nonpolar and polar solvents, respectively, under the reported conditions. Furthermore, the source of the hydroxyl group and hydrogen in the reaction is indirectly confirmed with isotope labeling studies.

From its initial report, the development of nitrile functionalization reactions has become a cornerstone in synthetic chemistry and has garnered intense interest within the chemical community.[1] Nitrile and its derivatives are among the most basic chemicals and are important structural motifs in natural compounds and pharmaceuticals, as they exhibit various biological activities.[2] In contrast to the heterodifunctionalization reactions (for example), homodifunctionalization reactions are far less investigated.[3] Especially, in the classical approach from acid−base condensation to transition-metal/metal-free transformation, several synthetic strategies have been developed in an efficient pathway for value-added nitrile-functionalized skeletons,[4] because of their availability from commercial sources or from plethora of established synthetic strategies.[5] However, the metal-free solvent/base-switchable reactions of nitrile are mutually incompatible and have been scarcely documented because of their lower reactivity and electron density in contrast to the other functional groups such as alkenes,[6] alkynes,[7] carbonyl,[8] etc. Furthermore, the accomplishment of regioselective control of switchable intramolecular domino reactions from an identical substrate is highly desirable in modern organic chemistry. This transformation offers many advantages, such as atom economic, minimization of the multistep procedure, and fewer special starting materials required.

Dihydrofurans and their derivatives are pivotal building blocks in the organic synthesis used in many natural products, agrochemicals, and pharmaceuticals.[9] Prominent examples include flurtamone (acts as herbicide),[10] rofecoxib (anti-inflammatory drug),[11] hyperlactone C (anti-HIV agent),[12] 3(2*H*)-furanone (present in sponges, algae, animals, plants and insects), Bullatenone (known for antifungal activity),[13a] and longianone (antibiotic properties)[13b] (Figure 1). Due to their vital importance, the synthesis of dihydrofuran derivatives has captured long-term interest from the chemical community. In this arena, Maiti and co-worker developed the copper-catalyzed annulation of aryl ketones with aromatic olefins that supplies convenient access to 2,3-dihydrofuran derivatives (Scheme 1a).[14a] Additionally, Park et al. established a dual manifold synthetic method for the synthesis of 2-aminofurans and unsubstituted furans via [3 + 2] cycloaddition of diazo compounds with enamines (Scheme 1b).[14b] Similarly, Liao et

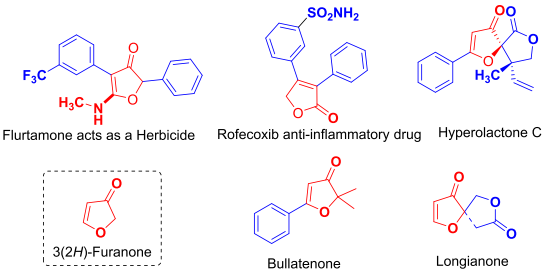

Figure 1. Furanone derivatives in biologically active agents.

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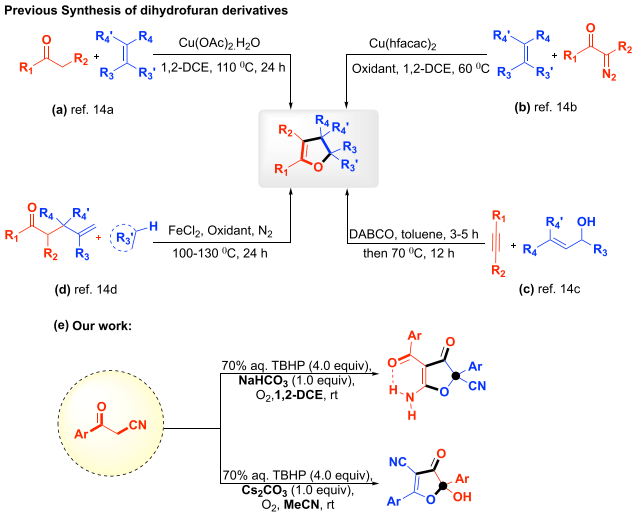
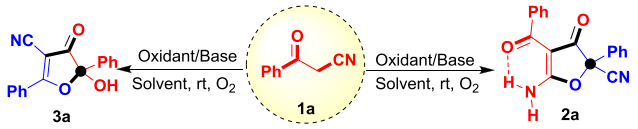
Scheme 1. Previous Work and Our Approach



al. synthesized functionalized 2,3-dihydrofurans via a Lewis base catalyzed tandem reaction of the hydroalkoxylation/Claisen rearrangement/Michael addition sequence (Scheme 1c).[14c] Zhou and co-workers reported $FeCl_2$-catalyzed radical cyclization of olefinic dicarbonyl compounds with saturated/unsaturated Csp^3−H bonds to build up a variety of dihydrofurans containing a quaternary carbon center, with moderate to good yields (Scheme 1d).[14d] In addition, other synthetic protocols have also been reported for the synthesis of functionalized dihydrofurans via metal-catalyzed[15a,b]/metal-free strategies,[15c−e] in asymmetric fashion, for example, Feist−Benary[16a] and Paal−Knorr syntheses,[16b,c] the Michael alkylation domino reaction,[17] cycloaddition reactions,[18] and rearrangement reactions,[19] among others. Although each of the reported methods has its own merits and demerits, increasing demand still exists for novel, flexible, convergent, atom economic chemical transformative procedures that are particularly welcome and have become an indispensable in the research field. Thus, as a component of our continued research interests in the nitrile functionalization, and green organic synthesis,[20] we present herein a metal-free solvent/base-switchable platform for selective conversion of β-ketonitriles to multisubstituted 2,3-dihydrofuran-2-carbonitriles and 4,5-dihydrofuran-3-carbonitriles via −CN and −CO attack, respectively (Scheme 1e).

We began our investigation with benzoylacetonitrile (**1a**) as a model substrate to optimize the various reaction parameters. To our delight, a mixture of the desired products of 2,3-dihydrofuran-2-carbonitrile **2a** and 4,5-dihydrofuran-3-carbonitrile **3a** in 23% and 47% yields, respectively, was obtained in the presence of 70% aq. TBHP (2.0 equiv) as the oxidant and K_2CO_3 (2.0 equiv) at room temperature for 24 h under an O_2 atmosphere (Table 1, entry 1). To slow the formation of the **3a** product, various bases were tested (Table 1, entries 2−11) with $NaHCO_3$ showing the best efficiency in producing **2a** with 56% isolated yield. After decreasing and increasing the quantity of base and oxidant, respectively (Table 1, entries 12−15), **2a** was exclusively isolated as a major product in 72% yield. Among the various solvents, only 1,2-DCE showed an improved yield (Table 1, entries 16−17). As solvents, MeOH and DMF were deleterious to this transformation (Table 1, entries 18 and 19). The yield of **2a** was diminished when the reaction was conducted at 0 and 50 °C and was also largely

Table 1. Optimization of Reaction Parameters for the Switchable Formation of Products[a,b]



Sr. No.	Solvent	Base (X equiv)	Oxidant (Y equiv)	Yield (%) **2a**/**3a**
1	PhCl	K_2CO_3 (2.0)	TBHP (2.0)	23/47
2	PhCl	Na_2CO_3 (2.0)	TBHP (2.0)	35/31
3	PhCl	NaOH (2.0)	TBHP (2.0)	5/21
4	PhCl	*t*-BuOK (2.0)	TBHP (2.0)	−/−
5	PhCl	DBU (2.0)	TBHP (2.0)	−/−
6	PhCl	Et_3N (2.0)	TBHP (2.0)	−/−
7	PhCl	DIPA (2.0)	TBHP (2.0)	−/−
8	PhCl	K_3PO_4 (2.0)	TBHP (2.0)	18/51
9	PhCl	NaOAc (2.0)	TBHP (2.0)	24/42
10	PhCl	Cs_2CO_3 (2.0)	TBHP (2.0)	18/56
11	PhCl	$NaHCO_3$ (2.0)	TBHP (2.0)	56/18
12	PhCl	$NaHCO_3$ (1.0)	TBHP (2.0)	59/13
13	PhCl	$NaHCO_3$ (1.0)	TBHP (3.0)	65/9
14	PhCl	$NaHCO_3$ (1.0)	TBHP (4.0)	72/5
15	PhCl	$NaHCO_3$ (1.0)	TBHP (5.0)	70/5
16	**1,2-DCE**	**$NaHCO_3$ (1.0)**	**TBHP (4.0)**	**76/5**
17	DCM	$NaHCO_3$ (1.0)	TBHP (4.0)	52/7
18	MeOH	$NaHCO_3$ (1.0)	TBHP (4.0)	−/−
19	DMF	$NaHCO_3$ (1.0)	TBHP (4.0)	−/−
20[c]	1,2-DCE	$NaHCO_3$ (1.0)	TBHP (4.0)	46/25
21[d]	1,2-DCE	$NaHCO_3$ (1.0)	TBHP (4.0)	23/21
22[e]	1,2-DCE	$NaHCO_3$ (1.0)	TBHP (4.0)	61/10
23[f]	1,2-DCE	$NaHCO_3$ (1.0)	TBHP (4.0)	49/12
24	MeCN	$NaHCO_3$ (1.0)	TBHP (4.0)	−/46
25	**MeCN**	**Cs_2CO_3 (1.0)**	**TBHP (4.0)**	**−/79**
26	MeCN	Cs_2CO_3 (3.0)	TBHP (4.0)	−/59
27	1,2-DCE	$NaHCO_3$ (1.0)	DTBP (4.0)	−/−
28	1,2-DCE	$NaHCO_3$ (1.0)	CHP (4.0)	−/−
29	1,2-DCE	$NaHCO_3$ (1.0)	$K_2S_2O_8$ (4.0)	−/−

[a]Reaction conditions **1a** (0.2 mmol), base (X equiv), oxidant (Y equiv), rt, O_2. [b]Isolated yield. [c]Reaction conducted at 0 °C. [d]Reaction conducted at 50 °C. [e]Reaction stirred under N_2. [f]Reaction conducted under open air. TBHP, *tert*-butyl hydroperoxide (70% aq. TBHP was used). DTBP, di-*tert*-butyl hydroperoxide. CHP, cumene hydroperoxide.

affected by the reaction atmosphere (Table 1, entries 20−23). When the solvent was switched from 1,2-DCE to acetonitrile, only **3a** was formed, albeit in 46% yield (Table 1, entry 24). The crucial attempt in attaining a good yield proved successful with the use of Cs_2CO_3 instead of $NaHCO_3$ as the reaction base (Table 1, entry 25). By further increasing the Cs_2CO_3 amounts to 2.0 and 3.0 equiv, the yield of **3a** was decreased accordingly (Table 1, entries 26). Finally, certain classic oxidants were investigated (Table 1, entries 27−29) and showed inferior reactivities in contrast to the optimized parameters (Table 1, entries 16 and 25) for **2a** and **3a**.

With the best reaction conditions at hand (Table 1 entry 16), we initially examined the scope for 2,3-dihydrofuran-2-carbonitriles using substituted β-ketonitriles (**1**) as shown in Scheme 2. It was found that reaction of β-ketonitriles with various electron-donating groups (products **2b**−**2g**) successfully led to product formation in 49−76% yields. To our surprise, the reaction of the fused ring system also afforded the

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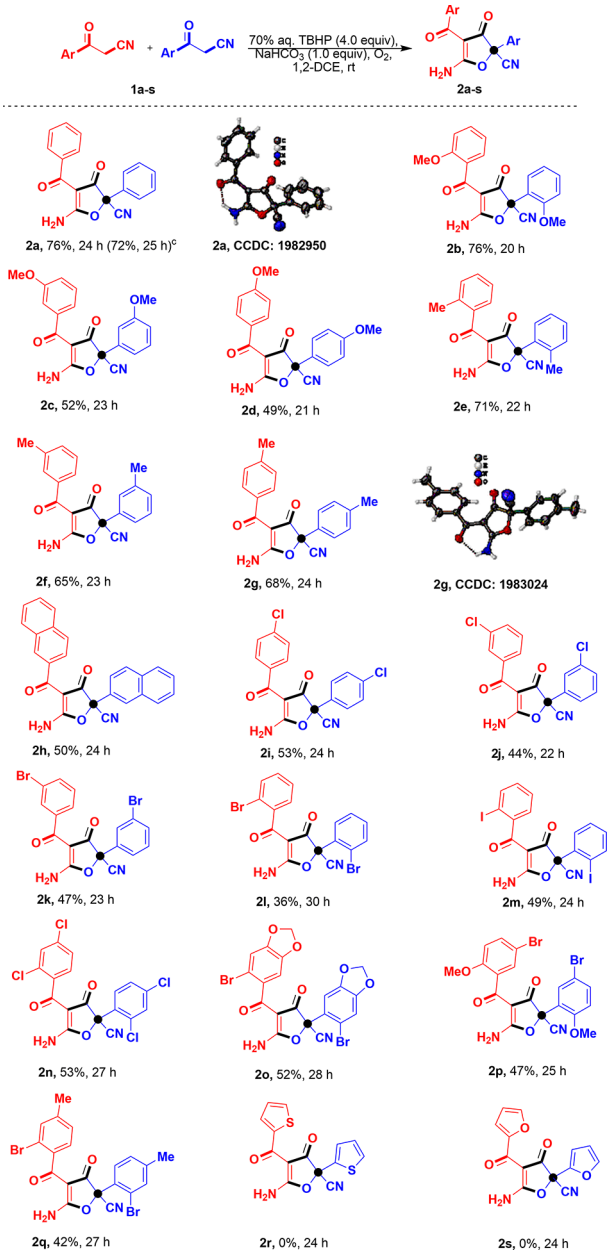
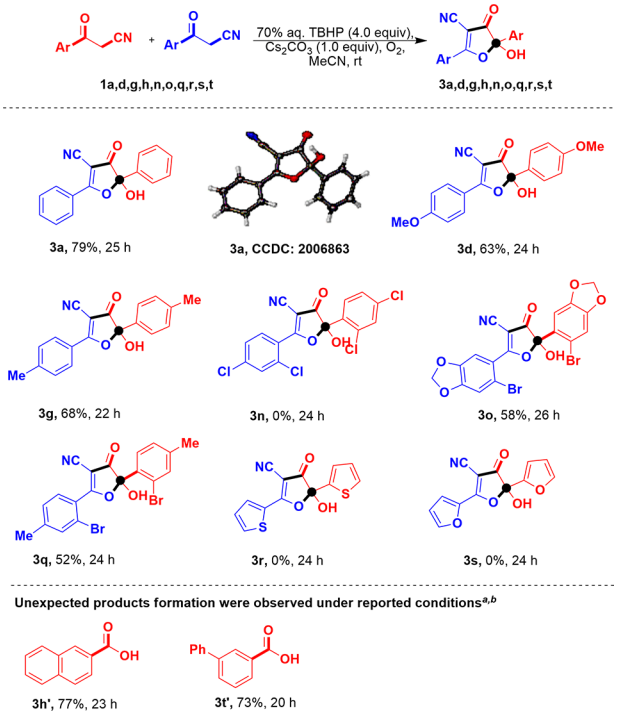
Scheme 2. Substrate Scope of 5-Amino-4-aroyl-3-oxo-2-aryl-2,3-dihydrofuran-2-carbonitriles[a,b]



[a]Reaction conditions: **1a−s** (0.2 mmol), $NaHCO_3$ (1.0 equiv), 70% aq. TBHP (4.0 equiv), O_2, 1,2-DCE (1 mL), rt. [b]Isolated yields. [c]Reaction conducted at 1.0 mmol scale.

desired product **2h** in moderate yield. The case of the electron-withdrawing halo functionality of *β*-ketonitrile, including ortho-substituents, allowed product formation, but at reduced yield (products **2i−2m**). In addition, the reaction with dichloro-substituted *β*-ketonitrile also showed satisfactory tolerance at 53% yield (product **2n**). Moreover, the reaction of electron-donating/-withdrawing derivatives also smoothly worked under standard conditions (**2o−q**). However, it should be noted that the reaction of heterocyclic species led to negative results (product **2r−2s**). In light of our success with 2,3-dihydrofuran-2-carbonitrile derivatives, we explored the substrate scope for preparation of 4,5-dihydrofuran-3-carbonitriles via −CO attack (Scheme 3). Herein, we developed an efficient divergent strategy to construct such potential valuable scaffolds by slightly modifying optimized conditions (Table 1 entry 25).

Scheme 3. Substrate Scope of 5-Hydroxy-4-oxo-2,5-diaryl-4,5-dihydrofuran-3-carbonitriles[a,b]



[a]Reaction conditions: **1a,d,g,h,n,o,q,r,s,t** (0.2 mmol), Cs_2CO_3 (1.0 equiv), 70% aq. TBHP (4.0 equiv), O_2, MeCN 1 mL, rt, [b]Isolated yields.

We elucidated the substrate scope with simple *β*-ketonitriles and with electron-donating/-withdrawing *β*-ketonitriles. All of the substrates were efficiently converted into the corresponding 4,5-dihydrofuran-3-carbonitrile analogues in yields ranging from 52% to 79% (Products **3a**, **d**, **g**, **o**, and **p**). Unfortunately, dichloro-substituted (**3n**) and heterocyclic *β*-ketonitriles (**3r−s**) were shut down in the reaction. Presumably, the reason for this behavior is unclear. In the case of fused ring and biaryl systems, instead of the desired product, we observed hydrolyzed products (**3h′** and **3t′**) in quantitative yields. The structures of **2a**, **2g**, and **3a** were unambiguously confirmed by X-ray analysis.[21] To demonstrate the practicality and synthetic application of this protocol, a gram-scale reaction with **1a** as a model substrate was performed under standard conditions and 64% of **2a** and 61% of **3a** yields were obtained, respectively (Scheme 4a). The multifunctionalized 2,3-dihydrofuran-2-carbonitriles (**2**) with a reactive amine ($-NH_2$) group can be transformed into a variety of other functionalized products. Considering these facts, we treated **2a** with methylene iodide in the presence of K_2CO_3, and a mixture of mono-/dimethylation was observed to afford major and minor products (**4a** and **4a′**) (Scheme 4b). However, when methylene iodide was replaced by phenacyl bromide, the amine functionality (**2k**) was converted only to the *N*-substituted moiety (**5k**) as a sole product without affecting the other functionality (Scheme 4c).

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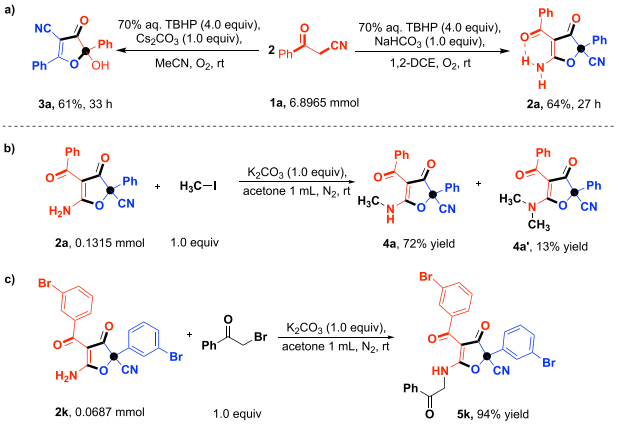
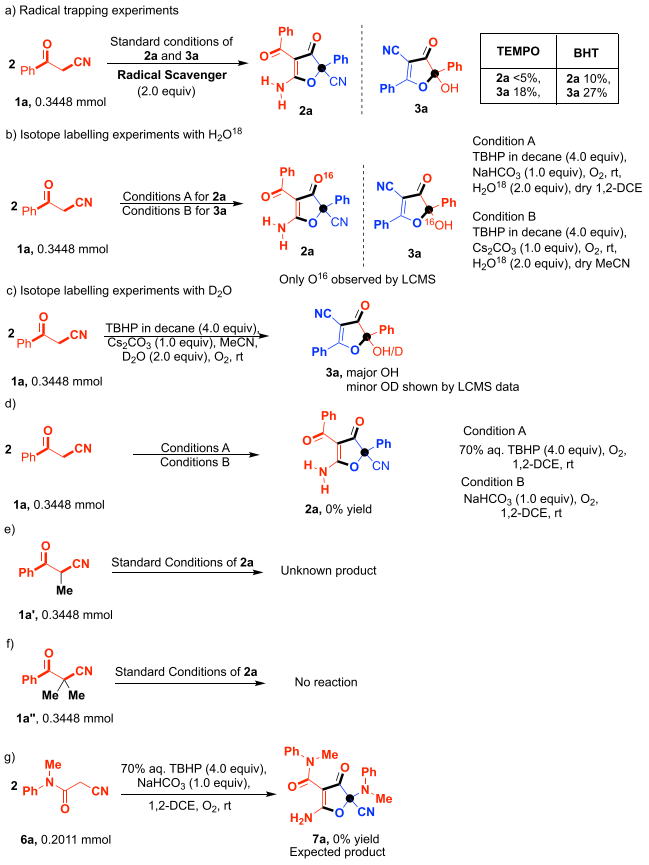
Scheme 4. Gram Scale Experiment and Post-synthetic Applications



To gain further insights into the reaction mechanism, a series of control experiments were conducted (Scheme 5).

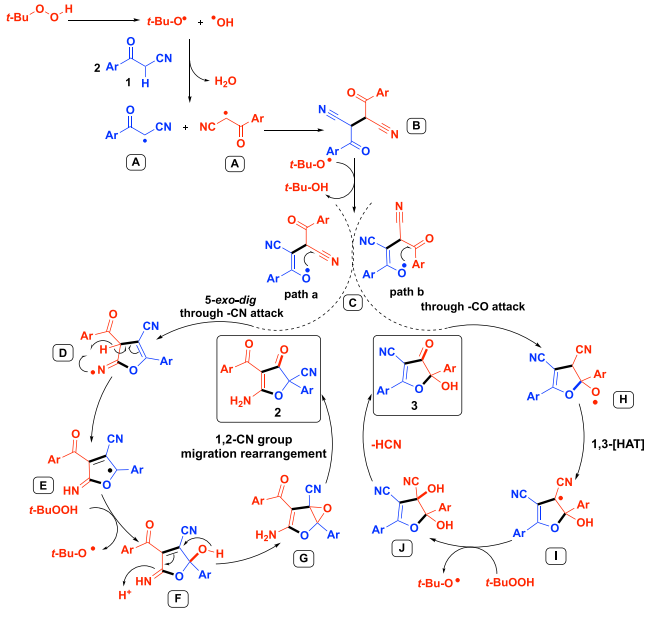
Scheme 5. Mechanistic Studies



First, upon addition of a stoichiometric amount of well-known radical inhibitors TEMPO and BHT, the formation of **2a** was completely shut down, but the reaction partially proceeded in the case of product **3a** (Scheme 5a). Furthermore, to track the source of the hydroxy group, the model reaction was first performed in the presence of 2.0 equiv of $H_2{}^{18}O$, and only ^{16}O-labeled desired products (**2a**/**3a**) were observed by LCMS (Scheme 5b).[22] Additionally, to identify the source of hydrogen, an isotope labeling experiment was conducted in the presence an amount of D_2O in the model reaction (Scheme 5c). The expected deuterated product (**3a**) in a minor amount was observed by LCMS.[22] These results indicated that the source of the hydroxy group and the hydrogen of the product originated from TBHP rather than from water. We also separately performed the reaction in the absence of the base and oxidant, but to our disappointment, the reaction failed to give the desired product **2a** (Scheme 5d). This experiment confirms that the reaction purely depends on the base and oxidant and proceeds via a radical intermediate. Furthermore, when an α-substituted substrate (**1a′**) was applied, the reaction resulted in an unknown product (Scheme 5e). However, when the α,α-disubstituted substrate (**1a′′**) was treated under standard conditions, the reaction did not proceed (Scheme 5f), suggesting that unsubstituted β-ketonitriles seem to play an important role in the system because the reactions were appreciably retarded in the presence of α-monosubstituted/α,α-disubstituted β-ketonitriles. Although we could not isolate any characterizable intermediates from the reaction at this stage, there is clearly room for future studies in this field. Finally, we also performed the reaction of compound **6a** under the designed condition, but the reaction did not produce the desired product (Scheme 5g).

Based on the above mechanistic investigation, a plausible catalytic cycle is shown in Scheme 6. The intermediate **B** was

Scheme 6. Proposed Mechanistic Scenario



formed by homodimerization of radical species **A**, which was generated from the reaction of the hydroxy radical and β-ketonitriles **2**. Intermediate **B** underwent reaction with the *tert*-butoxy radical, which resulted in the formation of O-centered radical intermediate **C**. In a nonpolar solvent, the O-centered radical species **C**, which is prone to conversion to the iminyl radical intermediate **D** via the 5-*exo*-dig pathway via −CN attack, was created as a result. The intermediate **D** was transformed into a stable benzylic radical species **E**, which could undergo reaction with *tert*-butyl hydroperoxide to produce intermediate **F**, which is further transformed to the epoxy species **G**. Finally, intramolecular 1,2-CN group migration arrangement leads to the final product **2**.

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Interestingly, when the reaction is performed in a polar solvent under strong basic conditions, due to the solvation stabilization effect, the intermediate **C** is apt to be attacked on the carbonyl carbon to produce the new five-membered O-centered radical species **H**. Subsequently, intermediate **H** undergoes 1,3-[HAT] to another C-centered secondary radical intermediate **I**, which delivers the 2,3-dihydroxy product **J** by reaction with *tert*-butyl hydroperoxide. Finally, the elimination of hydrogen cyanide from intermediate **J** leads to the desired product **3**.

In conclusion, we have developed an efficient metal-free solvent/base switchable protocol for the synthesis of multi-substituted 2,3-dihydrofuran-2-carbonitriles and 4,5-dihydrofuran-3-carbonitriles. In addition, H_2O^{18} and deuterium labeling studies revealed that aqueous TBHP acts as a hydroxyl and hydrogen source. Moreover, the potential synthetic applications are demonstrated by a gram-scale reaction and late-stage modifications. This strategy offers expedient functional group tolerance with average to good yields. Further extensive studies and application of this particular methodology are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02240.

Experimental procedures; mechanistic studies; spectral characterizations; copies of ^1H, ^{13}C NMR spectra for all products; HRMS data; crystal data for **2a**, **2g**, and **3a** (PDF)

Accession Codes

CCDC 1982950, 1983024, and 2006863 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(21) The CCDC numbers for compounds **2a**, **2g**, and **3a** are CCDC 1982950, CCDC 1983024, and CCDC 2006863, respectively.

(22) See Supporting Information for LCMS details.

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