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Unexpected Solvent-Free Cycloadditions of 1,3-Cyclohexanediones to 1-(Pyridin-2-yl)-enones Mediated by Manganese(III) Acetate in a Ball Mill

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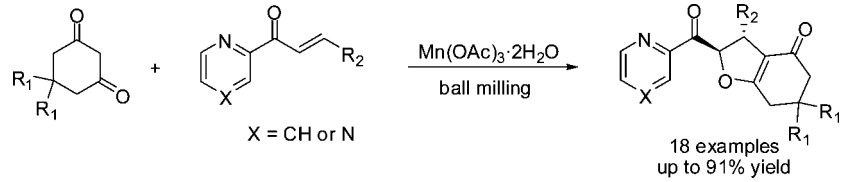

Under solvent-free ball-milling conditions, manganese(III) acetate dihydrate-mediated cycloadditions of 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione to various 1-(pyridin-2-yl)-enones proceeded efficiently to afford *trans*-2-acyl-3-aryl/alkyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone derivatives. The cyclization reactions exhibited good to excellent yields, as well as extremely high diastereoselectivity and unexpected regioselectivity. Manganese(III) acetate behaved both as an oxidant and as a Lewis acid.

Introduction

During the past two decades, significant development has been achieved in manganese(III) acetate [$Mn(OAc)_3$]-mediated oxidative radical reactions, in which $Mn(OAc)_3$ is most commonly used as a single-electron-transfer reagent to generate carbon-centered radicals from various carbonyl compounds.[1] However, with a review of the general radical reactions promoted by $Mn(OAc)_3$, the obvious drawback arises from the harsh reaction conditions. Because of the poor solubility of $Mn(OAc)_3$ in common organic solvents, $Mn(OAc)_3$-mediated reactions are often carried out in acetic acid, although other organic solvents (e.g., alcohols, acetonitrile, dichloromethane, benzene, toluene, chlorobenzene)[2] have also been employed in some cases. Problems are thus encountered for the complete removal of these organic solvents as well as acetic acid. The latter generally requires a large quantity of water or aqueous sodium hydrogen carbonate, resulting in a tedious separation procedure.

To circumvent the aforementioned problems, an attractive alternative is to carry out the reactions under solvent-free conditions. Solvent-free reactions[3] have drawn much attention recently due to the increasingly stringent requirement of eliminating/reducing the use of harmful organic solvents. Solvent-free reactions usually exhibit much higher yield and selectivity than their liquid-phase counterparts.[4] One of our contributions to solvent-free reactions is focused on those promoted by the ball-milling technique.[5] In continuation of our interest in this field,[6,7] herein we report the novel $Mn(OAc)_3$-

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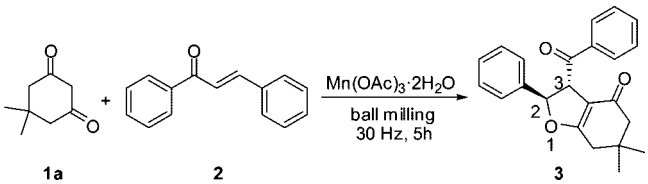
SCHEME 1. $Mn(OAc)_3 \cdot 2H_2O$-Mediated Reaction of Dimedone 1a with Chalcone 2



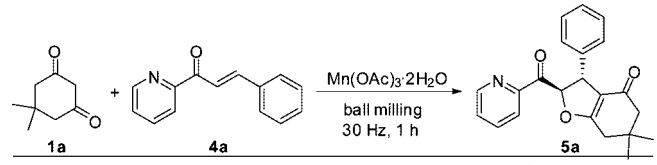
promoted cycloadditions of 1,3-cyclohexanediones to 1-(pyridin-2-yl)-enones affording *trans*-2-acyl-3-aryl/alkyl-benzofuranone derivatives as single diastereoisomers with unexpected regioselectivity.

Results and Discussion

Recently, we have reported the $Mn(OAc)_3 \cdot 2H_2O$-mediated unusual radical additions of 1,3-cyclohexanediones to in situ generated imines under ball-milling conditions.[6c] The intriguing nonreductive addition mode of 1,3-cyclohexanediones to imines prompted us to investigate their additions to C=C double bonds under the same conditions. We first examined the $Mn(OAc)_3 \cdot 2H_2O$-promoted reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1a**) with (*E*)-1,3-diphenylprop-2-en-1-one (**2**) under our ball-milling conditions. Product **3** was obtained in only 23% yield from the reaction of dimedone **1a** with chalcone **2** and $Mn(OAc)_3 \cdot 2H_2O$ in a molar ratio of 1.2:1:2.4 for 5 h (Scheme 1).

The structure of product **3** was assigned as *trans*-3-benzoyl-6,6-dimethyl-2-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one on the basis of its ^1H NMR, ^{13}C NMR, HRMS, and FT-IR spectra. This assignment was consistent with the formation of *trans* diastereoisomers from the $Mn(OAc)_3$-mediated radical reactions of β-ketoesters with cinnamates/cinnamides.[8] The *trans* stereochemistry was unambiguously established by an X-ray structure determination.[8a] The coupling constants between the two methine protons of dihydrofuran derivatives were reported to be obviously larger for the *cis* diastereoisomers ($J = 10-11$ Hz) than for the *trans* diastereoisomers ($J = 4-7$ Hz).[9] The observed coupling constant of 5.7 Hz for product **3** was pretty close to the reported data for the *trans* diastereoisomers,[8,9] further supporting its assigned stereochemistry. Deduced from the above arguments, the previously assigned *cis* stereochemistry should likely be the *trans* stereochemistry for the products from the $Mn(OAc)_3$-mediated radical reactions of 1,3-dicarbonyl compounds with chalcones[10] and from the ceric ammonium nitrate (CAN)-promoted radical reactions of 1,3-dicarbonyl compounds with cinnamtes[11a] or β-aryl-α,β-unsaturated ketotones,[11b] as these products had coupling constants of 5.8−7.2 Hz.

TABLE 1. Oxidative Radical Reaction of Dimedone 1a with 2-Cinnamoylpyridine 4a under Various Conditions[a]



entry	oxidant	base	ratio of reagents[b]	yield (%)
1	$Mn(OAc)_3 \cdot 2H_2O$		1.2:1:2.4	78
2	$Cu(OAc)_2 \cdot H_2O$		1.2:1:2.4	0
3	$FeCl_3 \cdot 6H_2O$		1.2:1:2.4	trace
4	CAN		1.2:1:2.4	28
5	$Mn(OAc)_3 \cdot 2H_2O$		1:1:2.4	73
6	$Mn(OAc)_3 \cdot 2H_2O$		1:1.2:2.4	91
7	$Mn(OAc)_3 \cdot 2H_2O$	$NaHCO_3$	1:1.2:2.4:2.4	91
8	$Mn(OAc)_3 \cdot 2H_2O$	K_2CO_3	1:1.2:2.4:2.4	83
9	$Mn(OAc)_3 \cdot 2H_2O$	K_3PO_4	1:1.2:2.4:2.4	87
10	$Mn(OAc)_3 \cdot 2H_2O$	DMAP	1:1.2:2.4:2.4	46
11	$Mn(OAc)_3 \cdot 2H_2O$	DBU	1:1.2:2.4:2.4	8
12	$Mn(OAc)_3 \cdot 2H_2O$	DABCO	1:1.2:2.4:2.4	26

[a] All reactions were carried out by ball milling at 30 Hz for 1 h. [b] For entries 1−6, the reagent ratio refers to **1a**:**4a**:oxidant; for entries 7−12, the reagent ratio refers to **1a**:**4a**:oxidant:base.

Because of the poor yield for the employed chalcone, we then turned our attention to 2-cinnamoylpyridines. (*E*)-3-Phenyl-1-(pyridin-2-yl)prop-2-en-1-one (**4a**) was chosen as the model substrate for 2-cinnamoylpyridines to optimize the reaction conditions. To our gratification, the reaction of dimedone **1a** with 2-cinnamoylpyridine **4a** and $Mn(OAc)_3 \cdot 2H_2O$ in a molar ratio of 1.2:1:2.4 for only 1 h afforded *trans*-6,6-dimethyl-3-phenyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (**5a**) in 78% yield (entry 1, Table 1). Other oxidants such as Ce(IV), Cu(II), and Fe(III), which have proved to be efficient for the generation of carbon-centered radicals,[1a] were also examined. However, none or only trace amount of the desired product was obtained in the presence of cupric acetate or ferric trichloride (entries 2 and 3, Table 1). This situation was hardly improved when CAN, which has been widely employed in radical reactions, was used (entry 4, Table 1). Product **5a** constituted a very small portion in the complicated reaction mixture, and only 28% yield was obtained. We then optimized the $Mn(OAc)_3 \cdot 2H_2O$-promoted reaction by adjusting the reagent ratio and adding bases. Reducing the amount of dimedone **1a** to 1 equiv (based on the amount of **4a**), the yield dropped slightly to 73% (entry 5, Table 1). Much to our delight, the reaction of **1a** with **4a** and $Mn(OAc)_3 \cdot 2H_2O$ in a molar ratio

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of 1:1.2:2.4 gave product **5a** in 91% yield (entry 6, Table 1). The effect of bases on the reaction was also explored. It was found that the addition of $NaHCO_3$ had no beneficial effect on the reaction, and other inorganic bases such as K_2CO_3 and K_3PO_4 were detrimental to the product yield (entries 7−9, Table 1). Organic bases such as 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), and 1,4-diazabicyclo-[2.2.2]octane (DABCO) afforded product **5a** in only 8−46% yield with poor chemical selectivity (entries 10−12, Table 1). Traditional $Mn(OAc)_3$-mediated radical reactions carried out in organic solvents usually require two or more equivalents of conventional bases.[2h,10] In contrast, the presence of a base in our solvent-free reaction was not profitable to the yield of target product **5a**.

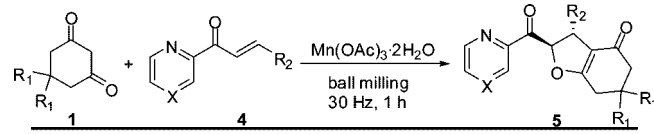
To demonstrate the advantages of our current protocol, we carried out the reaction in organic solvents. For example, when the $Mn(OAc)_3 \cdot 2H_2O$-promoted reaction of **1a** and **4a** in the presence of sodium acetate was carried out in acetic acid at 80 °C under argon atmosphere, a very complicated reaction mixture was obtained, and the yield of the desired product **5a** was 32%. When the reaction was carried out with the existence of potassium carbonate in absolute ethanol at refluxing temperature for 12 h, a mixture of 2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivative **5a** (15%) and 6,7-dihydrobenzofuran-4(5*H*)-one derivative **6a** (vide infra, 48%) was obtained. Either of these results turned out to be less efficient compared with the present mechanical milling procedure.

Under the optimized reaction conditions, we next extended the $Mn(OAc)_3 \cdot 2H_2O$-mediated reaction to other 2-cinnamoylpyridines **4b**−**h** and 1,3-cyclohexanedione **1b**. The detailed results for the reactions of 2-cinnamoylpyridines **4a**−**h** (1.2 equiv) with 1,3-cyclohexanediones **1a,b** (1.0 equiv) and $Mn(OAc)_3 \cdot 2H_2O$ (2.4 equiv) are summarized in Table 2.

As can be seen from Table 2, 2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivatives **5a**−**o** were obtained in good to excellent yields (up to 91% yield) under our solvent-free conditions (entries 1−15, Table 2). The efficiency of the current solvent-free protocol could be ascribed to an enhanced reaction rate resulted from ultimately high concentrations of reactants and the high mechanical energy that can greatly reinforce the reaction.[5c,6a,12] Notably, the product yields for **1a** were obviously higher than those for **1b**, probably due to the higher reactivity of **1a**. Furthermore, no correlation could be found between the product yield and the electronic property of the different substituents on the phenyl ring of 2-cinnamoylpyridines. Besides these 2-cinnamoylpyridines, other enones (**4i**−**k**) had also been investigated to examine the scope and limitation of the reaction. When (*E*)-3-phenyl-1-(pyrazin-2-yl)prop-2-en-1-one (**4i**) was used as the substrate in this reaction, a lower yield (59%) was obtained even with prolonged reaction time (3 h) (entry 16 vs entry 1, Table 2). The reason of the lower efficiency for the chalcone substituted with two nitrogen atoms is not clear right now. When aliphatic substrates such as (*E*)-1-(pyridin-2-yl)hex-2-en-1-one (**4j**) and (*E*)-5-methyl-1-(pyridin-2-yl)hex-2-en-1-one (**4k**) were used, only moderate yields (entries 17 and 18, Table 2) were achieved, reflecting the lower reactivity of substrates **4j** and **4k**.

Compared with the $Mn(OAc)_3 \cdot 2H_2O$ and CAN-promoted radical reactions of 1,3-dicarbonyl compounds and α,β-unsatur-

TABLE 2. Solvent-Free Radical Reactions of 1,3-Cyclohexanediones 1a,b with 1-(Pyridin-2-yl)-enones 4a−k Promoted by $Mn(OAc)_3 \cdot 2H_2O$



1 4 5

entry	1	4	product[a]	yield (%)
1	**1a**	**4a**	**5a**	91
2	**1a**	**4b**	**5b**	88
3	**1a**	**4c**	**5c**	85
4	**1a**	**4d**	**5d**	91
5	**1a**	**4e**	**5e**	78
6	**1a**	**4f**	**5f**	83
7	**1a**	**4g**	**5g**	87
8	**1a**	**4h**	**5h**	90
9	**1b**	**4a**	**5i**	75
10	**1b**	**4b**	**5j**	76
11	**1b**	**4c**	**5k**	75
12	**1b**	**4d**	**5l**	82
13	**1b**	**4f**	**5m**	72
14	**1b**	**4g**	**5n**	79
15	**1b**	**4h**	**5o**	82
16[b]	**1a**	**4i**	**5p**	59
17	**1a**	**4j**	**5q**	62
18	**1a**	**4k**	**5r**	57

[a] Properly characterized by FT-IR, ^1H NMR, ^{13}C NMR, and HRMS spectra data. [b] The reaction time was 3 h.

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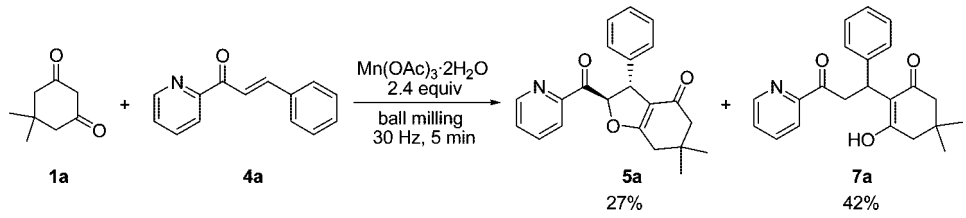
SCHEME 2. $Mn(OAc)_3 \cdot 2H_2O$-Mediated Reaction of Dimedone 1a with 2-Cinnamoylpyridine 4a



ated compounds[8,10,11] including the reaction shown in Scheme 1, reversed regioselectivity was observed for the $Mn(OAc)_3 \cdot 2H_2O$-mediated reactions of 1,3-cyclohexanediones with 1-(pyridin-2-yl)-enones. These results were quite unexpected and interesting. In order to better understand the current solvent-free reaction, we attempted to get some key intermediates. Treatment of dimedone **1a** (1.2 equiv) with 2-cinnamoylpyridine **4a** (1.0 equiv) and $Mn(OAc)_3 \cdot 2H_2O$ (2.4 equiv) for a short reaction time (5 min) afforded **5a** in 27% yield along with another major product (**7a**, 42%) (Scheme 2). Product **7a** was characterized as a Michael addition product. Compound **7a** was converted into **5a** gradually with prolonged reaction time. Compound **7a** could also be obtained from the reaction of dimedone **1a** with 2-cinnamoylpyridine **4a** mediated by K_2CO_3 and $ZnCl_2$, which were often used in Michael reactions as a base[6a,13] and a Lewis acid,[14] in 92% and 90%, further confirmed the identity of **7a** as a Michael addition product.

Compounds **5a**−**r** were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and FT-IR spectra. The HRMS spectra of products **5a**−**r** exhibited corresponding accurate molecular ions. In the ^{1}H NMR spectra of **5a**−**p**, the two methine protons (H2 and H3) of the dihydrofuran moiety had chemical shifts at 6.29−6.40 and 4.26−4.43 ppm with a coupling constant of 3.8−4.2 Hz. Their $\Delta\delta_H$ were in the range of 1.93−2.10 ppm. In their ^{13}C NMR spectra, the dihydrofuran carbons showed chemical shifts at 91.1−92.1, 48.1−49.0, 114.1−116.7, and 177.1−179.1 ppm, while the two carbonyl carbons were located at 193.0−194.1, and 193.6−194.6 ppm. Whereas in the ^{1}H NMR spectra of **5q** and **5r**, the low-field methine proton remained nearly the same chemical shift (6.22−6.23 ppm) as those of **5a**−**p**, the high-field methine proton showed drastic upfield shift (3.24−3.26 ppm) due to the electron-donating property of the attached alky group.

For *cis* and *trans* isomers of ethyl 5-benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylate (*cis*-**8** and *trans*-**8**, Figure 1), the $\Delta\delta_H$ of the two methine protons of the dihydrofuran heterocycle were pretty close, being 1.52 and 1.33 ppm, respectively.[9b] In contrast, its regioisomer, i.e., *trans*-ethyl 4-benzoyl-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (*trans*-**9**, Figure 1), had a smaller $\Delta\delta_H$ value (0.53 ppm).[11b] For tetrahydrobenzofuranones bearing a similar dihydrofuran heterocycle should have the same trend for the $\Delta\delta_H$ values. Taken into account of the corresponding $\Delta\delta_H$ values of *trans*-3-benzoyl-2-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (**3**) (0.86 ppm) and *trans*-3-benzoyl-2-(4-methoxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (*trans*-**10**, Figure 1) (0.74 ppm),[11b] compounds **5a**−**p** with much larger $\Delta\delta_H$ should be assigned as 2-acyl-3-aryl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranones rather than as their regioisomers 3-acyl-2-aryl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranones. Similarly, products **5q** and **5r** should also have the same regioselectivity.

The assigned regioselectivity was confirmed by the HMBC spectrum of **5j**, which clearly indicated the three-bond correlation of the 2′-proton (H2′, 7.47 ppm) of the nitrophenyl moiety with the methine carbon (C3) at 48.8 ppm, and no correlation between the 2′-proton and the methine carbon (C2) at 91.1 ppm bonding to the oxygen atom.

The measured coupling constants (3.4−4.2 Hz) of compounds **5a**−**r** were close to those of compounds **3**, *trans*-**8**, *trans*-**9**, *trans*-**10**, and other *trans* diastereoisomers of dihydrofuran derivatives,[8] and we were confident to assign compounds **5a**−**r** as *trans* isomers. The *trans* stereochemistry was proved by theoretical calculations together with the NOESY spectrum of product **5j**. The latter showed correlations between H2′/H6′ of the nitrophenyl group and one (H2 or H3) of the two methine protons as well as between the methine protons. The key parameters and formation energies for the optimized structures of the *trans*-**5j** and *cis*-**5j** isomers (Figure 2) are listed in Table 3. As seen from Table 3, the distance between the H2′ atom and one of the two methine protons (H2−H2′) is much longer than the other two for the *cis*-**5j** isomer, while the three key space distances are close to each other for the *trans*-**5j** isomer. The calculated space distances of the *trans*-**5j** isomer can explain the observed NOESY spectrum very well, suggesting that

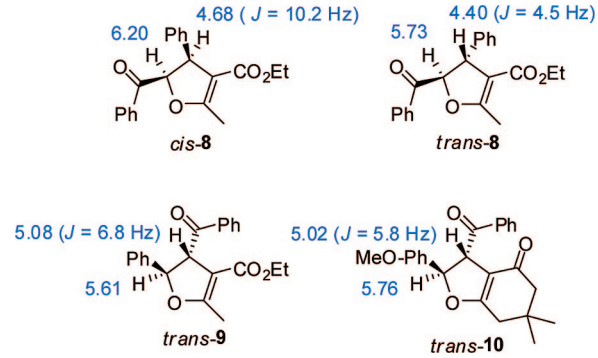


FIGURE 1. Selected chemical shifts and coupling constants of *cis*-**8**, *trans*-**8**, *trans*-**9**, and *trans*-**10**.

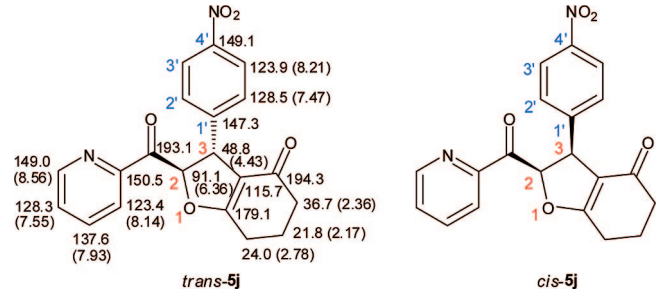


FIGURE 2. Structures of *trans*-**5j** (with chemical shift assignments) and *cis*-**5j**.

(13) Rosnati, V.; Saba, A.; Salimbeni, A. *Tetrahedron Lett.* **1981**, *22*, 167–168.

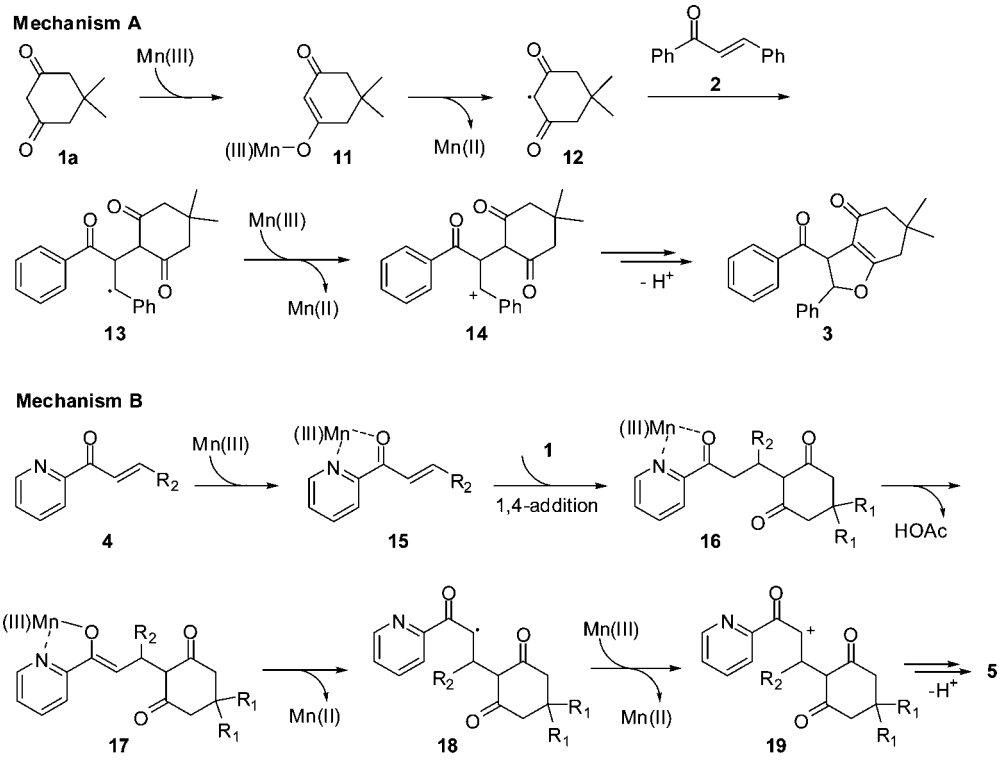
(14) (a) Yamazaki, S.; Morikawa, S.; Iwata, Y.; Yamamoto, M.; Kuramoto, K. *Org. Biomol. Chem.* **2004**, *2*, 3134–3138. (b) Ahmed, M. G.; Ahmed, S. A.; Uddin, M. K.; Rahman, M. T.; Romman, U. K. R.; Fujio, M.; Tsuda, Y. *Tetrahedron Lett.* **2005**, *46*, 8217–8220.

TABLE 3. Key Parameters and Formation Energies of *trans*-5j and *cis*-5j[a]

compound	distance (Å)[b]	dihedral angle (deg)[c]	J (Hz)[d]	formation energy (kcal/mol)[e]
trans-**5j**	H2−H3 = 2.89; H2−H2′ = 2.40; H3−H6′ = 2.33	108.7	3.0	0
cis-**5j**	H2−H3 = 2.28; H2−H2′ = 4.15; H3−H6′ = 2.29	15.7	10.6	1.50

[a] The calculation were performed at B3LYP/6-31G* level. [b] Shortest distances in the optimized structures. [c] Dihedral angle of H2−C2−C3−H3 of the optimized structures. [d] Coupling constant between the two methine protons H2 and H3. [e] Energy relative to *trans*-**5j**.

SCHEME 3. Plausible Reaction Mechanisms for the Formation of Products 3 and 5a−r



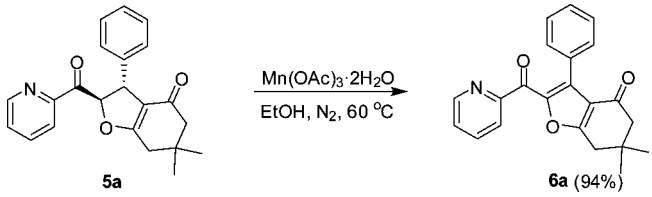
compound **5j** should have a *trans* stereochemistry at the C2 and C3 carbon atoms. Additional evidence for the assigned *trans* stereochemistry came from the calculated coupling constants for the two methine protons of *trans*-**5j** and *cis*-**5j**. The observed coupling constant of 4.2 Hz was very close to the calculated value of 3.0 Hz for the *trans*-**5j** isomer, but far away from that (10.6 Hz) for the *cis*-**5j** isomer. Furthermore, the formation energy of the *trans* isomer of **5j** was lower than its *cis* isomer, consistent with the fact that the *trans*-**5j** isomer was isolated as the product.

The proposed plausible reaction mechanisms to explain the formation of products **3** and **5a−r** are shown in Scheme 3. The formation of compound **3** probably follows the commonly accepted pathway[8,10,11] (mechanism A, Scheme 3). The addition of radical **12**, which is generated from the Mn(III)-enolate complex of dimedone **1a**, to chalcone **2** gives radical intermediate **13**. Subsequent oxidative cyclization affords product **3**. The reversed regioselectivities of 1-(pyridin-2-yl)-enones and chalcones toward the additions of 1,3-cyclohexanediones in the presence of $Mn(OAc)_3$ can only be attributed to the role played by the nitrogen atom of the pyridine ring. The plausible reaction pathway for the formation of compounds **5a−r** is shown as mechanism B in Scheme 3. The coordination of the nitrogen atom and oxygen atom to metal salts is well-known in the literature.[15] The concerted chelation of the pyridinyl and carbonyl moieties of 1-(pyridin-2-yl)-enones **4** to Mn(III) increases the electron deficiency of the C=C bond, thus facilitates the conjugate addition of 1,3-cyclohexanedione **1**, and produces Mn(III)-complexed intermediate **16**. The enolization of intermediate **16**, followed by the loss of a Mn(II) species, gives radical **18**. Oxidation of radical **18** by another molecule of $Mn(OAc)_3$ affords carbocation **19**, which cyclizes to generate the final product **5**. Thus, $Mn(OAc)_3$ behaves as a Lewis acid as well as a radical initiator.

The obtained 2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivatives **5** bearing a dihydrofuran moiety could be further converted into 6,7-dihydrobenzofuran-4(5*H*)-one derivatives oxidized by $Mn(OAc)_3 \cdot 2H_2O$ in alcoholic solution. For instance, treatment of compound **5a** in the presence of $Mn(OAc)_3 \cdot 2H_2O$ (2.4 equiv) in absolute ethanol under N_2 protection at 60 °C for 3 h affords product **6a** in 94% yield (Scheme 4). Compound **6a** was a byproduct for the $Mn(OAc)_3 \cdot 2H_2O$-mediated reaction of **1a** and **4a** in ethanol. However, product **6a** was hardly detected for the corresponding solvent-free ball-milling reaction and for the treatment of compound **5a** with $Mn(OAc)_3 \cdot 2H_2O$ (2.4 equiv) under our ball-milling conditions.

(15) (a) Otto, S.; Boccaletti, G.; Engberts, B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238–4239. (b) Abu-Youseef, M. A. M.; Escuer, A.; Gatteschi, D.; Goher, M. A. S.; Mautner, F. A.; Vicente, R. *Inorg. Chem.* **1999**, *38*, 5716–5723. (c) Cossy, J.; Bouzide, A. *Tetrahedron* **1999**, *55*, 6483–6496. (d) Martínez, A. P.; García, M. P.; Lahoz, F. J.; Oro, L. A. *Inorg. Chim. Acta* **2003**, *347*, 86–98. (e) Milios, C. J.; Stamatatos, T. C.; Kyritsis, P.; Terzis, A.; Raptopoulou, C. P.; Vicente, R.; Escuer, A.; Perlepes, S. P. *Eur. J. Inorg. Chem.* **2004**, 2885–2901. (f) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157–3172. (g) Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176–5186.

SCHEME 4. $Mn(OAc)_3 \cdot 2H_2O$-Mediated Oxidation of Compound 5a



Conclusion

We have developed the synthesis of *trans*-2-acyl-3-aryl/alkyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone derivatives through the radical reactions of 1-(pyridin-2-yl)-enones with 1,3-cyclohexanediones mediated by $Mn(OAc)_3 \cdot 2H_2O$. The present solvent-free radical reactions were very efficient, affording the unexpected products in as high as 91% yield under our ball-milling conditions. More importantly, the reversed regioselectivity of 1-(pyridin-2-yl)-enones was uncovered for the first time. $Mn(OAc)_3 \cdot 2H_2O$ played the role both as an oxidant and as a Lewis acid, and thus altered the reaction pathway of 1-(pyridin-2-yl)-enones.

Experimental Section

$Mn(OAc)_3 \cdot 2H_2O$-Catalyzed Reaction of Dimedone 1a with Chalcone 2 by Ball Milling. A mixture of dimedone **1a** (16.8 mg, 0.12 mmol), chalcone **2** (20.8 mg, 0.10 mmol), and $Mn(OAc)_3 \cdot 2H_2O$ (64.3 mg, 0.24 mmol) along with a stainless-steel ball (7 mm) were placed into a stainless-steel jar (10 mL). The same mixture was introduced into another parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany) and were milled vigorously at a rate of 1800 rpm at room temperature for 5 h (sequential intervals of 1 h milling followed by a 1 h pause). The resulting mixtures were extracted with ethyl acetate, and the combined solution was evaporated to remove the solvent in vacuo. The residue was separated by flash column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 3:1 v/v) to afford 3-benzoyl-6,6-dimethyl-2-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (**3**, 15.9 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.39−7.29 (m, 5H), 7.22−7.16 (m, 2H), 5.81 (d, J = 5.7 Hz, 1H), 4.95 (d, J = 5.7 Hz, 1H), 2.44 (d, J = 17.9 Hz, 1H), 2.41 (d, J = 17.9 Hz, 1H), 2.21 (d, J = 16.2 Hz, 1H), 2.18 (d, J = 16.2 Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 193.6, 177.4, 139.7, 136.5, 133.8, 129.3, 129.24 (2C), 129.20 (2C), 128.7 (2C), 125.9 (2C), 113.0, 90.3, 54.8, 51.1, 38.1, 34.6, 28.8, 28.7; FT-IR (KBr) ν/cm^{-1} 2955, 1685, 1638, 1450, 1400, 1351, 1336, 1281, 1221, 1053, 1004, 931, 765, 695; HR-MS (+EI) calcd for $C_{23}H_{22}O_3$ (M^+) 346.1569, found 346.1566.

General Procedure for the $Mn(OAc)_3 \cdot 2H_2O$-Mediated Reactions of 1,3-Cyclohexanediones 1a,b with 1-(Pyridin-2-yl)-enones 4a−k by Ball Milling. The two stainless-steel jars, containing a mixture of 1,3-cyclohexanedione **1a** (or **1b**, 0.10 mmol), enone **4a** (or **4b**−**k**, 0.12 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (64.3 mg, 0.24 mmol), and a stainless-steel ball in each of the two reaction vessels, were milled vigorously at a rate of 1800 rpm at room temperature for 1 h. The resulting mixtures were extracted with ethyl acetate, and the combined solution was evaporated to remove the solvent in vacuo. The residue was separated by flash column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 2.5:1 v/v) to afford 6,6-dimethyl-3-phenyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **5a** (or **5b**−**r**).

6,6-Dimethyl-3-phenyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.36−7.23 (m, 5H), 6.40 (d, J = 3.8 Hz, 1H), 4.33 (d, J = 3.8 Hz, 1H), 2.66 (d, J = 17.8 Hz, 1H), 2.57 (d, J = 17.8 Hz, 1H), 2.25 (d, J = 16.3 Hz, 1H), 2.22 (d, J = 16.3 Hz, 1H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 193.8, 177.5, 150.9, 149.1, 141.7, 137.3, 128.7 (2C), 128.0, 127.5 (2C), 127.3, 123.3, 115.2, 92.0, 51.3, 48.8, 37.8, 34.4, 29.1, 28.6; FT-IR (KBr) ν/cm^{-1} 2952, 1710, 1655, 1640, 1395, 1218, 1141, 1034, 951, 878, 769, 700, 617; HR-MS (+EI) calcd for $C_{22}H_{21}NO_3$ (M^+) 347.1521, found 347.1520.

6,6-Dimethyl-3-(4-nitrophenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 7.7 Hz, 1H), 7.93 (t, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.7, 4.4 Hz, 1H), 7.47 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 4.1 Hz, 1H), 4.42 (d, J = 4.1 Hz, 1H), 2.69 (d, J = 17.9 Hz, 1H), 2.59 (d, J = 17.9 Hz, 1H), 2.26 (d, J = 15.9 Hz, 1H), 2.22 (d, J = 15.9 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 193.0, 178.1, 150.5, 149.2, 149.1, 147.3, 137.6, 128.5 (2C), 128.3, 124.0 (2C), 123.5, 114.5, 91.3, 51.1, 48.8, 37.8, 34.5, 29.0, 28.6; FT-IR (KBr) ν/cm^{-1} 2961, 1712, 1662, 1634, 1518, 1395, 1345, 1221, 1038, 945, 852, 788, 733, 700, 619; HR-MS (+EI) calcd for $C_{22}H_{20}N_2O_5$ (M^+) 392.1372, found 392.1374.

3-(4-Cyanophenyl)-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 4.5 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.92 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.54 (dd, J = 7.7, 4.5 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 6.36 (d, J = 4.1 Hz, 1H), 4.37 (d, J = 4.1 Hz, 1H), 2.67 (d, J = 17.8 Hz, 1H), 2.58 (d, J = 17.8 Hz, 1H), 2.25 (d, J = 16.5 Hz, 1H), 2.22 (d, J = 16.5 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 193.1, 178.0, 150.5, 149.0, 147.1, 137.5, 132.5 (2C), 128.4 (2C), 128.3, 123.4, 118.9, 114.4, 111.2, 91.3, 51.1, 48.9, 37.8, 34.4, 29.0, 28.6; FT-IR (KBr) ν/cm^{-1} 2956, 2226, 1717, 1655, 1638, 1398, 1220, 1166, 1039, 941, 882, 790, 686, 554; HR-MS (+EI) calcd for $C_{23}H_{20}N_2O_3$ (M^+): 372.1474, found 372.1467.

3-(4-Chlorophenyl)-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.90 (t, J = 7.7 Hz, 1H), 7.53 (dd, J = 7.7, 4.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 6.35 (d, J = 3.8 Hz, 1H), 4.29 (d, J = 3.8 Hz, 1H), 2.66 (d, J = 17.8 Hz, 1H), 2.56 (d, J = 17.8 Hz, 1H), 2.24 (d, J = 16.3 Hz, 1H), 2.21 (d, J = 16.3 Hz, 1H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 193.6, 177.7, 150.8, 149.1, 140.3, 137.4, 133.1, 128.9 (2C), 128.8 (2C), 128.1, 123.4, 114.9, 91.8, 51.2, 48.4, 37.8, 34.4, 29.1, 28.6; FT-IR (KBr) ν/cm^{-1} 2960, 1706, 1656, 1638, 1489, 1393, 1220, 1089, 948, 884, 787; HR-MS (+EI) calcd for $C_{22}H_{20}NO_3{}^{37}Cl$ (M^+) 383.1102, found 383.1096.

3-(3,4-Dichlorophenyl)-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.4 Hz, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.92 (t, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.7, 4.4 Hz, 1H), 7.42 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.32 (d, J = 3.9 Hz, 1H), 4.28 (d, J = 3.9 Hz, 1H), 2.66 (d, J = 17.8 Hz, 1H), 2.58 (d, J = 17.8 Hz, 1H), 2.25 (d, J = 16.7 Hz, 1H), 2.24 (d, J = 16.7 Hz, 1H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 193.3, 178.0, 150.6, 149.1, 142.0, 137.5, 132.7, 131.3, 130.6, 129.7, 128.3, 126.9, 123.4, 114.4, 91.6, 51.2, 48.1, 37.8, 34.4, 29.0, 28.7; FT-IR (KBr)ν/cm^{-1} 2965, 1706, 1659, 1642, 1584, 1469, 1391, 1217, 1029, 918, 791, 684; HR-MS (+EI) calcd for $C_{22}H_{19}NO_3{}^{35}Cl_2$ (M^+) 415.0742, found 415.0746.

3-(3,4-Dimethylphenyl)-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.03 (s, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.36 (d, J = 3.8 Hz, 1H), 4.26 (d, J = 3.8 Hz, 1H), 2.65 (d, J = 17.7 Hz, 1H), 2.57 (d, J = 17.7 Hz, 1H), 2.29−2.17 (m, 8H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 193.8, 177.2, 151.0, 149.1,

139.2, 137.3, 136.7, 135.5, 130.0, 128.8, 127.9, 124.8, 123.3, 115.3, 92.1, 51.3, 48.5, 37.8, 34.4, 29.1, 28.6, 20.0, 19.5; FT-IR (KBr) ν/cm^{-1} 2967, 1713, 1652, 1638, 1584, 1391, 1219, 1194, 1091, 1037, 995, 960, 952, 932, 802, 776, 744, 679, 618; HR-MS (+EI) calcd for $C_{24}H_{25}NO_3$ (M^+) 375.1834, found 375.1840.

6,6-Dimethyl-2-picolinoyl-3-*p*-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.4 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.37 (d, J = 3.9 Hz, 1H), 4.28 (d, J = 3.9 Hz, 1H), 2.65 (d, J = 17.7 Hz, 1H), 2.56 (d, J = 17.7 Hz, 1H), 2.34 (s, 3H), 2.24 (d, J = 16.3 Hz, 1H), 2.21 (d, J = 16.3 Hz, 1H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 193.8, 177.3, 151.0, 149.1, 138.8, 137.3, 136.8, 129.4 (2C), 127.9, 127.3 (2C), 123.3, 115.3, 92.0, 51.3, 48.5, 37.8, 34.4, 29.1, 28.6, 21.2; FT-IR (KBr) ν/cm^{-1} 2961, 1707, 1659, 1632, 1394, 1223, 1038, 961, 884, 802, 746, 676, 524; HR-MS (+EI) calcd for $C_{23}H_{23}NO_3$ (M^+) 361.1678, found 361.1679.

3-(4-Methoxyphenyl)-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.4 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 3.8 Hz, 1H), 4.28 (d, J = 3.8 Hz, 1H), 3.80 (s, 3H), 2.65 (d, J = 17.7 Hz, 1H), 2.56 (d, J = 17.7 Hz, 1H), 2.24 (d, J = 16.4 Hz, 1H), 2.22 (d, J = 16.4 Hz, 1H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 193.9, 177.3, 158.8, 151.0, 149.1, 137.3, 133.9, 128.4 (2C), 127.9, 123.3, 115.2, 114.1 (2C), 92.1, 55.3, 51.3, 48.2, 37.8, 34.3, 29.1, 28.6; FT-IR (KBr) ν/cm^{-1} 2961, 1707, 1647, 1631, 1608, 1509, 1394, 1249, 1224, 1174, 1031, 960, 804, 674, 535; HR-MS (+EI) calcd for $C_{23}H_{23}NO_4$ (M^+) 377.1627, found 377.1621.

3-Phenyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.36−7.24 (m, 5H), 6.38 (d, J = 4.0 Hz, 1H), 4.34 (d, J = 4.0 Hz, 1H), 2.79−2.72 (m, 2H), 2.35 (t, J = 6.4 Hz, 2H), 2.19−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 193.9, 178.4, 150.9, 149.1, 141.6, 137.3, 128.6 (2C), 128.0, 127.5 (2C), 127.3, 123.3, 116.4, 91.7, 48.8, 36.9, 24.0, 21.8; FT-IR (KBr) ν/cm^{-1} 2944, 1712, 1650, 1633, 1454, 1397, 1228, 1171, 944, 752, 699; HR-MS (+EI) calcd for $C_{20}H_{17}NO_3$ (M^+) 319.1208, found 319.1202.

3-(4-Nitrophenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5j). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 7.7 Hz, 1H), 7.93 (t, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.7, 4.4 Hz, 1H), 7.47 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 4.2 Hz, 1H), 4.43 (d, J = 4.2 Hz, 1H), 2.82−2.75 (m, 2H), 2.36 (t, J = 6.4 Hz, 2H), 2.21−2.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 193.1, 179.1, 150.5, 149.1, 149.0, 147.3, 137.6, 128.5 (2C), 128.3, 123.9 (2C), 123.4, 115.8, 91.1, 48.8, 36.7, 24.0, 21.8; FT-IR (KBr) ν/cm^{-1} 2945, 1709, 1660, 1632, 1514, 1394, 1343, 1228, 1171, 1107, 957, 946, 852, 792, 751; HR-MS (+EI) calcd for $C_{20}H_{16}N_2O_5$ (M^+) 364.1059, found 364.1053.

3-(4-Cyanophenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5k). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 4.5 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.92 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 7.7, 4.5 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 6.34 (d, J = 4.2 Hz, 1H), 4.38 (d, J = 4.2 Hz, 1H), 2.81−2.74 (m, 2H), 2.35 (t, J = 6.4 Hz, 2H), 2.21−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 193.2, 179.0, 150.6, 149.1, 147.1, 137.6, 132.5 (2C), 128.4 (2C), 128.3, 123.5, 119.0, 115.8, 111.2, 91.1, 49.0, 36.8, 24.0, 21.8; FT-IR (KBr) ν/cm^{-1} 2933, 2228, 1713, 1655, 1638, 1388, 1229, 1180, 1061, 962, 939, 877, 796, 558; HR-MS (+EI) calcd for $C_{21}H_{16}N_2O_3$ (M^+) 344.1161, found 344.1161.

3-(4-Chlorophenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5l). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 4.6 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.90 (t, J = 7.7 Hz, 1H), 7.53 (dd, J = 7.7, 4.6 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.33 (d, J = 4.1 Hz, 1H), 4.30 (d, J = 4.1 Hz, 1H), 2.79−2.72 (m, 2H), 2.35 (t, J = 6.5 Hz, 2H), 2.19−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 193.6, 178.6, 150.8, 149.1, 140.2, 137.4, 133.1, 128.9 (2C), 128.8 (2C), 128.1, 123.3, 116.2, 91.5, 48.4, 36.8, 24.0, 21.8; FT-IR (KBr) ν/cm^{-1} 2933, 1715, 1654, 1639, 1491, 1389, 1227, 1177, 1089, 963, 946, 795, 657, 512; HR-MS (+EI) calcd for $C_{20}H_{16}NO_3{}^{35}Cl$ (M^+) 353.0819, found 353.0818.

3-(3,4-Dimethylphenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5m). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.34 (d, J = 4.0 Hz, 1H), 4.27 (d, J = 4.0 Hz, 1H), 2.77−2.73 (m, 2H), 2.34 (t, J = 6.3 Hz, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 2.19−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 194.1, 178.2, 151.1, 149.1, 139.1, 137.3, 136.7, 135.5, 130.0, 128.7, 128.0, 124.8, 123.3, 116.7, 91.9, 48.5, 36.9, 24.1, 21.9, 20.1, 19.6; FT-IR (KBr) ν/cm^{-1} 2939, 2919, 1707, 1645, 1623, 1395, 1226, 1180, 1013, 955, 932, 788, 774, 658; HR-MS (+EI) calcd for $C_{22}H_{21}NO_3$ (M^+) 347.1521, found 347.1517.

2-Picolinoyl-3-*p*-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5n). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.35 (d, J = 3.9 Hz, 1H), 4.30 (d, J = 3.9 Hz, 1H), 2.78−2.72 (m, 2H), 2.36−2.32 (m, 5H), 2.17−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 194.0, 178.3, 150.9, 149.1, 138.7, 137.3, 136.8, 129.3 (2C), 127.9, 127.3 (2C), 123.2, 116.5, 91.8, 48.5, 36.9, 24.0, 21.8, 21.2; FT-IR (KBr) ν/cm^{-1} 2951, 1707, 1646, 1625, 1394, 1228, 1168, 1015, 956, 945, 785, 767; HR-MS (+EI) calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365, found 333.1359.

3-(4-Methoxyphenyl)-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5o). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.33 (d, J = 3.9 Hz, 1H), 4.29 (d, J = 3.9 Hz, 1H), 3.80 (s, 3H), 2.78−2.72 (m, 2H), 2.35 (t, J = 6.3 Hz, 2H), 2.16−2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 194.0, 178.2, 158.8, 151.0, 149.1, 137.3, 133.8, 128.4 (2C), 128.0, 123.3, 116.5, 114.1 (2C), 91.9, 55.3, 48.1, 36.9, 24.0, 21.9; FT-IR (KBr) ν/cm^{-1} 2936, 2920, 1719, 1637, 1609, 1511, 1392, 1243, 1226, 1178, 1036, 964, 943, 877, 795, 650; HR-MS (+EI) calcd for $C_{21}H_{19}NO_4$ (M^+) 349.1314, found 349.1307.

6,6-Dimethyl-3-phenyl-2-(pyrazine-2-carbonyl)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5p). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J = 1.5 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H), 8.58 (dd, J = 2.4, 1.5 Hz, 1H), 7.36−7.24 (m, 5H), 6.29 (d, J = 3.9 Hz, 1H), 4.33 (d, J = 3.9 Hz, 1H), 2.64 (d, J = 17.7 Hz, 1H), 2.56 (d, J = 17.7 Hz, 1H), 2.25 (d, J = 16.3 Hz, 1H), 2.22 (d, J = 16.3 Hz, 1H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 193.3, 177.1, 148.7, 145.5, 145.0, 143.6, 141.3, 128.8 (2C), 127.5, 127.4 (2C), 115.2, 91.5, 51.3, 48.8, 37.8, 34.4, 29.0, 28.7; FT-IR (KBr) ν/cm^{-1} 2965, 1712, 1636, 1624, 1396, 1220, 1020, 968, 947, 890, 709; HR-MS (+EI) calcd for $C_{21}H_{20}N_2O_3$ (M^+) 348.1474, found 348.1466.

6,6-Dimethyl-2-picolinoyl-3-propyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5q). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.87 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.5 Hz, 1H), 6.23 (d, J = 3.9 Hz, 1H), 3.27−3.20 (m, 1H), 2.54 (d, J = 17.6 Hz, 1H), 2.40 (d, J = 17.6 Hz, 1H), 2.23 (d, J = 16.5 Hz, 1H), 2.21 (d, J = 16.5 Hz, 1H), 1.93−1.70 (m, 2H), 1.53−1.39 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 194.6, 177.2, 151.4, 149.0, 137.3, 127.8, 123.2, 114.6, 88.9, 51.5, 43.9, 37.9, 35.4, 34.3, 29.1, 28.5, 19.4, 14.3; FT-IR (KBr) ν/cm^{-1} 2960, 1709, 1633, 1582, 1407, 1395, 1222, 1034, 960, 938, 742, 691; HR-MS (+EI) calcd for $C_{19}H_{23}NO_3$ (M^+) 313.1678, found 313.1679.

3-Isobutyl-6,6-dimethyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (5r). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J

= 4.8 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.87 (t, J = 7.7 Hz, 1H), 7.51 (dd, J = 7.7, 4.8 Hz, 1H), 6.22 (d, J = 3.4 Hz, 1H), 3.28−3.22 (m, 1H), 2.55 (d, J = 17.7 Hz, 1H), 2.40 (d, J = 17.7 Hz, 1H), 2.23 (d, J = 16.1 Hz, 1H), 2.20 (d, J = 16.1 Hz, 1H), 2.06−1.96 (m, 1H), 1.72−1.58 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 194.3, 177.0, 151.3, 148.9, 137.2, 127.7, 123.1, 115.5, 89.1, 51.4, 43.8, 41.9, 37.7, 34.1, 28.9, 28.3, 25.4, 23.4, 22.1; FT-IR (KBr) ν/cm^{-1} 2957, 1712, 1639, 1397, 1217, 1033, 939, 745, 687; HR-MS (+EI) calcd for $C_{20}H_{25}NO_3$ (M^+) 327.1834, found 327.1840.

Synthesis of Michal Product 7a by the $Mn(OAc)_3\cdot 2H_2O$-Mediated Reaction of Dimedone 1a with 2-Cinnamoylpyridine 4a. The two stainless-steel jars, containing a mixture of dimedone **1a** (14.0 mg, 0.10 mmol), 2-cinnamoylpyridine **4a** (25.1 mg, 0.12 mmol), $Mn(OAc)_3\cdot 2H_2O$ (64.3 mg, 0.24 mmol), and a stainless-steel ball in each of the two reaction vessels, were milled vigorously at a rate of 1800 rpm at room temperature for 5 min. The resulting mixtures were extracted with ethyl acetate, and the combined solution was evaporated to remove the solvent in vacuo. The residue was separated by flash column chromatography on silica gel (gradient eluent, petroleum ether/ethyl acetate = 2.5:1 and 1:1 v/v) to afford 6,6-dimethyl-3-phenyl-2-picolinoyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **5a** (18.8 mg, 27%) and 3-hydroxy-5,5-dimethyl-2-(3-oxo-1-phenyl-3-(pyridin-2-yl)propyl)cyclohex-2-enone **7a** (29.1 mg, 42%). **7a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (bs, 1H), 8.70 (bs, 1H), 7.95 (bs, 1H), 7.85 (bs, 1H), 7.61 (bs, 1H), 7.19−7.10 (m, 4H), 7.06 (t, J = 7.0 Hz, 1H), 4.80 (bs, 1H), 4.16 (bs, 1H), 3.67 (bs, 1H), 2.27−2.11 (m, 4H), 0.95 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.5, 153.1, 149.1, 144.8, 137.5, 127.7, 127.4, 125.2, 121.2, 115.8, 46.9, 33.7, 31.5, 27.8; FT-IR (KBr) ν/cm^{-1} 2958, 1698, 1602, 1377, 1315, 1250, 1151, 1070, 996, 764, 700; HR-MS (+EI) calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1671.

$Mn(OAc)_3\cdot 2H_2O$-Mediated Oxidation Reaction of Compound 5a. A mixture of **5a** (69.4 mg, 0.20 mmol) and $Mn(OAc)_3\cdot 2H_2O$ (128.6 mg, 0.48 mmol) was added to absolute ethanol (10 mL) in a round-bottomed flask wrapped with aluminum foil, and the suspension was stirring for 3 h under the nitrogen protection at 60 °C. After completion of the reaction, the solvent was removed in vacuo, and the residue was separated by flash column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 2.5:1 v/v) to afford 6,6-dimethyl-3-phenyl-2-picolinoyl-6,7-dihydrobenzofuran-4(5*H*)-one **6a** (64.9 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 3.9 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.27−7.05 (m, 6H), 2.93 (s, 2H), 2.44 (s, 2H), 1.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 183.9, 169.4, 154.1, 148.6, 147.5, 136.5, 134.0, 130.4 (2C), 130.3, 128.2, 127.4 (2C), 126.0, 123.8, 119.8, 53.3, 38.1, 34.8, 28.6 (2C); FT-IR (KBr) ν/cm^{-1} 2961, 2929, 1692, 1642, 1581, 1537, 1488, 1451, 1436, 1421, 1411, 1349, 1339, 1246, 1167, 1050, 984, 929, 770, 745, 707, 689; HR-MS (+EI) calcd for $C_{22}H_{19}NO_3$ (M^+) 345.1365, found 345.1362.

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Supporting Information Available: NMR spectra of **5a**−**r**, ^{1}H−^{13}C HMBC and ^{1}H−^{1}H NOESY spectra of **5j**, and computational details for **5j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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